Neutrophil-to-lymphocyte ratio has limited predictive value for determining outcomes in perforated colon cancer: a retrospective study.

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Research

Keywords: neutrophil-to-lymphocyte ratio; perforated colon cancer; leukocytosis; serum albumin; prognostic factor

Abstract

Background: The neutrophil-to-lymphocyte ratio (NLR) 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 if preoperative NLR was associated with survival outcomes in patients with perforated colon cancer.

Methods: One-to-one propensity score matching (PSM) was applied to minimize the difference between the higher- (>5) and lower- (≤5) NLR groups. Clinicopathological factors, long-term overall survival (OS), and disease-free survival (DFS) were analyzed and compared between the two groups. The main outcome measures were OS and DFS.

Results: Before PSM, the higher-NLR group had significantly higher prevalence of leukocytosis (lower- vs. higher-NLR groups: 12 [12.9%] vs. 46 [59.7%], p<0.001), lower serum albumin levels (lower- vs. higher-NLR groups: 30 [32.3%] vs. 42 [54.5%], p=0.003), and higher emergent operation rate (lower- vs. higher-NLR groups: 5 [5.4%] vs. 20 [26.0%], p<0.001). After one-to-one PSM, the groups comprised 41 patients each; none of the parameters were significantly different. The mean follow-up period was 76.3 months. Five-year OS and DFS were not significantly different (OS: p=0.637; DFS: p=0.827) between the higher- and lower-NLR groups.

Conclusion: NLR have limited predictive value for 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 the outcomes, long-term survival remains unsatisfactory. Increasing reports have shown that systemic inflammatory reactions increase the risk of cancer development [2, 3]. A number of studies have focused on inflammation-related prognostic variables, 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. NLR is considered not only a tumor-related inflammatory environment marker but also an indicator of anti-tumor host immunity. A high pre-operative NLR (> 5) has been associated with poor overall survival [8–10].

Preoperative NLR has been shown to influence disease-free survival in patients with stage I to III colorectal cancer; an elevated NLR (estimated cut-off value > 3) is also associated with worse outcomes (5-year disease-free survival: 66.3% vs. 78.9% for colon cancer; 60.5% vs. 66.2% for rectal cancer) [11].

However, there is a lack of evidence on the association between perforated colon cancer and the NLR. Therefore, we aimed to determine the association between preoperative NLR, clinicopathologic features, 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, between January 1, 1995 and December 31, 2015, were reviewed. All data were retrospectively reviewed from a prospectively maintained database after obtaining the 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, tumor stage and location, treatments, and cause of death (recurrence vs. second primary cancer) were also collected.

Preoperative patients' demographic characteristics included age, sex, comorbid diseases (hepatitis, diabetes status, and liver cirrhosis), serum albumin, carcinoembryonic antigen, and hemoglobin levels, white blood cell (WBC) count, and NLR. Perioperative factors included tumor location and whether the patient underwent an emergent operation or not. Tumor TNM staging, histology, and pathological features were also reviewed.

The NLR was calculated by dividing the number of neutrophils by the number of lymphocytes per the serum differential count. Preoperative NLR was calculated using the latest preoperative data, either at the emergency department or during admission. The cut-off value for the NLR in this study was defined as 5.0, which was equal to the cut-off value of the most reviewed articles.

The primary study outcomes were overall survival and disease-free survival. The cause of death was recorded as an event. Patients were recorded alive at the last follow-up, regardless of their disease status. Survival was measured from the operation date 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 higher- and lower-NLR groups; the matching tolerance was defined as 0.05.

Statistical analysis

Statistical analyses were performed using SPSS version 24.0 (IBM Corp., Armonk, NY), and p-values < 0.05 were considered statistically significant. Pearson's chi-squared test was used for clinicopathologic descriptive data to determine the differences between the higher- and lower-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 analyses to determine the independent risk factors for survival.

Results

All 240 patients underwent curative-intended surgical treatments, including laparoscopic colectomy, traditional (open) colectomy, and emergent exploratory laparotomy. Patients were excluded because they underwent polypectomy and surgery within 24 hours (n = 5), had early mortality (< 30 days postoperatively, n = 4), and had 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 lower NLR and 77 (45.3%) patients with higher NLR. The mean follow-up time was 73.5 months, ranging from 1.7 to 135.7 months.

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

Patients' characteristics before and after propensity score matching

		Before matching				After 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	≤ 65 y/o	99 (58.2%)	56 (60.2%)	43 (55.8%)	0.565	49 (59.8%)	24 (58.5%)	25 (61.0%)	0.822
	> 65 y/o	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	≤ 10 g/dL	75 (44.1%)	38 (40.9%)	37 (48.1%)	0.347	32 (39.0%)	16 (39.0%)	16 (39.0%)	1.000
	> 10 g/dL	95 (55.9%)	55 (59.1%)	40 (51.9%)		50 (61.0%)	25 (61.0%)	25 (61.0%)	
WBC count	≤ 12000/μL	112 (65.9%)	81 (87.1%)	31 (40.3%)	< 0.001	58 (70.7%)	29 (70.7%)	29 (70.7%)	1.000
	> 12000/μL	58 (34.1%)	12 (12.9%)	46 (59.7%)		24 (29.3%)	12 (29.3%)	12 (29.3%)	
CEA	≤ 5 ng/mL	70 (41.2%)	41 (44.1%)	29 (37.7%)	0.397	30 (36.6%)	15 (40.5%)	15 (41.7%)	0.922
	> 5 ng/mL	100 (58.8%)	52 (55.9%)	48 (62.3%)		43 (52.4%)	22 (59.5%)	21 (58.3%)	
Albumin	≤ 3.5 g/dL	72 (42.4%)	30 (32.3%)	42 (54.5%)	0.003	38 (46.3%)	19 (54.3%)	19 (54.3%)	1.000
	> 3.5 g/dL	98 (57.6%)	63 (67.7%)	35 (45.5%)		32 (39.0%)	16 (45.7%)	16 (45.7%)	
DM	No	146 (58.9%)	82 (88.2%)	64 (83.1%)	0.346	65 (79.3%)	35 (85.4%)	30 (73.2%)	0.173
	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%)	

NLR, neutrophil-to-platelet ratio; y/o, years old; Hb, hemoglobin; WBC, white blood cell; CEA, carcinoembryonic antigen; DM, diabetes mellitus

		Before matching				After matching			
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%)	
Histology 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%)	
Histology	Well differentiated	11 (6.5%)	9 (9.7%)	2 (2.6%)	0.166	3 (3.7%)	1 (2.4%)	2 (4.9%)	0.446
Grade	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%)	

NLR, neutrophil-to-platelet ratio; y/o, years old; Hb, hemoglobin; WBC, white blood cell; CEA, carcinoembryonic antigen; DM, diabetes mellitus

After one-to-one propensity score matching, no clinicopathological factor was significantly different between the higher- and lower-NLR groups (Table 1). In patients with stage I to III perforated colon cancer, the 3- and 5-year overall survival rates were 75% and 61%, respectively, in the lower-NLR group, whereas those of the higher-NLR group were 80% and 67%, respectively. We also analyzed the 3- and 5-year overall survival 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 overall survival rates were 90% and 84% in the lower-NLR group, respectively, whereas those of the higher-NLR group were 87% and 74%, respectively. Patients with stage III perforated colon cancer had 3- and 5-year overall survival rates of 60% and 41% in the lower-NLR group, respectively, whereas those of the higher-NLR group were 69% and 55%, respectively. The difference in overall survival rates between the higher- and lower-NLR groups in each subgroup comparison was not significant (p = 0.637 for stages I–III, p = 0.512 for stage II, and p = 0.500 for stage III; Fig. 2).

Disease-free survival was also not significantly different between the higher- and lower-NLR groups. In patients with stage I to III perforated colon cancer, the 3- and 5-year disease-free survival rates were both 70% in the lower-NLR group, whereas those of the higher-NLR group were 69% and 63%, respectively. In patients with stage II cancer, the 3- and 5-year disease-free survival rates were both 84% in the lower-NLR group, whereas those of the higher-NLR group were 74% and 69%, respectively. In patients with stage III cancer, the 3- and 5-year disease-free survival rates were 55% in both the lower- and higher-NLR group, whereas the corresponding values in the higher-NLR group were 58% and 50%, respectively (p = 0.827 for stage I–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 the neutrophil count [13]. Alternatively, the absolute lymphocyte count is assumed 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 anti-tumor immune factors.

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

A higher NLR has also been associated with 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 higher 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. Therefore, pre-operative NLR may be unable to reflect the balance between cancer-related inflammation and the immune response in patients with perforated colon cancer.

This study had 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 pathological reports. Some patients who might have initially presented with local abscess formation and not 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.

Conclusion

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

List Of Abbreviations

NLR – Neutrophil-to-lymphocyte ratio; PSM - propensity score matching; OS – overall survival; DFS - disease-free 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 of obtaining informed consent from the participants.

Consent for publication: Not applicable.

Availability of data and materials: The authors confirm that all data are fully available without restrictions on reasonable request.

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

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Authors' contributions: All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by Chun-Yi Wu. The first draft of the manuscript was written by Chun-Yi Wu and was supervised by Jy-Ming Chiang. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Figures
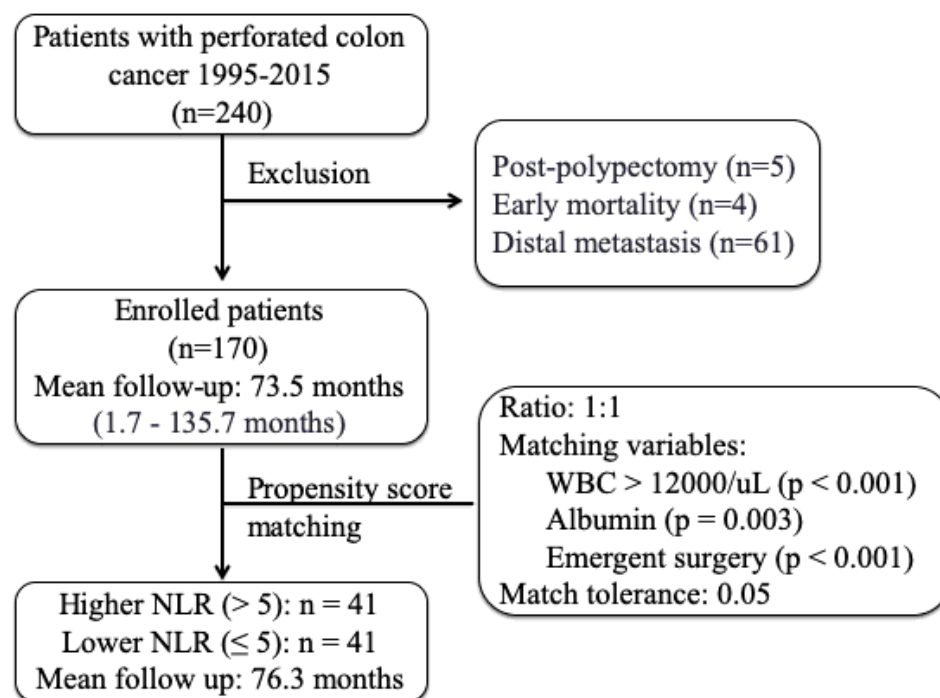
Figure 1

Flow chart of the study sample WBC, white blood cell; NLR, neutrophil-to-lymphocyte ratio
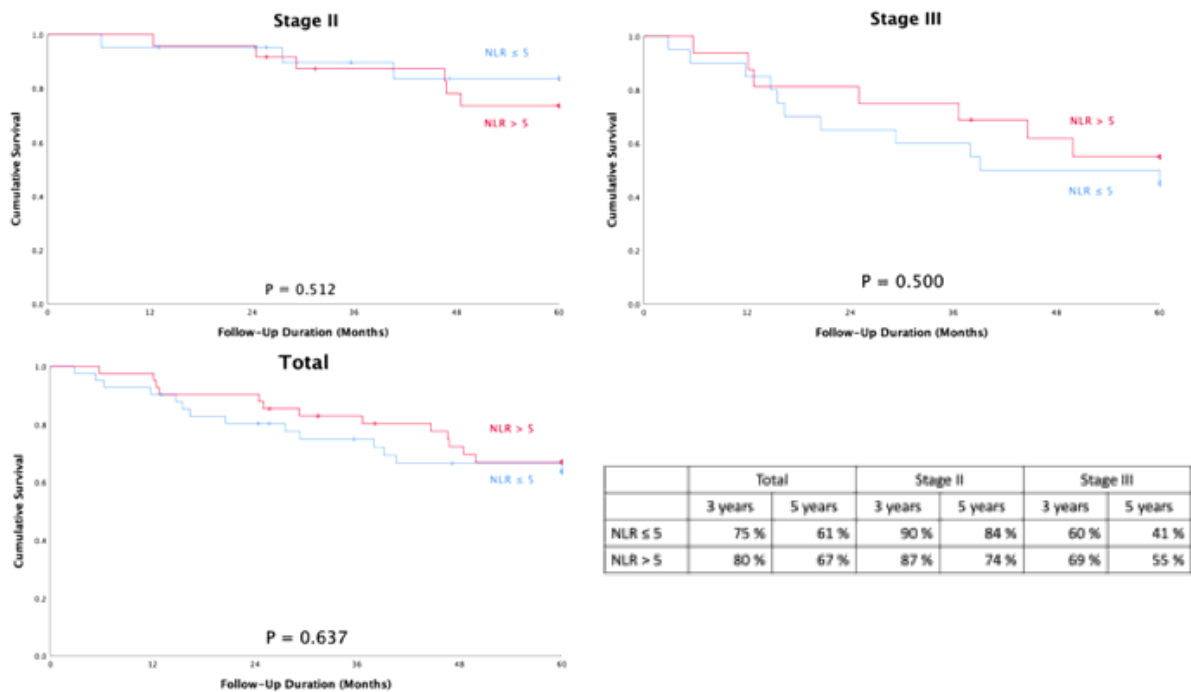
Figure 2

Overall survival rates between patients with higher- and lower-NLR groups NLR, neutrophil-to-lymphocyte ratio
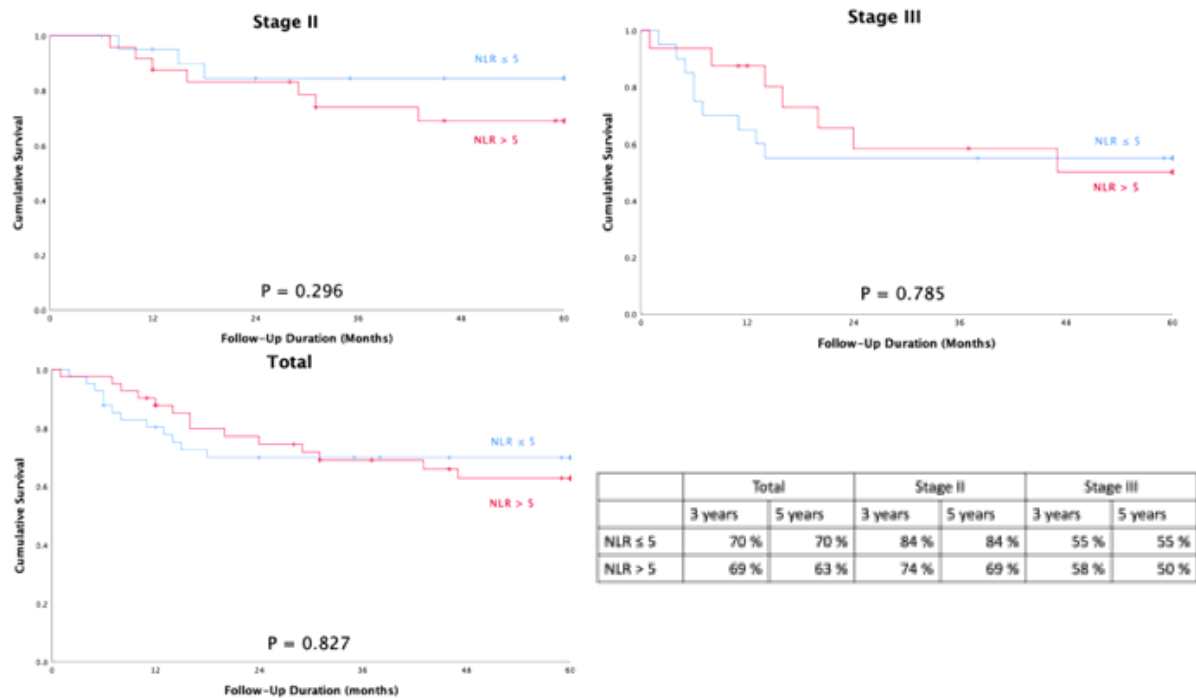
Figure 3

Disease-free survival rates between patients with higher-and lower-NLR groups NLR, neutrophil-to-lymphocyte ratio