Albumin and Derived Neutrophil-to-Lymphocyte Ratio is a Novel Prognostic Factor for Patients with Esophageal Squamous Cell Carcinoma

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Albumin and derived neutrophil-to-lymphocyte ratio is a novel prognostic factor for patients with esophageal squamous cell carcinoma

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ΔAlb-dNLR during nCT in ESCC patients

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Synopsis:

1 The Alb-dNLR ratio represents combination of nutritional and inflammatory status. We
2 have demonstrated that a change in the Alb-dNLR ratio during neoadjuvant chemotherapy
3 is an independent prognostic factor for overall survival in patients with ESCC.
4

Abstract

Background

Multidisciplinary treatment combining neoadjuvant treatment (NAT) and surgery has slightly improved the prognosis of patients with esophageal squamous cell carcinoma (ESCC). Although various biomarkers targeting nutrition and inflammation are associated with cancer prognosis, most studies have focused on conditions before NAT. Developing real-time and sensitive biomarkers that monitor changes in systemic conditions during NAT is important. We established a novel nutritional and inflammatory index, represented as the albumin to derived neutrophil-to-lymphocyte ratio (Alb-dNLR ratio), and calculated the change in Alb-dNLR ratio (ΔAlb-dNLR) during neoadjuvant chemotherapy (nCT). Herein, we aimed to evaluate whether ΔAlb-dNLR is associated with prognosis in patients with ESCC.

Methods

We investigated 172 patients who underwent nCT before esophagectomy between April 2010 and March 2018. dNLR was calculated as the ratio of neutrophil count to (white blood cell count - neutrophil count), Alb-dNLR ratio was calculated by dividing serum albumin level by dNLR, and ΔAlb-dNLR was evaluated by dividing the post-Alb-dNLR ratio by the pre-Alb-dNLR ratio. Patients were divided into "high" and "low" groups according to ΔAlb-dNLR.

Results

Thirty-nine patients (22.7%) had a low ΔAlb-dNLR (≤0.8). The 5-year overall survival (OS) rates in patients with low and high ΔAlb-dNLR were 38.1% and 53.6%, respectively ($p = 0.0072$). Multivariate analyses demonstrated that estimated blood loss ($p = 0.044$), pathological T stage ($p = 0.0005$), pathological N stage ($p = 0.017$), and ΔAlb-

dNLR ($p = 0.005$) were independent prognostic factors for OS.

Conclusions

ΔAlb-dNLR is a useful prognostic factor for OS in patients with ESCC receiving nCT.

Introduction

Globally, esophageal cancer is the tenth most common carcinoma, and the sixth leading cause of cancer-related deaths.[1] Multidisciplinary treatment that combines surgery, chemotherapy, and chemoradiotherapy has dramatically improved outcomes. In the Japan Clinical Oncology Group (JOCG) 9907 study,[2] comprising patients with clinical stage II or III esophageal squamous cell carcinoma (ESCC), the overall survival (OS) in patients who underwent surgery following neoadjuvant chemotherapy (nCT) was superior to that of those who underwent surgery with adjuvant chemotherapy. However, even in the nCT group, the 5-year OS rate was 55%, which was not sufficient. Thus, it is necessary to identify prognostic factors in patients with ESCC after nCT to explore better treatment strategies.

Previous reports have revealed that nutritional and inflammatory biomarkers could be an independent prognostic factor in various cancers. It has also been reported that dynamic changes in indicators such as the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) after neoadjuvant treatment (NAT) could be predictors of the therapeutic effect and prognosis of several cancers.[3,4,5,6,7] Previously, we reported that a change in the modified Glasgow prognostic score (mGPS) could be a prognostic factor for ESCC patients.[8] Furthermore, we reported that the combination of serum albumin and derived NLR (dNLR) could also be a useful prognostic factor for OS and cause-specific survival in ESCC patients.[9] However, this factor was based on laboratory data obtained before nCT. It is more desirable to develop more real-time and sensitive prognostic factors, featuring changes in systemic conditions during NAT. Few studies have

focused on changes in biomarkers during NAT in ESCC patients. Herein, we defined a new nutritional and inflammatory index called "Alb-dNLR ratio," which is essentially the ratio of albumin level to dNLR. The aim of this study was to evaluate whether changes in the Alb-dNLR ratio during nCT are associated with prognosis in patients with ESCC.

Methods

Patients

From April 2010 to March 2018, 319 patients who underwent esophagectomy for thoracic ESCC at Kobe University Hospital were assessed. Patients who had distant metastases, underwent neoadjuvant chemoradiation therapy, salvage surgery, and had missing records were excluded. Finally, 172 patients who underwent nCT before surgery were included in this study. Based on a biopsy analysis prior to administering nCT, the patient was diagnosed with ESCC. All patients were staged according to the 8th edition of the TNM staging system by the American Joint Committee on Cancer and Union for International Cancer Control (UICC) for ESCC.[10]

Treatment strategy

A nCT followed by surgery at our hospital was performed for patients, excluding those with clinical T1N0M0 status. A nCT regimen consisted of 2 cycles of intravenous cisplatin (80 mg/m^2) and 5-fluorouracil (800 mg/m^2) provided by continuous intravenous infusion on days 1–5. Esophagectomies were performed after nCT.

Data collection and definition

Body weight (BW) and blood measurements such as white blood cell count, neutrophil count, and albumin levels were obtained at two points: one at the first visit to the doctor and the other just before surgery. Clinicopathological data (including patient factors, tumor factors, operative data, and postoperative complications) were obtained from the patients' medical records. Complications, such as anastomotic leakage and pneumonia, were evaluated according to the Clavien–Dindo classification system.[11] The change in body wight during nCT (ΔBW) was calculated by dividing post-BW by pre-BW. Informed consent was obtained from all individuals, and this study design was approved by the Institutional Review Board and Ethics Committee of Kobe University.

dNLR, Alb-dNLR ratio, and ΔAlb-dNLR

The dNLR was calculated as the ratio of neutrophil count to (leukocyte count - neutrophil count), according to a previous report.[12] The Alb-dNLR ratio was calculated by dividing serum albumin by dNLR. We calculated the Alb-dNLR ratio before nCT (pre-Alb-dNLR ratio) and after nCT (post-Alb-dNLR ratio). The change in the Alb-dNLR ratio during nCT (ΔAlb-dNLR) was calculated by dividing the post-Alb-dNLR ratio by the pre-Alb-dNLR ratio. The cutoff value of ΔAlb-dNLR was determined using receiver operating characteristic (ROC) analysis.[13,14]

Statistical analysis

Categorical variables were compared using the Chi-squared test, and continuous

variables were compared using the Student's t-test or Kruskal-Wallis H nonparametric test, as appropriate. Survival curves were generated based on the ΔAlb-dNLR using the Kaplan–Meier method and compared using the log-rank test. Univariate and multivariate analyses using Cox proportional hazards regression models were performed to identify independent prognostic factors for OS. The optimal cutoff values of the continuous variables were determined using ROC analysis, if necessary. All analyses were conducted using the JMP 13 software program (SAS Institute, Cary, NC, USA). Any variable deemed significant ($p < 0.05$) in the univariate analysis was a candidate for multivariate analysis. Statistical significance was defined as a p-value <0.05.

Results

Characteristics of patients

A total of 172 Japanese patients were included in the database. Of which, 150 patients were men and 22 were women, with a median age of 68 years (range 27–82 years). All patients underwent nCT based on the CF regimen. The median pre- and post-Alb-dNLR ratio were 2.200 (0.614–10.461) and 2.594 (0.445–7.382), respectively. The median ΔAlb-dNLR was 1.211 (0.369–3.894). Based on the ROC analysis, the cutoff value of ΔAlb-dNLR was 0.79, and the AUC was 0.52 for OS ($p = 0.9755$). Patients were divided into two groups according to ΔAlb-dNLR. We designated ΔAlb-dNLR ≤0.8 as the "low ΔAlb-dNLR group" and ΔAlb-dNLR >0.8 as the "high ΔAlb-dNLR group." Thirty-nine patients (22.7%) had a low ΔAlb-dNLR. The distribution of ΔAlb-dNLR is shown in Figure 1. Table 1 summarizes the clinical characteristics of the two groups. There was a

significant difference between the two groups in the occurrence of anastomotic leakage (p = 0.0144). In the low ΔAlb-dNLR group, the pre-Alb-dNLR ratio was higher (p = 0.0003) whereas the post-Alb-dNLR ratio was lower than the corresponding scores in the high ΔAlb-dNLR group (p < 0.0001).

Correlations between the ΔAlb-dNLR and OS

We generated survival curve using the Kaplan-Meier method and analyzed significant differences of ΔAlb-dNLR using the log-rank test. The median follow-up period was 39.8 months (range, 1–127 months). The OS in patients with all stages of disease according to ΔAlb-dNLR is shown in Figure 2a. The 5-year OS rates were 38.1% and 53.6% in patients in the low and high ΔAlb-dNLR groups, respectively (p = 0.0072). Among patients with pathological stage 0–II ESCC, the 5-year OS rates were 62.7% and 73.5% in patients with low and high ΔAlb-dNLR groups, respectively (p = 0.099, Figure 2b). Among patients with pathological stage III ESCC, the 5-year OS rates were 15.0% and 28.9% in patients with low and high ΔAlb-dNLR groups, respectively (p = 0.022, Figure 2c).

Impact of ΔAlb-dNLR on OS

Univariate and multivariate analyses were performed using Cox proportional hazard models in 172 patients. For OS, according to the ROC curve, the cutoff values of age, operative time, estimated blood loss, pre-albumin, post-albumin and pre-Alb-dNLR ratio were 52 years, 694 min, 234 mL, 4.0, 4.0 and 0.236, respectively. Table 2 shows that

estimated blood loss (hazard ratio [HR] =1.659; 95% confidence interval [CI]: 1.013-2.744; p = 0.044), pathological T stage (pT) (HR = 2.309; 95% CI: 1.434-3.785; p = 0.0005), pathological N stage (pN) (HR = 1.893; 95% CI: 1.116-3.316; p = 0.017), and ΔAlb-dNLR (HR = 2.063; 95% CI: 1.253-3.329; p = 0.005) were independent prognostic factors in the multivariate analysis of OS.

Discussion

We demonstrated that ΔAlb-dNLR during nCT was an independent prognostic factor for OS in patients with ESCC. To the best of our knowledge, this is the first study to demonstrate the correlation between ΔAlb-dNLR and the prognosis of patients with ESCC. While analyzing clinicopathological characteristics, we found that ΔAlb-dNLR was unrelated to pT and N. And, ΔAlb-dNLR was an independent prognostic factor, similar to pT and pN in the multivariate analysis for OS.

Previous studies have provided evidence on the fact that systemic inflammation is closely related to cancer prognosis.[15,16] Proctor et al.[12] firstly reported that dNLR and NLR are inflammatory indices that are associated with prognosis in various types of cancers. Albumin is a common nutritional index that is also associated with inflammation. Previous reports have shown that serum albumin level is a useful nutritional and inflammatory predictor of cancer survival.[17-19] Biomarkers that combine nutritional and inflammatory indices, such as mGPS, controlling nutritional status score, C reactive protein-albumin ratio, and fibrinogen and albumin (FA) score, have also been reported as prognostic predictors for patients with ESCC.[20-23] Moreover, the dynamic change in NLR during NAT

has been reported to be correlated with prognosis in various cancers.[5,7,24] In patients with esophageal cancer, a change in the FA score during NAT was an independent prognostic factor.[25] The change in systemic inflammation induced by NAT affected prognosis and response to NAT in patients undergoing NAT followed by surgery for advanced ESCC. We have reported that the Alb-dNLR score is a useful prognostic factor in patients with ESCC.[9] Although the Alb-dNLR score was a novel factor, it had one limitation which was that the post-nCT status could not be taken into account. To overcome this limitation, we developed a more real-time and sensitive predictor of albumin and dNLR during nCT. In this study, we revealed that ΔAlb-dNLR was associated with prognosis in patients with ESCC treated with nCT. The Alb-dNLR ratio is easily calculated based on indices that are routinely used in daily clinical practice. Subsequently, we assessed the utility of ΔAlb-dNLR in patients with ESCC. Consequently, a decrease of less than 80% in ΔAlb-dNLR was associated with worse prognosis in patients with ESCC. What is noteworthy about this result is that the decrease in ΔAlb-dNLR is a stronger prognostic factor than the pre-Alb-dNLR ratio. Decreased ΔAlb-dNLR indicates a decrease in albumin and/or an increase in dNLR during nCT; that is, both reactions reflect tumor progression during nCT. The degree of tumor shrinkage during nCT was poor in low ΔAlb-dNLR group (data not shown). Moreover, it is independent of pT and pN and is superior to the pathological therapeutic effect. Similar results were also observed in advanced-stage patients. On the other hand, in early-stage patients, ΔAlb-dNLR was not an independent prognostic factor (only a tendency was observed). During the early stage, the degree of tumor progression is mild; due to which, it is possible that the utility of ΔAlb-dNLR could not be proven for patients with early-

stage disease. In cases with less than 80% decrease in ΔAlb-dNLR during nCT, subsequent surgery alone may be insufficient, and adjuvant therapy such as programmed death 1 inhibitor may be required.[26]

Anastomotic leakage after esophagectomy is one of the most severe complications leading to short-term outcomes, such as prolonged hospital stay and increased risk of mortality.[27] Anastomotic leakage was also associated with the long-term survival of patients with esophageal cancer.[28] Previous reports have revealed that malnutrition is a risk factor for anastomotic leakage.[29,30] In addition, studies have reported that inflammatory indices such as white blood cells and C-reactive protein are risk factors for anastomotic leakage.[31,32] In this study, the ΔAlb-dNLR was associated with anastomotic leakage. A decrease in the ΔAlb-dNLR, a combination indicator of nutrition and inflammation, indicates malnutrition during nCT and could be a useful predictor of anastomotic leakage. No studies have yet demonstrated that nutritional intervention reduce anastomotic leakage in esophageal cancer. But preoperative nutritional treatment was reported to improve postoperative nutritional and inflammatory indexes, which might contribute to reduce anastomotic leakage.[33] Further prospective studies are warranted to identify that preoperative nutritional intervention is beneficial to reduce anastomotic leakage in low ΔAlb-dNLR patients.

There are several limitations in the current study, such as the fact that it was a single-center retrospective study with a limited number of patients. Owing to these limitations, the optimal cutoff value of ΔAlb-dNLR would change. Therefore, large scale, multicenter and prospective studies are needed to confirm our results.

Conclusion

The ΔAlb-dNLR is an easy-to-use and useful prognostic factor for OS in patients with ESCC receiving nCT.

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Figure legends

Figure 1. Distribution of ΔAlb-dNLR.

Based on the ROC analysis for OS, the cutoff value of ΔAlb-dNLR was 0.8 (black arrow).

Alb, serum albumin level; dNLR, derived neutrophil-to-lymphocyte ratio; ΔAlb-dNLR, change in Alb-dNLR ratio during neoadjuvant chemotherapy, ROC: receiver operating characteristic, OS: overall survival.

Figure 2. Kaplan–Meier survival curves for OS according to ΔAlb-dNLR in ESCC patients.

a) The 5-year OS rates were 38.1% and 53.6% in all patients in the low and high ΔAlb-dNLR groups, respectively (p = 0.0072).

b) The 5-year OS rates were 62.7% and 73.5% in early-stage patients in the low and high ΔAlb-dNLR groups, respectively (p = 0.099).

c) The 5-year OS rates were 15.0% and 28.9% in advanced-stage patients in the low and high ΔAlb-dNLR groups, respectively (p = 0.022).

OS, overall survival; Alb, serum albumin level; dNLR, derived neutrophil-to-lymphocyte ratio; ΔAlb-dNLR, change in Alb-dNLR ratio during neoadjuvant chemotherapy; ESCC, esophageal squamous cell carcinoma

Tables

Table 1. Patient characteristics

	ΔAlb-dNLR ≤0.8 group (n=39)	**ΔAlb-dNLR >0.8 group (n=133)**	***p***
Age (years)	66 (44–82)	69 (27–82)	0.71
Sex (M/F)	34/5	116/17	0.99
ΔBW	0.958 (0.849-1.115)	0.976 (0.874-1.104)	**0.050**
Tumor location (Ut/Mt/Lt)	4/22/13	25/60/48	0.32
Thoracic procedure (thoracoscopy/open)	39/0	127/6	0.076
Lymph node dissection (3-field/2-field)	15/24	60/73	0.46
Operative time (min)	687 (460–1116)	687 (354–1361)	0.58
Estimated blood loss (mL)	190 (0–922)	237.5 (0–2605)	0.10
Anastomotic leakage (CD ≥2/<2)	11/28	15/118	**0.014**
Pneumonia (CD ≥2/<2)	7/32	29/104	0.60
pT (0/is/1/2/3/4)	0/0/18/2/19/0	2/4/46/16/65/0	0.22
pN (0/1/2/3)	14/13/6/6	51/47/19/16	0.95
Therapeutic effect (≥2/<2)	4/35	22/111	0.32
Residual tumor (R0/R1/R2)	32/6/1	115/16/2	0.78
Pre-albumin	4.1 (3-6.4)	4.1 (2.8-5)	0.91
Post-albumin	4.0 (2.5-4.7)	4.0 (2.4-4.9)	0.25
Pre-Alb-dNLR ratio	2.877 (0.614–10.461)	2.118 (0.702–5.982)	**0.0003**
Post-Alb-dNLR ratio	1.752 (0.445–6.100)	3.116 (1.152–7.382)	**<0.0001**

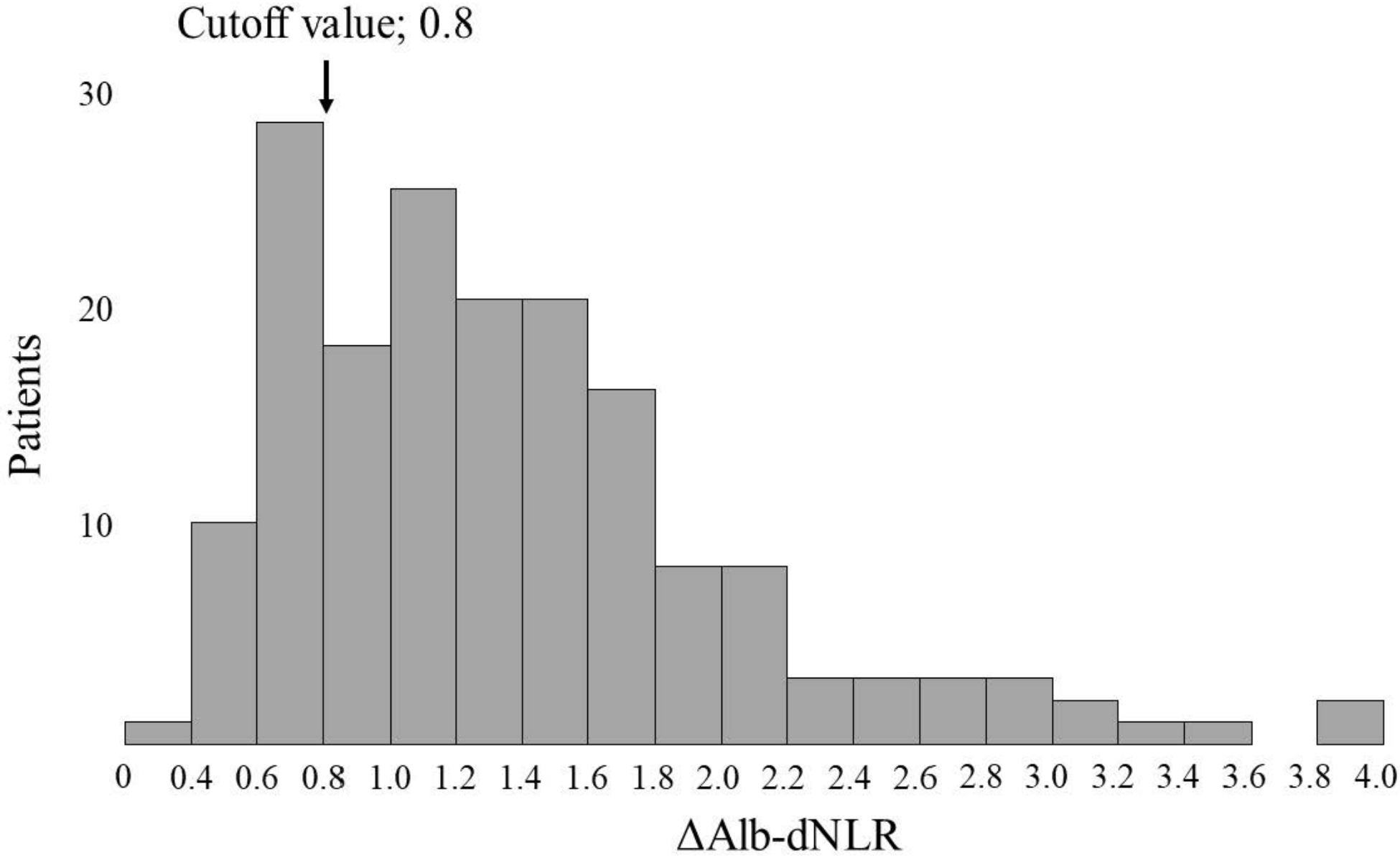
dNLR, derived neutrophil-to-lymphocyte ratio; Alb, serum albumin value; ΔAlb-dNLR, change in Alb-dNLR ratio before and after neoadjuvant chemotherapy; M, male; F, female; ΔBW, change in body weight before and after neoadjuvant chemotherapy; CD, Clavien-Dindo classification grade; pT, pathological T stage; pN, pathological N stage; Pre-albumin, serum albumin value before neoadjuvant chemotherapy; Post-albumin, serum albumin value after neoadjuvant chemotherapy; Pre-Alb-dNLR ratio, Alb-dNLR ratio before neoadjuvant chemotherapy; Post-Alb-dNLR ratio, Alb-dNLR ratio after neoadjuvant chemotherapy.

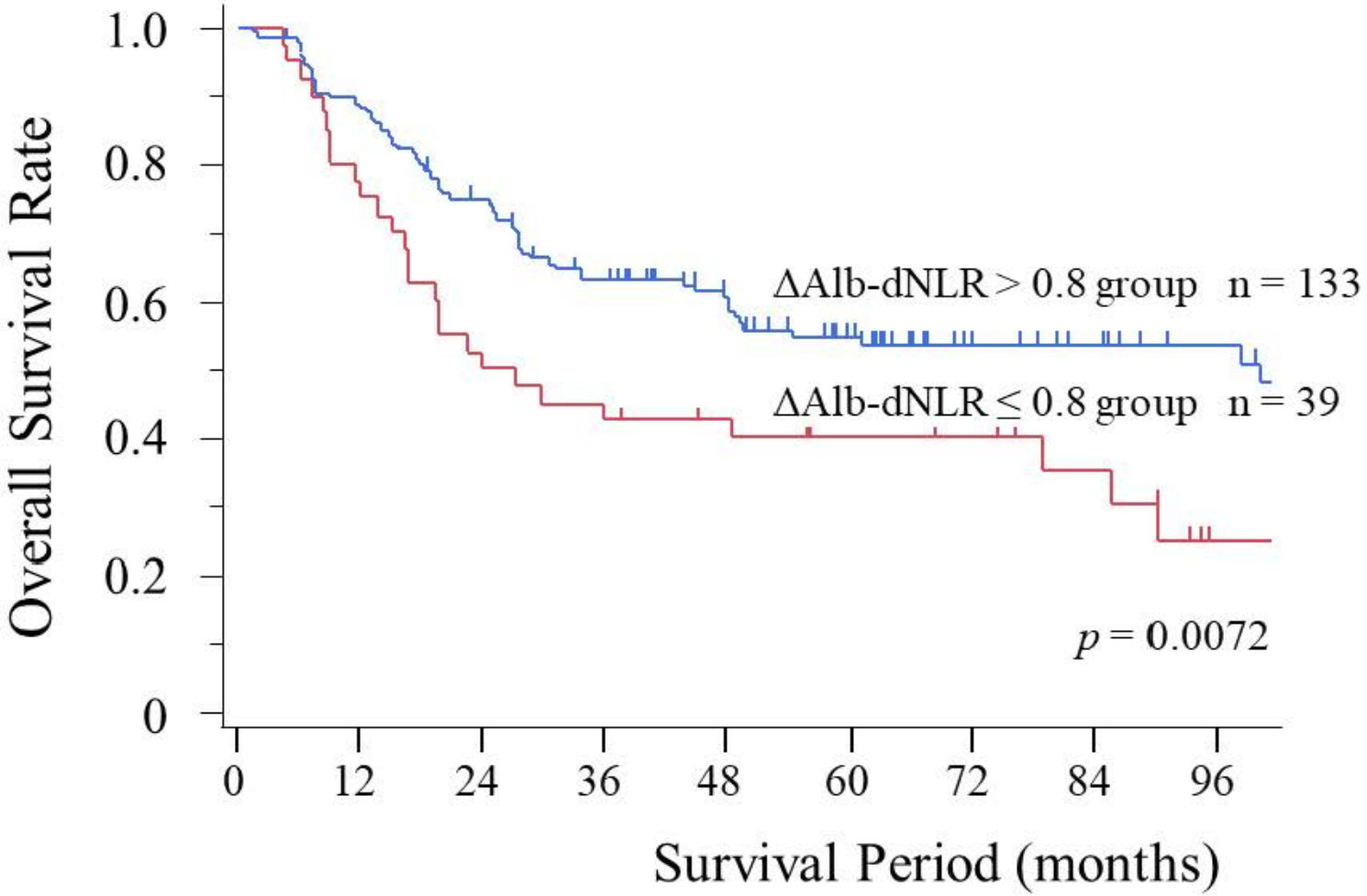
Table 2. Univariate and multivariate Cox proportional hazards regression models for overall survival in patients with esophageal squamous cell carcinoma

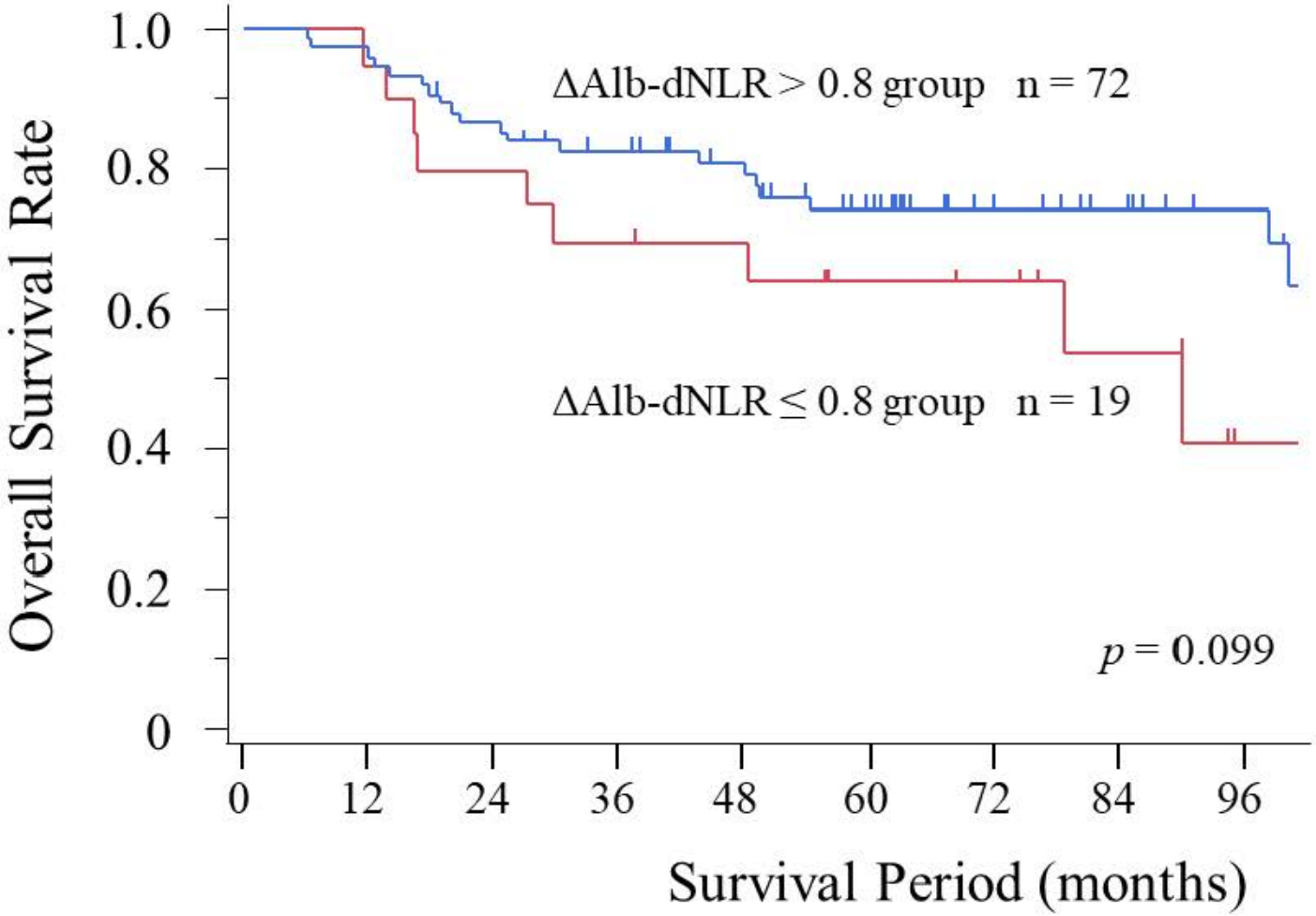
	Univariate		Multivariate	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Age (years, ≥52/<52)	0.447 (0.228–1.010)	0.053		
Sex (M/F)	1.086 (0.590–2.238)	0.80		
ΔBW (≥1.0/<1.0)	0.684 (0.404-1.105)	0.12		
Tumor location Ut Mt Lt	 1.000 0.980 (0.563–1.792) 0.825 (0.454–1.555)	 - 0.94 0.54		
Thoracic procedure Thoracoscopy/open	 1.944 (0.613–11.822)	 0.30		
Lymph node dissection (3-field/2-field or less)	1.135 (0.743–1.728)	0.55		
Operative time (≥694min/<694min)	1.837 (1.208–2.814)	**0.0045**	1.466 (0.929–2.333)	0.10
Estimated blood loss (≥234 mL/<234 mL)	1.833 (1.197–2.846)	**0.0052**	1.659 (1.013-2.744)	**0.044**
Anastomotic leakage (CD ≥2/<2)	1.225 (0.676–2.073)	0.48		
Pneumonia (CD ≥2/<2)	1.744 (1.069–2.751)	**0.027**	1.315 (0.750-2.241)	0.33
pT (≥3/<3)	2.822 (1.831–4.424)	**<0.0001**	2.309 (1.434-3.785)	**0.0005**
pN (+/-)	2.720 (1.693–4.555)	**<0.0001**	1.893 (1.116-3.316)	**0.017**
Therapeutic effect (≥2/<2)	0.479 (0.223–0.904)	**0.021**	0.840 (0.372-1.712)	0.65
Residual tumor (R0/R1 or R2)	0.293 (0.182–0.491)	**<0.0001**	0.638 (0.368-1.140)	0.13
Pre-albumin (≥4.0/ <4.0)	0.634 (0.417-0.972)	**0.037**	0.860 (0.539-1.378)	0.53
Post-albumin (≥4.0/ <4.0)	0.628 (0.411-0.956)	**0.030**	0.674 (0.427-1.058)	0.43
Pre-Alb-dNLR ratio (≥0.236/ <0.236)	0.599 (0.382-0.22)	**0.019**	0.930 (0.542-1.574)	0.79
ΔAlb-dNLR (≤0.8/>0.8)	1.848 (1.155–2.881)	**0.011**	2.063 (1.253-3.329)	**0.005**

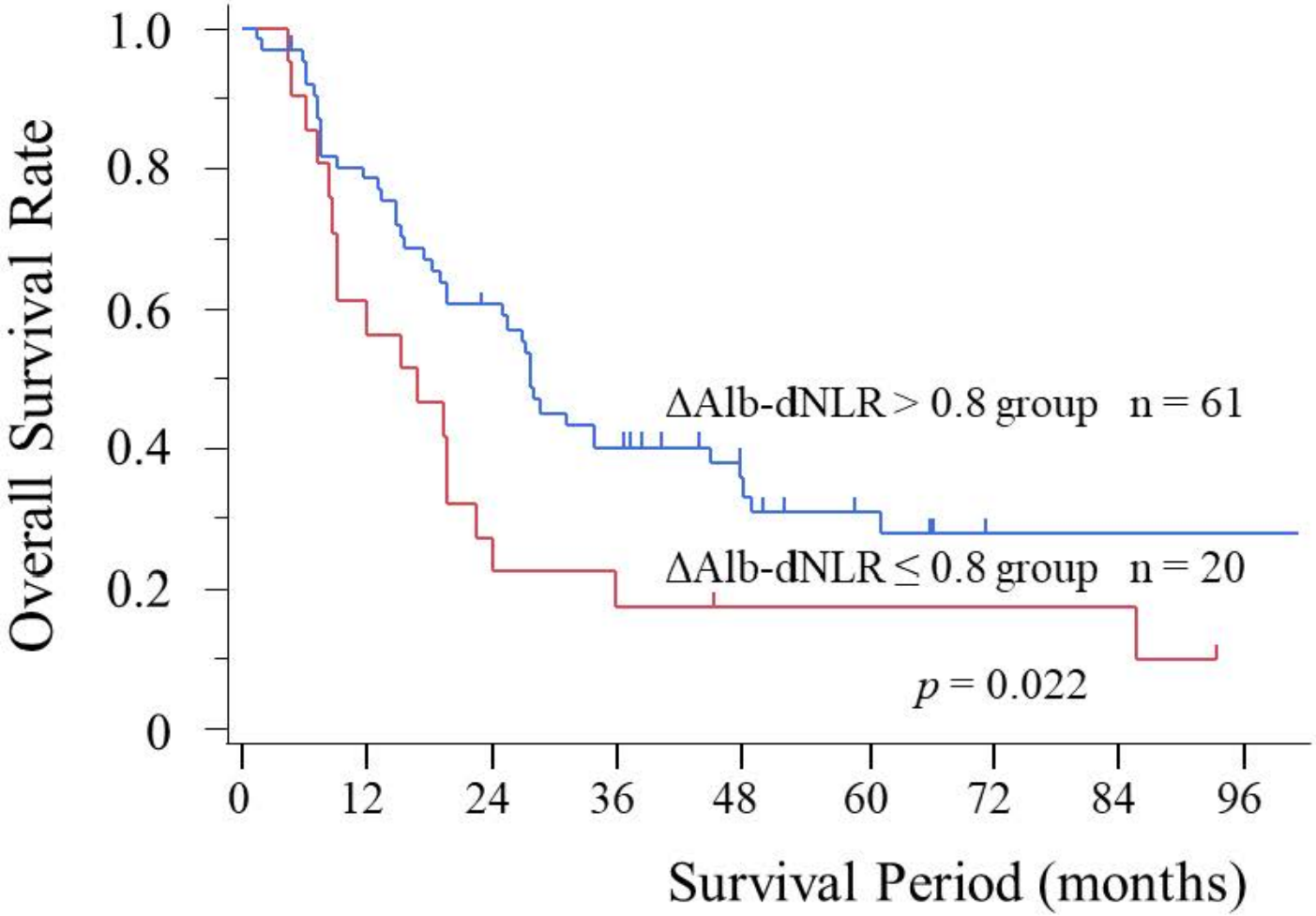
M, male; F, female; ΔBW, change in body weight before and after neoadjuvant chemotherapy; CD, Clavien-Dindo classification grade; pT, pathological T stage; pN, pathological N stage; Pre-albumin, serum albumin value before neoadjuvant chemotherapy; Post-albumin, serum albumin value after neoadjuvant chemotherapy; Pre-Alb-dNLR ratio, Alb-dNLR ratio before neoadjuvant chemotherapy; dNLR, derived neutrophil-to-lymphocyte ratio; Alb, serum albumin value; ΔAlb-dNLR, change in Alb-

dNLR ratio before and after neoadjuvant chemotherapy; HR, hazard ratio; CI, confidence interval.


Cutoff value; 0.8
30
20
10
Patients
0
0.4
0.6
0.8
1.0
1.2
1.4
1.6
1.8
2.0
2.2
2.4
2.6
2.8
3.0
3.2
3.4
3.6
3.8
4.0
ΔAlb-dNLR


Overall Survival Rate
1.0
0.8
0.6
0.4
0.2
0
0
12
24
36
48
60
72
84
96
Survival Period (months)
ΔAlb-dNLR > 0.8 group n = 133
ΔAlb-dNLR ≤ 0.8 group n = 39
p = 0.0072


1.0
0.8
0.6
0.4
0.2
0
Overall Survival Rate
ΔAlb-dNLR > 0.8 group n = 72
ΔAlb-dNLR ≤ 0.8 group n = 19
p = 0.099
0
12
24
36
48
60
72
84
96
Survival Period (months)


1.0
0.8
0.6
0.4
0.2
0
Overall Survival Rate
ΔAlb-dNLR > 0.8 group n = 61
ΔAlb-dNLR ≤ 0.8 group n = 20
p = 0.022
0
12
24
36
48
60
72
84
96
Survival Period (months)