



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

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11
12 **Manuscript title:**

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

15
16 **Manuscript subtitle:**

17 Δ Alb-dNLR during nCT in ESCC patients

18
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20 The authors have no conflicts of interest or financial ties to disclose.

21
22 **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 (Δ Alb-dNLR) during neoadjuvant chemotherapy (nCT). Herein, we aimed to evaluate whether Δ Alb-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 Δ Alb-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 Δ Alb-dNLR.

Results

Thirty-nine patients (22.7%) had a low Δ Alb-dNLR (≤ 0.8). The 5-year overall survival (OS) rates in patients with low and high Δ Alb-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 Δ Alb-

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

2 **Conclusions**

3 Δ Alb-dNLR is a useful prognostic factor for OS in patients with ESCC receiving
4 nCT.

5

1 **Introduction**

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

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

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

6 **Methods**

7 ***Patients***

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

17 ***Treatment strategy***

18 A nCT followed by surgery at our hospital was performed for patients, excluding
19 those with clinical T1N0M0 status. A nCT regimen consisted of 2 cycles of intravenous
20 cisplatin (80 mg/m²) and 5-fluorouracil (800 mg/m²) provided by continuous intravenous
21 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 weight 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 Δ Alb-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 (Δ Alb-dNLR) was calculated by dividing the post-Alb-dNLR ratio by the pre-Alb-dNLR ratio. The cutoff value of Δ Alb-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 $\Delta\text{Alb-dNLR}$ 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 $\Delta\text{Alb-dNLR}$ was 1.211 (0.369–3.894). Based on the ROC analysis, the cutoff value of $\Delta\text{Alb-dNLR}$ was 0.79, and the AUC was 0.52 for OS ($p = 0.9755$). Patients were divided into two groups according to $\Delta\text{Alb-dNLR}$. We designated $\Delta\text{Alb-dNLR} \leq 0.8$ as the “low $\Delta\text{Alb-dNLR}$ group” and $\Delta\text{Alb-dNLR} > 0.8$ as the “high $\Delta\text{Alb-dNLR}$ group.” Thirty-nine patients (22.7%) had a low $\Delta\text{Alb-dNLR}$. The distribution of $\Delta\text{Alb-dNLR}$ 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 $\Delta\text{Alb-dNLR}$ 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 $\Delta\text{Alb-dNLR}$ group ($p < 0.0001$).

Correlations between the $\Delta\text{Alb-dNLR}$ and OS

We generated survival curve using the Kaplan-Meier method and analyzed significant differences of $\Delta\text{Alb-dNLR}$ 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 $\Delta\text{Alb-dNLR}$ is shown in Figure 2a. The 5-year OS rates were 38.1% and 53.6% in patients in the low and high $\Delta\text{Alb-dNLR}$ 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 $\Delta\text{Alb-dNLR}$ 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 $\Delta\text{Alb-dNLR}$ groups, respectively ($p = 0.022$, Figure 2c).

Impact of $\Delta\text{Alb-dNLR}$ 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 Δ Alb-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 Δ Alb-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 Δ Alb-dNLR and the prognosis of patients with ESCC. While analyzing clinicopathological characteristics, we found that Δ Alb-dNLR was unrelated to pT and N. And, Δ Alb-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 Δ Alb-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 Δ Alb-dNLR in patients with ESCC. Consequently, a decrease of less than 80% in Δ Alb-dNLR was associated with worse prognosis in patients with ESCC. What is noteworthy about this result is that the decrease in Δ Alb-dNLR is a stronger prognostic factor than the pre-Alb-dNLR ratio. Decreased Δ Alb-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 Δ Alb-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, Δ Alb-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 Δ Alb-dNLR could not be proven for patients with early-

stage disease. In cases with less than 80% decrease in Δ Alb-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 Δ Alb-dNLR was associated with anastomotic leakage. A decrease in the Δ Alb-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 Δ Alb-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 Δ Alb-dNLR would change. Therefore, large scale, multicenter and prospective studies are needed to confirm our results.

1

2 **Conclusion**

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

5

1 **Acknowledgments:** Not applicable

References

1. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin.* 2021;71:209-249.
2. Ando N, Kato H, Igaki H, et al. A randomized trial comparing postoperative adjuvant chemotherapy with cisplatin and 5-fluorouracil versus preoperative chemotherapy for localized advanced squamous cell carcinoma of the thoracic esophagus (JCOG9907). *Ann Surg Oncol.* 2012;19:68-74.
3. Jin F, Han A, Shi F, Kong L, Yu J. The postoperative neutrophil-to-lymphocyte ratio and changes in this ratio predict survival after the complete resection of stage I non-small cell lung cancer. *Onco Targets Ther.* 2016;9:6529-6537.
4. Peng W, Li C, Zhu WJ, et al. Prognostic value of the platelet to lymphocyte ratio change in liver cancer. *J Surg Res.* 2015;194:464-470.
5. Oshima M, Okano K, Suto H, et al. Changes and prognostic impact of inflammatory nutritional factors during neoadjuvant chemoradiotherapy for patients with resectable and borderline resectable pancreatic cancer. *BMC Gastroenterol.* 2020;20:423.
6. Fukuoka T, Maeda K, Nagahara H, et al. Change in PMI During Neoadjuvant Therapy Is a Predictive Prognostic Marker in Rectal Cancer. *Anticancer Res.* 2019;39:5157-5163.
7. Kim KH, Hwang HK, Kang IC, Lee WJ, Kang CM. Oncologic impact of preoperative prognostic nutritional index change in resected pancreatic cancer following neoadjuvant chemotherapy. *Pancreatol.* 2020;20:247-253.

8. Otowa Y, Nakamura T, Takiguchi G, et al. Changes in modified Glasgow prognostic score after neoadjuvant chemotherapy is a prognostic factor in clinical stage II/III esophageal cancer. *Dis Esophagus*. 2016;29:146-151.
9. Abe T, Oshikiri T, Goto H, et al. Albumin-Derived NLR Score is a Novel Prognostic Marker for Esophageal Squamous Cell Carcinoma. *Ann Surg Oncol*. (2021). <http://doi.org/10.1245/s10434-021-11012-y>
10. Brierley J, Gospodarowicz MK, Wittekind C, Sauvage M, Union internationale contre le c. *TNM Classification of Malignant Tumours*. 2017.
11. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg*. 2004;240:205-213.
12. Proctor MJ, McMillan DC, Morrison DS, Fletcher CD, Horgan PG, Clarke SJ. A derived neutrophil to lymphocyte ratio predicts survival in patients with cancer. *Br J Cancer*. 2012;107:695-699.
13. Hajian-Tilaki K. Receiver Operating Characteristic (ROC) Curve Analysis for Medical Diagnostic Test Evaluation. *Caspian J Intern Med*. Spring. 2013;4:627-635.
14. Park SH, Goo JM, Jo CH. Receiver operating characteristic (ROC) curve: practical review for radiologists. *Korean J Radiol*. 2004;5:11-18.
15. Kato T, Oshikiri T, Urakawa N, et al. Preoperative neutrophil-to-lymphocyte ratio predicts the prognosis of esophageal squamous cell cancer patients undergoing minimally invasive esophagectomy after neoadjuvant chemotherapy. *J Surg Oncol*. 2021;124:1022-1030.

16. Coussens LM, Werb Z. Inflammation and cancer. *Nature*. 2002;420:860-867.
17. Chandrasinghe PC, Ediriweera DS, Kumarage SK, Deen KI. Pre-operative hypoalbuminaemia predicts poor overall survival in rectal cancer: a retrospective cohort analysis. *BMC Clin Pathol*. 2013;13:12-12.
18. Crumley ABC, Stuart RC, McKernan M, McMillan DC. Is hypoalbuminemia an independent prognostic factor in patients with gastric cancer? *World J Surg*. 2010;34:2393-2398.
19. Gupta D, Lis CG. Pretreatment serum albumin as a predictor of cancer survival: a systematic review of the epidemiological literature. *Nutr J*. Dec 22 2010;9:69.
20. Wang Y, Chen L, Wu Y, Li P, Che G. The prognostic value of modified Glasgow prognostic score in patients with esophageal squamous cell cancer: a Meta-analysis. *Nutr Cancer*. 2020;72(7):1146-1154.
21. Sakai M, Sohda M, Saito H, et al. Comparative Analysis of Immunoinflammatory and Nutritional Measures in Surgically Resected Esophageal Cancer: A Single-center Retrospective Study. *In Vivo*. Mar-Apr 2020;34(2):881-887.
22. Matsuda S, Takeuchi H, Kawakubo H, et al. Validation Study of Fibrinogen and Albumin Score in Esophageal Cancer Patients Who Underwent Esophagectomy: Multicenter Prospective Cohort Study. *Annals of Surgical Oncology*. 2021/02/01 2021;28(2):774-784.
23. Nakamura M, Iwahashi M, Nakamori M, et al. A new prognostic score for the survival of patients with esophageal squamous cell carcinoma. *Surgery Today*. 2014/05/01 2014;44(5):875-883.

24. Dan J, Tan J, Huang J, et al. The dynamic change of neutrophil to lymphocyte ratio is predictive of pathological complete response after neoadjuvant chemotherapy in breast cancer patients. *Breast Cancer*. Sep 2020;27(5):982-988.
25. Matsuda S, Takeuchi H, Kawakubo H, et al. Prognostic Impact of Change in the Fibrinogen and Albumin Score During Preoperative Treatment in Esophageal Cancer Patients. *World J Surg*. Nov 2017;41(11):2788-2795.
26. Kelly RJ, Ajani JA, Kuzdzal J, et al. Adjuvant Nivolumab in Resected Esophageal or Gastroesophageal Junction Cancer. *N Engl J Med*. 2021384:1191-1203.
27. Kassis ES, Kosinski AS, Ross P Jr., Koppes KE, Donahue JM, Daniel VC. Predictors of anastomotic leak after esophagectomy: an analysis of the society of thoracic surgeons general thoracic database. *Ann Thorac Surg*. Dec 201396:1919-1926.
28. Fransen LFC, Berkelmans GHK, Asti E, et al. The Effect of Postoperative Complications After Minimally Invasive Esophagectomy on Long-term Survival: An International Multicenter Cohort Study. *Ann Surg*. 2021274:e1129-e1137.
29. Aoyama T, Atsumi Y, Hara K, et al. Risk Factors for Postoperative Anastomosis Leak After Esophagectomy for Esophageal Cancer. *In Vivo*. 202034:857-862.
30. Herzberg J, Strate T, Guraya SY, Honarpisheh H. Risk factors for anastomotic leakage after surgical resections for esophageal cancer. *Langenbecks Arch Surg*. 2021406:1859-1866.
31. Sun ZW, Du H, Li JR, Qin HY. Constructing a risk prediction model for anastomotic leakage after esophageal cancer resection. *J Int Med Res*. 202048:300060519896726.

- 1 32. Huang C, Yao H, Huang Q, Lu H, Xu M, Wu J. A novel nomogram to predict the
2 risk of anastomotic leakage in patients after oesophagectomy. *BMC Surg.* 2020;20:64.
- 3 33. Giger U, Büchler M, Farhadi J, et al. Preoperative immunonutrition suppresses
4 perioperative inflammatory response in patients with major abdominal surgery-a
5 randomized controlled pilot study. *Ann Surg Oncol.* Oct 2007;14(10):2798-2806.
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Figure legends

Figure 1. Distribution of Δ Alb-dNLR.

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

Alb, serum albumin level; dNLR, derived neutrophil-to-lymphocyte ratio; Δ Alb-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 Δ Alb-dNLR in ESCC patients.

a) The 5-year OS rates were 38.1% and 53.6% in all patients in the low and high Δ Alb-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 Δ Alb-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 Δ Alb-dNLR groups, respectively ($p = 0.022$).

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

Tables

Table 1. Patient characteristics

	$\Delta\text{Alb-dNLR} \leq 0.8$ group (n=39)	$\Delta\text{Alb-dNLR} > 0.8$ group (n=133)	<i>p</i>
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; $\Delta\text{Alb-dNLR}$, 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)	<i>p</i> value	HR (95% CI)	<i>p</i> value
Age (years, ≥ 52 / <52)	0.447 (0.228–1.010)	0.053		
Sex (M/F)	1.086 (0.590–2.238)	0.80		
Δ BW (≥ 1.0 / <1.0)	0.684 (0.404–1.105)	0.12		
Tumor location				
Ut	1.000	-		
Mt	0.980 (0.563–1.792)	0.94		
Lt	0.825 (0.454–1.555)	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 (≥ 694 min/ <694 min)	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 (0.382–0.922)	0.019	0.930 (0.542–1.574)	0.79
Δ Alb-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; Δ BW, 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; Δ Alb-dNLR, change in Alb-

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







