Albumin-Derived NLR Score is a Novel Prognostic Marker for Esophageal Squamous Cell Carcinoma

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Albumin-derived NLR score is a novel prognostic marker for esophageal squamous cell carcinoma

Short running head: Alb-dNLR for esophageal carcinoma

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Synopsis

The albumin-dNLR score is a combination of nutritional and inflammatory status. We found that the albumin-dNLR score was an independent poor prognostic factor for overall survival and cancer-specific survival in esophageal squamous cell carcinoma patients.

Abstract

Background

Multidisciplinary treatment for esophageal squamous cell carcinoma (ESCC) has improved outcomes, but the prognosis for ESCC remains poor. Nutritional and inflammatory indicators were reported to be associated with cancer prognosis. The combination of albumin and the derived neutrophil-to-lymphocyte ratio (Alb-dNLR) score was established for measuring the immune system and nutritional status. We hypothesized that the Alb-dNLR score could be a new reliable prognostic factor for ESCC patients.

Methods

We evaluated 269 patients who underwent esophagectomy between April 2010 and March 2018, including 185 patients who received neoadjuvant chemotherapy. The Alb-dNLR score was calculated using serum albumin and the dNLR. The dNLR was calculated as neutrophils to (leukocyte-neutrophil count). The cutoff value of the albumin and dNLR for overall survival (OS) were determined using receiver operating characteristic curve. Patients were divided into “high” and “low” groups according to the Alb-dNLR score.

Results

A high Alb-dNLR score was found in 61 cases (22.7%). The 5-year OS was 34.0% in the high Alb-dNLR group and 66.2% in the low Alb-dNLR group ($p < 0.0001$). The 5-year cause-specific survival (CSS) was 51.5% in the high Alb-dNLR group and 74.7% in the low Alb-dNLR group ($p < 0.0001$). Multivariate analyses demonstrated that the Alb-dNLR score was an independent prognostic factor for OS (hazard ratio [HR], 2.198; 95% confidence interval [CI], 1.460–3.263; $p = 0.0002$) and CSS (HR, 1.733; 95% CI, 1.035–2.835; $p = 0.0371$).

Conclusions

The Alb-dNLR score is an extremely useful, easy-to-use parameter to predict OS and CSS in ESCC patients.

Introduction

Esophageal cancer ranks 10th in incidence and is the 6th most common cause of cancer-related deaths.[1] In East Asian countries, the major histologic type is esophageal squamous cell carcinoma (ESCC). Although multidisciplinary treatment has improved outcomes, the prognosis for ESCC remains poor. Identification of prognostic factors in ESCC patients is necessary to define better treatment strategies.

Nutrition and inflammation play an important role in cancer progression and prognosis. Previous reports have revealed that various biomarkers targeting nutrition and inflammation were associated with prognosis for ESCC patients. Systemic inflammatory response biomarkers, such as the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), lymphocyte-to-monocyte ratio (LMR),[2-5] and systemic immune-inflammation index (SII),[6] have been used to evaluate the systemic inflammatory response and predict cancer prognoses in esophageal cancer. Nutritional status has also been a prognostic biomarker for esophageal cancer. Indicators that combine inflammation and nutrition markers (e.g., serum albumin and total cholesterol levels) have been reported useful for predicting cancer prognosis. The prognostic nutritional index (PNI),[6,7] modified Glasgow prognostic score (mGPS),[8-10] controlling nutritional status (CONUT) score,[11] C-reactive protein-to-albumin ratio (CAR), [12] and fibrinogen and albumin score (FA score),[13] although all useful, are complicated to calculate. The derived NLR (dNLR) was reported as a simpler indicator than the NLR, calculated with the total leukocyte and neutrophil count. Like the NLR, the dNLR has been reported to be a prognostic biomarker for various cancers.[14] The albumin-dNLR (Alb-dNLR) score, consisting of the serum albumin value and the dNLR, was established for measuring the immune system and nutritional status.[14] The Alb-dNLR score was reported as a useful marker to estimate disease activity in

rheumatoid arthritis.[15] However, the potential diagnostic value of the Alb-dNLR score for ESCC patients remains unclear.

This study aimed to evaluate whether the Alb-dNLR score is associated with patient prognosis in ESCC.

Methods

Patients

A total of 319 patients who underwent esophagectomy for thoracic ESCC between April 2010 and March 2018 at our institute were evaluated. Patients with distant metastases, neoadjuvant chemoradiation therapy, salvage surgery, and missing records were excluded. Finally, 269 patients were analyzed. The diagnosis of esophageal cancer was based on a biopsy analysis before surgery or neoadjuvant chemotherapy (nCT). All cases were staged according to the 8th version of the TNM staging system for ESCC of the American Joint Committee on Cancer and the Union for International Cancer Control.[16]

Treatment strategy

At our institute, a cisplatin/5-fluorouracil (CF) nCT regimen was administered for patients, excluding clinical T1, N0, M0 status. The CF regimen consisted of 800 mg/m^2 of 5-fluorouracil provided as a continuous 24-h intravenous infusion and 80 mg/m^2 of intravenous cisplatin on days 1–5. Esophagectomies were performed after two cycles of nCT.

Data collection and definition

Blood samples for total white blood cell count, neutrophil count, albumin levels, and others were obtained at the first doctor visit. Clinicopathological data (age, gender, postoperative complications, etc.) were obtained from the patients' medical records. Complications, such as pneumonia and anastomotic leakage, were evaluated according to the Clavien–Dindo classification system.[17] All data were extracted from a registered database. This study was approved by the Institutional Review Board and Ethics Committee of Kobe University.

dNLR and Alb-dNLR score

The dNLR was calculated using the formula: neutrophil count/(leukocyte count − neutrophil count), as previously reported.[14] The serum albumin and dNLR cutoff values were determined using receiver operating characteristics (ROC) analysis.[18,19] The Alb-dNLR score was classified into three groups: Alb-dNLR score 2 for patients with both low albumin and high dNLR, score 1 for patients with either of the two abnormalities, and score 0 for patients with a high albumin level and low dNLR.[15]

Statistical analysis

Categorical variables were compared using the chi-square test. Continuous variables were compared using Student's t-test or the Kruskal–Wallis H nonparametric test, as appropriate. We generated survival curves based on the Alb-dNLR score using the Kaplan–Meier method and compared the results with the log-rank test. Univariate and multivariate analyses using Cox proportional hazards regression models were performed to identify independent prognostic factors for overall survival (OS) and cause-specific survival (CSS). The optimal cutoff values of the continuous variables were determined

using ROC analysis, if necessary. All analyses were conducted with 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. The statistical significance was defined as a p-value < 0.05.

Results

Patient characteristics

A total of 269 patients from our database were included; 233 patients were men and 36 were women with a median age of 67 years (range, 27–82). Preoperative therapy was performed in 185 cases (68.8%). On the basis of the ROC analysis, the cutoff value of serum albumin was 4.0 g/dL, and the area under the curve (AUC) was 0.65 for OS ($p < 0.0001$, Figure 1a). The cutoff value of the dNLR was 1.48, and the AUC was 0.57 for OS ($p = 0.1210$, Figure 1b). The cutoff value of the Alb-dNLR score was 1, and the AUC was 0.66 for OS ($p < 0.0001$, Figure 1c). Thus, patients were divided into two groups based on the Alb-dNLR score classification (score 2 vs. 0 or 1). We designated an Alb-dNLR score of 2 as the "high Alb-dNLR score group" and an Alb-dNLR score of 0 or 1 as the "low Alb-dNLR score group." A high Alb-dNLR score was found in 61 cases (22.7%). The clinical characteristics of the two patient groups are summarized in Table 1. There was a significant difference between the two groups in age ($p = 0.0015$), pathological T ($p = 0.0004$), and pathological N ($p = 0.0337$) (Table 1).

Correlations between the Alb-dNLR score, OS, and CSS

Kaplan–Meier curves of OS and CSS between patients with high and low Alb-dNLR scores were compared. All pathological stages, including patients with

pathological stage 0–II (n = 178, 66.2%) and pathological stage III (n = 91, 33.8%) ESCC, were evaluated. The median follow-up period was 49 (range, 1–130) months. Among all patients, the 1-, 3-, and 5-year OS rates in the high Alb-dNLR score group were 73.3%, 36.2%, and 34.0%, respectively. The 1-, 3-, and 5-year OS rates in the low Alb-dNLR score group were 91.3%, 73.2%, and 66.2%, respectively. Significant differences were observed across groups ($p < 0.0001$) (Figure 2). Among patients with pathological stage 0–II ESCC, the 5-year OS rate in the high Alb-dNLR score group was significantly lower than that in the low Alb-dNLR score group (43.1% vs. 82.0%; $p < 0.0001$). Among patients with pathological stage III ESCC, there was no significant difference in the 5-year OS rate between the high and low Alb-dNLR score groups (25.1% vs. 26.0%; $p = 0.4250$).

Among all patients, the 1-, 3-, and 5-year CSS rates in the high Alb-dNLR score group were 79.2%, 51.5%, and 51.5%, respectively. The 1-, 3-, and 5-year CSS rates in the low Alb-dNLR score group were 92.2%, 78.4%, and 74.7%, respectively. Significant differences were observed across groups ($p < 0.0001$) (Figure 3). Among patients with pathological stage 0–II ESCC, the 5-year CSS rate in the high Alb-dNLR score group was significantly lower than that in the low Alb-dNLR score group (63.6% vs. 91.1%; $p < 0.0001$). Among patients with pathological stage III ESCC, there was no significant difference in the 5-year CSS rate between the high and low Alb-dNLR score groups (37.9% vs. 32.4%; $p = 0.9914$).

Evaluation of the Alb-dNLR score as an independent poor prognostic factor

The different parameters were analyzed to determine independent prognostic factors. Univariate and multivariate analyses using the Cox proportional hazard model in

269 patients were performed. According to the ROC curve, the cutoff values of age, operative time, and estimated blood loss were 73 years, 721 min, and 240 mL, respectively, for OS. Table 2 shows that the estimated blood loss (HR = 1.689; 95% CI: 1.116–2.571; $p = 0.0131$), pathological T stage (HR = 2.915; 95% CI: 1.910–4.511; $p < 0.0001$), resection margin (HR = 0.434; 95% CI: 0.271–0.709; $p = 0.0011$), and Alb-dNLR score (HR = 2.198; 95% CI: 1.460–3.263; $p = 0.0002$) were independent poor prognostic factors in the multivariate analysis for OS. The estimated blood loss (HR = 1.757; 95% CI: 1.060–2.931; $p = 0.0288$), pathological T stage (HR = 6.117; 95% CI: 3.416–11.610; $p < 0.0001$), pathological N stage (HR = 2.240; 95% CI: 1.252–4.237; $p = 0.0059$), resection margin (HR = 0.404; 95% CI: 0.241–0.692; $p = 0.0013$), and Alb-dNLR score (HR = 2.282; 95% CI: 1.390–3.648; $p = 0.0014$) were independent poor prognostic factors in the multivariate analysis for CSS (Table 3).

Discussion

We demonstrated that the Alb-dNLR score is an independent prognostic marker for OS in patients with ESCC. Regarding clinicopathological characteristics, Alb-dNLR status was strongly associated with pT and pN, which means that the Alb-dNLR reflects tumor progression. However, the Alb-dNLR has a significantly greater influence on OS than pN. OS reflects tumor-related death and death from other illnesses, including pneumonia, malnutrition, and others related to nutritional status. The Alb-dNLR includes Alb, which is a definitive marker to evaluate nutritional status. Thus, the fact that the Alb-dNLR surpasses pN as a prognostic factor in OS is reasonable.

On the other hand, in CSS, the Alb-dNLR is also an independent prognostic factor similar to blood loss, pT, pN, and resection margin. CSS reflects only tumor-related

survival. Thus, pN can be an independent prognostic marker, although not in OS. However, even in CSS, the Alb-dNLR is also an independent prognostic marker. It means that the Alb-dNLR strongly reflects both tumor and nutritional status.

Accumulated studies have revealed that systemic inflammation closely correlates with cancer progression and prognosis.[20] Tumor-infiltrating neutrophils play an important role in tumor progression by promoting angiogenesis, cell mobility, and migration. Associations between tumor-infiltrating neutrophils and poor prognosis have been described for several types of cancer, including esophageal cancer.[21] Lymphocytes play an important role in the immune response against tumors. The decrease in lymphocyte numbers could weaken the immune response against tumors and could worsen survival.[22] The NLR is an inflammatory index and has been reported to be associated with prognosis in cancer patients.[23,24] Previous reports have shown that the NLR is associated with prognosis and treatment response in esophageal cancer and other cancers.[2,3,25-30] The NLR can be easily calculated from laboratory parameters (neutrophil counts and lymphocyte counts) routinely performed before surgery.

Proctor et al.[14] first reported the utility of the dNLR. They showed that the NLR and dNLR had similar prognostic values in various kinds of cancers. In trial database registration, it is customary to register the total white blood cell count and absolute neutrophil count without lymphocytes, and the dNLR can be used in such a situation. It means that the dNLR is more convenient than the NLR. Subsequent reports showed that the dNLR could be a prognostic factor for colorectal cancer,[31,32] pancreatic cancer,[33] breast cancer,[34] diffuse large B-cell lymphoma,[35] and ovarian cancer.[36] However, there are a few reports on the dNLR for esophageal cancer. Cox et al.[37] reported that an elevated pretreatment dNLR was an independent prognostic biomarker in patients with

esophageal cancer treated with definitive chemoradiotherapy.

In esophageal cancer patients, some have poor oral intake due to tumor invasion.[38] These patients are likely to have weight loss and malnutrition at the time of diagnosis, leading to a poor prognosis.[39,40] Additionally, as mentioned above, systemic inflammation has been closely correlated with cancer progression and prognosis.[20] Albumin, commonly used in daily practice, is a well-known nutritional index and is related to inflammation. Indeed, previous reports showed that the serum albumin level is a useful predictor of prognosis of malignant tumors in terms of nutrition and inflammation.[41-43]

Biomarkers that combine the nutritional and inflammatory index, such as mGPS, the CONUT score, CAR, and the FA score, are also reported as prognostic factors for ESCC patients. [8,12,13,44] However, these markers are complicated to calculate. The Alb-dNLR score is a relatively new and simple index that combines the nutritional index Alb and the inflammation index dNLR. Chen et al.[15] reported that the Alb-dNLR is associated with DAS28, a measure of rheumatoid arthritis activity, and inflammatory biomarkers such as C-reactive protein, erythrocyte sedimentation rate, and IgA. They also showed that a combination of albumin and dNLR could be superior to albumin and dNLR alone in the diagnostic effectiveness of rheumatoid arthritis. On the other hand, two retrospective studies recently reported the association of the combined Alb and dNLR index with pancreatic and gastric cancers.[45,46] They suggested that the Alb-NLR might be a better systemic inflammatory and nutritional marker than the NLR, GPS, and PLR scores.

When Alb, dNLR, and Alb-dNLR were analyzed in multiple variables at the same time, Alb-dNLR did not to be a prognostic factor (data not shown). It was because that these factors are strong confounding factors each other. When albumin and Alb-dNLR

were added to multivariate analysis for OS at the same time, Alb-dNLR tended to be a prognostic factor, while albumin was not. Similarly, when dNLR and Alb-dNLR were added to multivariate analysis for OS at the same time, Alb-dNLR was an independent prognostic factor, while albumin was not. Additionally, Alb-dNLR showed a higher AUC value than Alb and dNLR alone (Figure 1a, b, c), suggesting that Alb-dNLR may be a better prognostic predictor for patients with ESCC. To the best of our knowledge, this is the first study to assess the usefulness of Alb-dNLR in patients who underwent esophagectomy for ESCC.

The Alb-dNLR score may be used to stratify patients according to their prognostic risk, and high-risk patients may opt for closer follow-up or more aggressive adjuvant chemotherapy. Among frail, older people and patients with sarcopenia, exercise and nutritional intervention (whey protein, branched-chain amino acids, vitamin D, etc.) were reported to improve inflammatory markers and nutritional indicators.[47,48] Among patients with cancer, previous reports showed that preoperative nutritional intervention improved prealbumin level, which is a nutritional indicator for gastric cancer,[49] and prehabilitation improved the disease-free survival of patients with colorectal cancer.[50] Similarly, among patients with ESCC, proper exercise and nutritional interventions are expected to improve prognosis, particularly in patients with malnutrition and hyperinflammatory conditions, such as cases with high Alb-dNLR scores.

We demonstrated that Alb-dNLR is a useful prognostic factor of both OS and CSS. We also separately assessed the utility of Alb-dNLR in patients with early- and advanced-stage ESCC. Alb-dNLR was a useful predictor of prognosis in the early stage, but not in the advanced stage. As aforementioned, tumor progression is strongly correlated with the nutritional and inflammatory statuses. In patients with advanced-stage ESCC, tumor

factors (T and N) and Alb-dNLR were strong confounding factors of each other, and these factors may not have been prognostic factors.

Our study has several limitations. This was a single-center retrospective study, and the sample size was relatively small. Owing to these limitations, the optimal cutoff value of albumin and dNLR would be changeable. Therefore, further multicenter prospective studies including a large sample are expected to confirm the clinical value of Alb-dNLR in ESCC patients.

Conclusion

In conclusion, the Alb-dNLR score is an extremely useful, easy-to-use parameter to predict OS and CSS of ESCC patients.

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: a cancer journal for clinicians.* May 2021;71(3):209-249.

2. Zhang X, Jiang Y, Wang Y, et al. Prognostic role of neutrophil-lymphocyte ratio in esophageal cancer: A systematic review and meta-analysis. *Medicine (Baltimore).* Dec 2018;97(49):e13585.

3. Yodying H, Matsuda A, Miyashita M, et al. Prognostic Significance of Neutrophil-to-Lymphocyte Ratio and Platelet-to-Lymphocyte Ratio in Oncologic Outcomes of Esophageal Cancer: A Systematic Review and Meta-analysis. *Ann Surg Oncol.* Feb 2016;23(2):646-654.

4. Hirahara N, Tajima Y, Fujii Y, et al. Preoperative Prognostic Nutritional Index Predicts Long-Term Surgical Outcomes in Patients with Esophageal Squamous Cell Carcinoma. *World J Surg.* Jul 2018;42(7):2199-2208.

5. Kosumi K, Baba Y, Ishimoto T, et al. Neutrophil/lymphocyte ratio predicts the prognosis in esophageal squamous cell carcinoma patients. *Surg Today.* Apr 2016;46(4):405-413.

6. Zhang H, Shang X, Ren P, et al. The predictive value of a preoperative systemic immune-inflammation index and prognostic nutritional index in patients with esophageal squamous cell carcinoma. *J Cell Physiol.* Feb 2019;234(2):1794-1802.

7. Xue Y, Zhou X, Xue L, Zhou R, Luo J. The role of pretreatment prognostic

nutritional index in esophageal cancer: A meta-analysis. *J Cell Physiol.* Nov 2019;234(11):19655-19662.

8. 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.

9. McSorley ST, Lau HYN, McIntosh D, Forshaw MJ, McMillan DC, Crumley AB. Staging the Tumor and Staging the Host: Pretreatment Combined Neutrophil Lymphocyte Ratio and Modified Glasgow Prognostic Score Is Associated with Overall Survival in Patients with Esophagogastric Cancers Undergoing Treatment with Curative Intent. *Ann Surg Oncol.* Feb 2021;28(2):722-731.

10. Jomrich G, Paireder M, Kristo I, et al. High Systemic Immune-Inflammation Index is an Adverse Prognostic Factor for Patients With Gastroesophageal Adenocarcinoma. *Annals of Surgery.* 2021;273(3).

11. Takagi K, Buettner S, Ijzermans JNM, Wijnhoven BPL. Systematic Review on the Controlling Nutritional Status (CONUT) Score in Patients Undergoing Esophagectomy for Esophageal Cancer. *Anticancer Res.* Oct 2020;40(10):5343-5349.

12. 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.

13. 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.

14. 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.* Aug 7 2012;107(4):695-699.

15. Chen S, Ying H, Du J, et al. The association between albumin-dNLR score and disease activity in patients with rheumatoid arthritis. *Journal of clinical laboratory analysis.* Mar 2019;33(3):e22695.

16. Brierley J, Gospodarowicz MK, Wittekind C, Sauvage M, Union internationale contre le c. *TNM classification des tumeurs malignes.* 2017.

17. 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.* Aug 2004;240(2):205-213.

18. Hajian-Tilaki K. Receiver Operating Characteristic (ROC) Curve Analysis for Medical Diagnostic Test Evaluation. *Caspian journal of internal medicine.* Spring 2013;4(2):627-635.

19. Park SH, Goo JM, Jo CH. Receiver operating characteristic (ROC) curve: practical review for radiologists. *Korean J Radiol.* Jan-Mar 2004;5(1):11-18.

20. Coussens LM, Werb Z. Inflammation and cancer. *Nature.* Dec 19-26 2002;420(6917):860-867.

21. Donskov F. Immunomonitoring and prognostic relevance of neutrophils in clinical trials. *Seminars in cancer biology.* 2013/06/01/ 2013;23(3):200-207.

22. Germano G, Allavena P, Mantovani A. Cytokines as a key component of cancer-related inflammation. *Cytokine.* Sep 2008;43(3):374-379.

23. Templeton AJ, McNamara MG, Šeruga B, et al. Prognostic role of neutrophil-to-lymphocyte ratio in solid tumors: a systematic review and meta-analysis. *J Natl Cancer Inst.* Jun 2014;106(6):dju124.

24. Guthrie GJ, Charles KA, Roxburgh CS, Horgan PG, McMillan DC, Clarke SJ. The systemic inflammation-based neutrophil-lymphocyte ratio: experience in patients with cancer. *Critical reviews in oncology/hematology.* Oct 2013;88(1):218-230.

25. Chen M-F, Chen P-T, Kuan F-C, Chen W-C. The Predictive Value of Pretreatment Neutrophil-To-Lymphocyte Ratio in Esophageal Squamous Cell Carcinoma. *Annals of Surgical Oncology.* 2019/01/01 2019;26(1):190-199.

26. Gao GD, Sun B, Wang XB, Wang SM. Neutrophil to lymphocyte ratio as prognostic indicator for patients with esophageal squamous cell cancer. *The International journal of biological markers.* Oct 31 2017;32(4):e409-e414.

27. Barbetta A, Nobel TB, Sihag S, et al. Neutrophil to Lymphocyte Ratio as Predictor of Treatment Response in Esophageal Squamous Cell Cancer. *Ann Thorac Surg.* Sep 2018;106(3):864-871.

28. McLaren PJ, Bronson NW, Hart KD, et al. Neutrophil-to-Lymphocyte and Platelet-to-Lymphocyte Ratios can Predict Treatment Response to Neoadjuvant Therapy in Esophageal Cancer. *Journal of gastrointestinal surgery : official journal of the Society for Surgery of the Alimentary Tract.* Apr 2017;21(4):607-

613.

29. Sharaiha RZ, Halazun KJ, Mirza F, et al. Elevated preoperative neutrophil:lymphocyte ratio as a predictor of postoperative disease recurrence in esophageal cancer. *Ann Surg Oncol.* Nov 2011;18(12):3362-3369.

30. 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. *Journal of Surgical Oncology.* 2021;in press.

31. Grenader T, Nash S, Adams R, et al. Derived neutrophil lymphocyte ratio is predictive of survival from intermittent therapy in advanced colorectal cancer: a post hoc analysis of the MRC COIN study. *Br J Cancer.* Mar 15 2016;114(6):612-615.

32. Absenger G, Szkandera J, Pichler M, et al. A derived neutrophil to lymphocyte ratio predicts clinical outcome in stage II and III colon cancer patients. *Br J Cancer.* Jul 23 2013;109(2):395-400.

33. Szkandera J, Stotz M, Eisner F, et al. External validation of the derived neutrophil to lymphocyte ratio as a prognostic marker on a large cohort of pancreatic cancer patients. *PLoS One.* 2013;8(11):e78225.

34. Dirican A, Kucukzeybek BB, Alacacioglu A, et al. Do the derived neutrophil to lymphocyte ratio and the neutrophil to lymphocyte ratio predict prognosis in breast cancer? *Int J Clin Oncol.* Feb 2015;20(1):70-81.

35. Troppan K, Deutsch A, Gerger A, et al. The derived neutrophil to lymphocyte

ratio is an independent prognostic factor in patients with diffuse large B-cell lymphoma. *Br J Cancer.* Jan 21 2014;110(2):369-374.

36. Wu YY, Qin YY, Qin JQ, Zhang X, Lin FQ. Diagnostic value of derived neutrophil-to-lymphocyte ratio in patients with ovarian cancer. *Journal of clinical laboratory analysis.* May 2019;33(4):e22833.

37. Cox S, Hurt C, Grenader T, Mukherjee S, Bridgewater J, Crosby T. The prognostic value of derived neutrophil to lymphocyte ratio in oesophageal cancer treated with definitive chemoradiotherapy. *Radiother Oncol.* Oct 2017;125(1):154-159.

38. Mariette C, De Botton ML, Piessen G. Surgery in esophageal and gastric cancer patients: what is the role for nutrition support in your daily practice? *Ann Surg Oncol.* Jul 2012;19(7):2128-2134.

39. van der Schaaf MK, Tilanus HW, van Lanschot JJ, et al. The influence of preoperative weight loss on the postoperative course after esophageal cancer resection. *J Thorac Cardiovasc Surg.* Jan 2014;147(1):490-495.

40. Zhang S, Tan Y, Cai X, Luo K, Wu Z, Lu J. Preoperative weight loss is associated with poorer prognosis in operable esophageal cancer patients: A single-center retrospective analysis of a large cohort of Chinese patients. *Journal of Cancer.* 2020;11(7):1994-1999.

41. 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.

42. Crumley ABC, Stuart RC, McKernan M, McMillan DC. Is Hypoalbuminemia an Independent Prognostic Factor in Patients with Gastric Cancer? *World Journal of Surgery.* 2010/10/01 2010;34(10):2393-2398.

43. 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.

44. 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.

45. Liu JX, Li A, Zhou LY, et al. Significance of combined preoperative serum Alb and dNLR for diagnosis of pancreatic cancer. *Future oncology (London, England).* Feb 2018;14(3):229-239.

46. Sun X, Wang J, Liu J, Chen S, Liu X. Albumin concentrations plus neutrophil lymphocyte ratios for predicting overall survival after curative resection for gastric cancer. *Onco Targets Ther.* 2016;9:4661-4669.

47. Rondanelli M, Klersy C, Terracol G, et al. Whey protein, amino acids, and vitamin D supplementation with physical activity increases fat-free mass and strength, functionality, and quality of life and decreases inflammation in sarcopenic elderly. *The American Journal of Clinical Nutrition.* 2016;103(3):830-840.

48. Caldo-Silva A, Furtado GE, Chupel MU, et al. Effect of Training-Detraining Phases of Multicomponent Exercises and BCAA Supplementation on Inflammatory Markers and Albumin Levels in Frail Older Persons. *Nutrients.*

Mar 28 2021;13(4).

49. Ding D, Feng Y, Song B, Gao S, Zhao J. Effects of preoperative and postoperative enteral nutrition on postoperative nutritional status and immune function of gastric cancer patients. *Turk J Gastroenterol.* Mar 2015;26(2):181-185.

50. Trépanier M, Minnella EM, Paradis T, et al. Improved Disease-free Survival After Prehabilitation for Colorectal Cancer Surgery. *Ann Surg.* Sep 2019;270(3):493-501.

Figure legends

Figure 1. ROC analysis of Alb and dNLR for overall survival.

The ROC analysis of the dNLR, albumin, and Alb-dNLR values is depicted. (a) The cutoff value of serum albumin was 4.0 g/dL, which yielded sensitivity of 67% and specificity of 57%. The AUC value for OS was 0.65. (b) The cutoff value of dNLR was 1.77, which yielded sensitivity of 68% and specificity of 49%. The AUC value for OS was 0.58. (c) The cutoff value of Alb-dNLR was 1, which yielded sensitivity of 88% and specificity of 36%. The AUC value of OS was 0.66.

ROC, receiver operating characteristic; dNLR, derived neutrophil-to-lymphocyte ratio; Alb, the serum albumin value; OS, overall survival**.**

Figure 2. Kaplan–Meier survival curves for OS according to the Alb-dNLR score in ESCC patients. Among all patients, the 5-year OS rate of patients in the high Alb-dNLR score group was significantly worse than that in the low Alb-dNLR score group (34.0% vs. 66.2%; $p < 0.001$). Among patients with pathological stage 0–II ESCC, the 5-year OS rate in the high Alb-dNLR score group was significantly lower than that in the low Alb-dNLR score group (43.1% vs. 82.0%; $p < 0.0001$). Among patients with pathological stage III ESCC, there was no significant difference in the 5-year OS rate between the high and low Alb-dNLR score groups (25.1% vs. 26.0%; $p = 0.4250$).

OS, overall survival; Alb, the serum albumin value; dNLR, derived neutrophil-to-lymphocyte ratio; ESCC, esophageal squamous cell carcinoma.

Figure 3. Kaplan–Meier survival curves for CSS according to the Alb-dNLR score in ESCC patients. The 5-year CSS rate of patients in the high Alb-dNLR score group was

significantly worse than that in the low Alb-dNLR score group (51.5% vs. 74.7%; $p < 0.001$). Among patients with pathological stage 0–II ESCC, the 5-year CSS rate in the high Alb-dNLR score group was significantly lower than that in the low Alb-dNLR score group (63.6% vs. 91.1%; $p < 0.0001$). Among patients with pathological stage III ESCC, there was no significant difference in the 5-year CSS rate between the high and low Alb-dNLR score groups (37.9% vs. 32.4%; $p = 0.9914$).

CSS, cancer-specific survival; Alb, the serum albumin value; dNLR, derived neutrophil-to-lymphocyte ratio; ESCC, esophageal squamous cell carcinoma.

Table 1. Patient characteristics

Characteristic	High Alb-dNLR score group (n = 61)	Low Alb-dNLR score group (n = 208)	*p*-value
Age, years	69 (43–82)	67 (27–82)	0.0015[a)]
Sex (M/F)	52/9	181/27	0.7232[b)]
Neoadjuvant chemotherapy (+/−)	48/13	137/71	0.0512[b)]
Tumor location (Ut/Mt/Lt)	7/31/23	37/106/65	0.4010[b)]
Thoracic procedure (thoracoscopy/open)	57/4	201/7	0.2941[b)]
Lymph node dissection (3-field/2-field/others)	25/35/1	78/129/1	0.2841[b)]
Operative time (min)	690.5 (302–1215)	680 (354–1361)	0.4706[c)]
Estimated blood loss (mL)	295 (0–3269)	220 (0–10000)	0.2698[c)]
Anastomotic leakage (CD ≥ 2/<2)	8/53	41/167	0.2265[b)]
Pneumonia (CD ≥ 2/<2)	17/44	38/170	0.1114[b)]
pT (0/is/1/2/3/4)	0/1/17/6/36/1	2/5/120/17/63/1	0.0008[b)]
pN (0/1/2/3)	24/15/13/9	102/69/20/17	0.0337[b)]
Resection (R0/R1/R2)	49/9/3	187/18/3	0.1208[b)]

[a)] Student's test; [b)] kai; [c)] Kruskal–Wallis

dNLR, derived neutrophil-to-lymphocyte ratio; Alb, the serum albumin value; CD, Clavien–Dindo classification grade; pT, pathological T stage; pN, pathological N stage.

Table 2. Univariate and multivariate Cox proportional hazards regression models for overall survival in patients with ESCC

	Univariate, HR (95% CI)	***p*-value**	**Multivariate, HR (95% CI)**	***p*-value**
Age (≥73/<73)	1.386 (0.865–2.135)	0.1686		
Sex (M/F)	1.112 (0.659–2.031)	0.7067		
NAC (+/−)	2.785 (1.758–4.641)	<0.0001	1.440 (0.861–2.521)	0.170
Tumor location				
Ut	1.000	-		
Mt	1.007 (0.611–1.846)	0.9789		
Lt	1.044 (0.612–1.846)	0.8758		
Thoracic procedure				
Thoracoscopy/open	1.342 (0.524–2.802)	0.5029		
Lymph node dissection (3-field/2-field or less)	1.255 (0.864–1.812)	0.2301		
Operative time (>721 min/≤721 min)	1.754 (1.208–2.533)	0.0034	1.332 (0.892–1.978)	0.1597
Estimated blood loss (>240 mL/≤240 mL)	1.737 (1.197–2.547)	0.0036	1.689 (1.116–2.571)	0.0131
Anastomotic leakage (CD ≥ 2/<2)	0.885 (0.531–1.401)	0.6152		
Pneumonia (CD ≥ 2/<2)	1.670 (1.095–2.484)	0.0182	1.312 (0.836–2.014)	0.2315
pT (≥3/<3)	4.583 (3.146–6.747)	<0.0001	2.915 (1.910–4.511)	<0.0001

pN (+/−)	2.723 (1.850–4.087)	<0.0001	1.521 (0.986–2.379)	0.0583
Resection (R0/R1 or R2)	0.189 (0.125–0.294)	<0.0001	0.434 (0.271–0.709)	0.0011
Alb-dNLR score (high/low)	2.936 (1.989–4.280)	<0.0001	2.198 (1.460–3.263)	0.0002

dNLR, derived neutrophil-to-lymphocyte ratio; Alb, the serum albumin value; CD, Clavien–Dindo classification grade; pT, pathological T stage; pN, pathological N stage; HR, hazard ratio; CI, confidence interval.

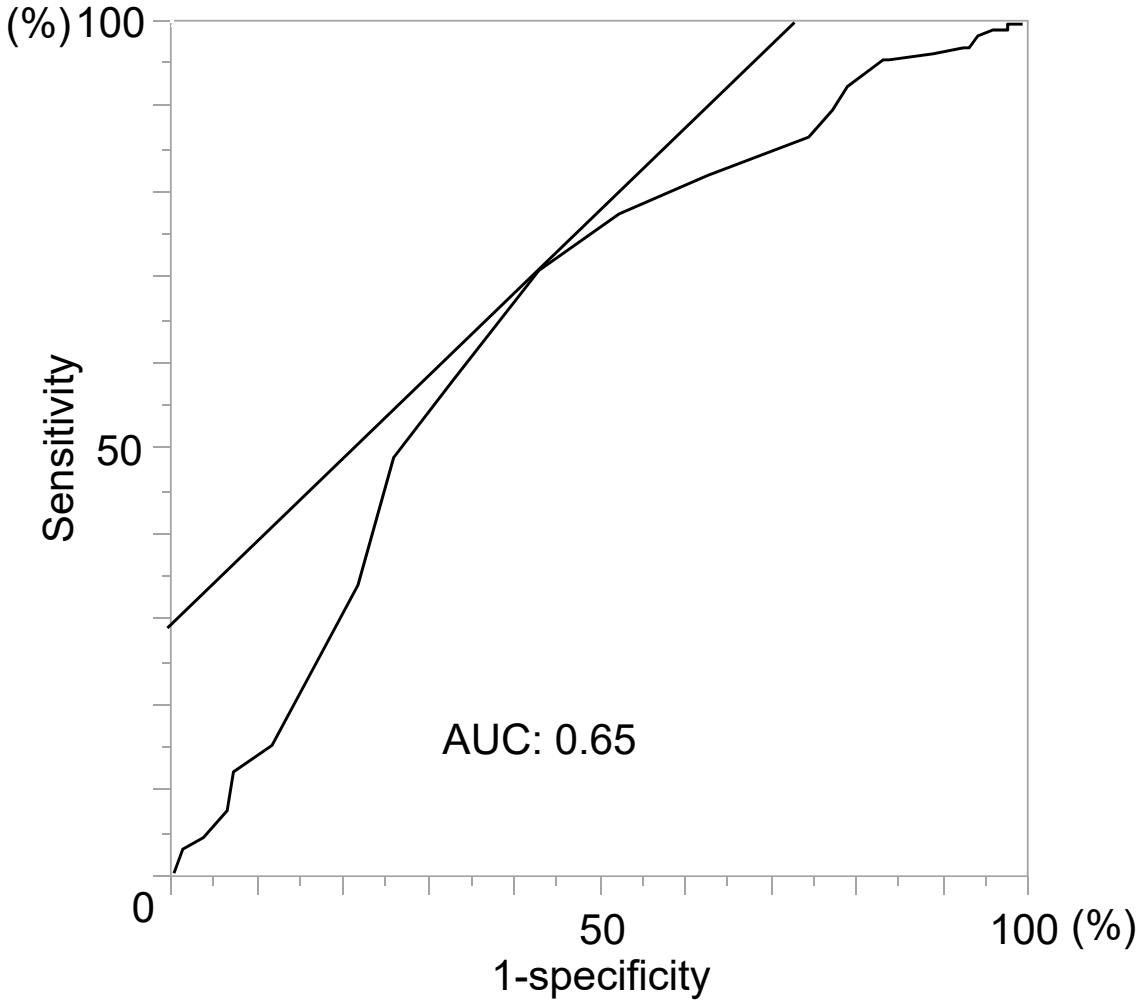
Table 3. Univariate and multivariate Cox proportional hazards regression models for cancer-specific survival in patients with ESCC.

Variable	Univariate, HR (95% CI)	*p*-value	Multivariate, HR (95% CI)	*p*-value
Age (≥73/<73)	1.152 (0.620–1.994)	0.6366		
Sex (M/F)	0.921 (0.508–1.843)	0.8023		
NAC (+/−)	3.751 (2.022–7.762)	<0.0001	1.356 (0.674–3.039)	0.4095
Tumor location				
Ut	1.000	-		
Mt	0.941 (0.512–1.843)	0.8521		
Lt	1.117 (0.590–2.229)	0.7401		
Thoracic procedure				
Thoracoscopy/open	1.828 (0.641–4.089)	0.2313		
Lymph node dissection (3-field/2-field or less)	1.415 (0.898–2.214)	0.1333		
Operative time (>721 min/≤721 min)	1.648 (1.037–2.591)	0.0349	1.276 (0.777–2.074)	0.3320
Estimated blood loss (>240 mL/≤240 mL)	1.737 (1.106–2.765)	0.0164	1.757 (1.060–2.931)	0.0288
Anastomotic leakage (CD ≥ 2/<2)	0.579 (0.269–1.099)	0.0987		
Pneumonia (CD ≥ 2/<2)	1.175 (0.655–1.986)	0.5730		
pT (≥3/<3)	10.064 (5.927–18.121)	<0.0001	6.117 (3.416–11.610)	<0.0001

pN (+/−)	4.827 (2.822–8.814)	<0.0001	2.240 (1.252–4.237)	0.0059
Resection (R0/R1 or R2)	0.158 (0.098–0.264)	<0.0001	0.404 (0.241–0.692)	0.0013
Alb-dNLR score (high/low)	2.453 (1.504–3.906)	0.0005	1.733 (1.035–2.835)	0.0371

dNLR, derived neutrophil-to-lymphocyte ratio; Alb, the serum albumin value; CD, Clavien–Dindo classification grade; pT, pathological T stage; pN, pathological N stage; HR, hazard ratio; CI, confidence interval.

a



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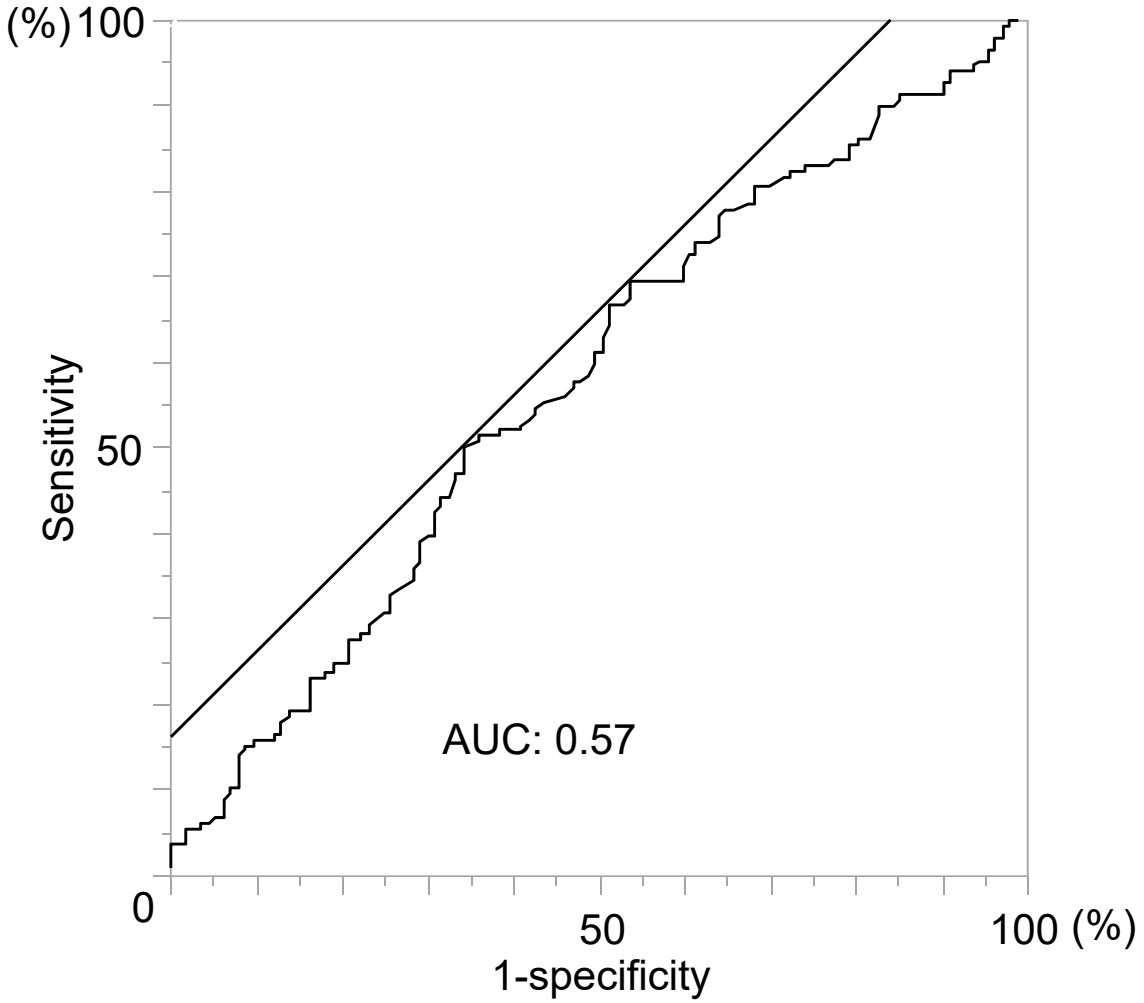

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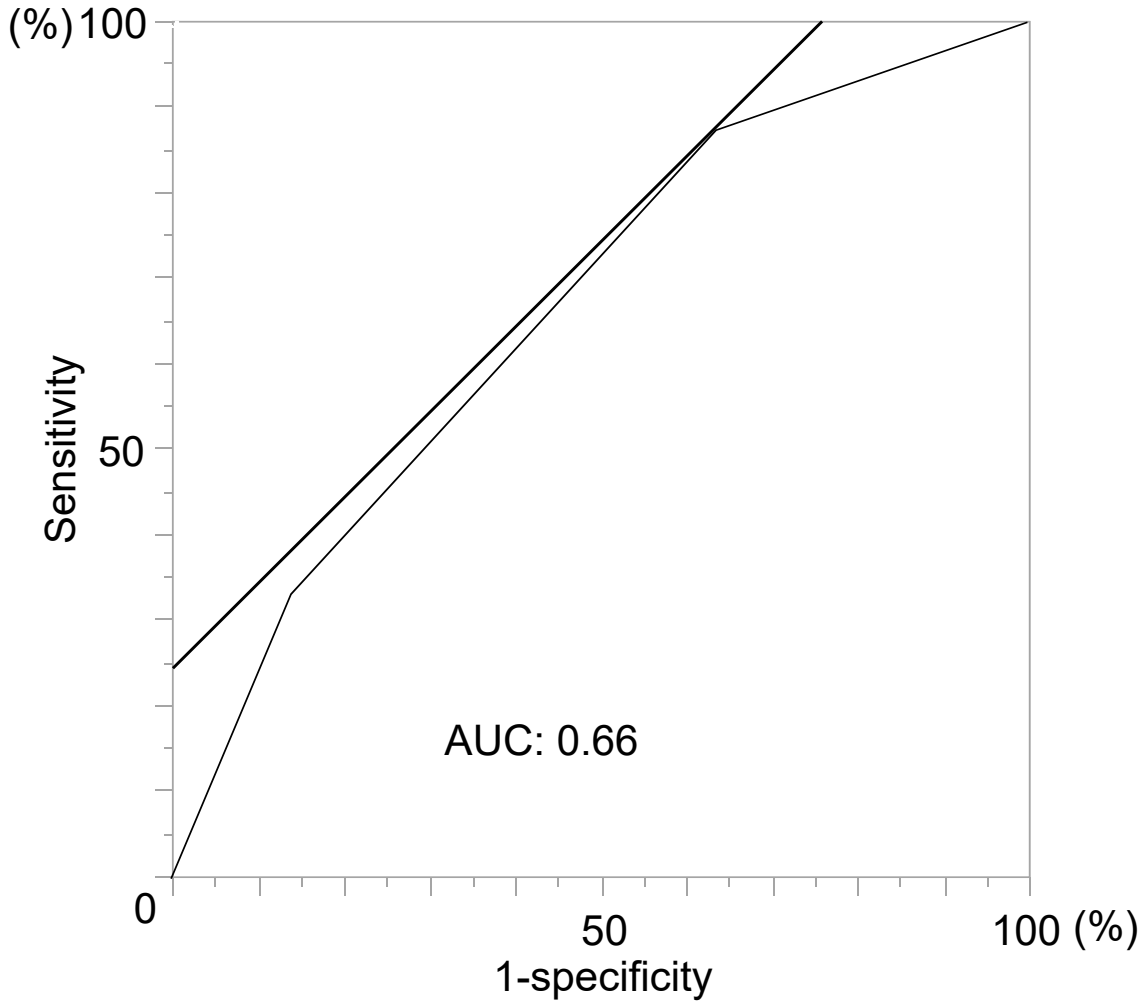

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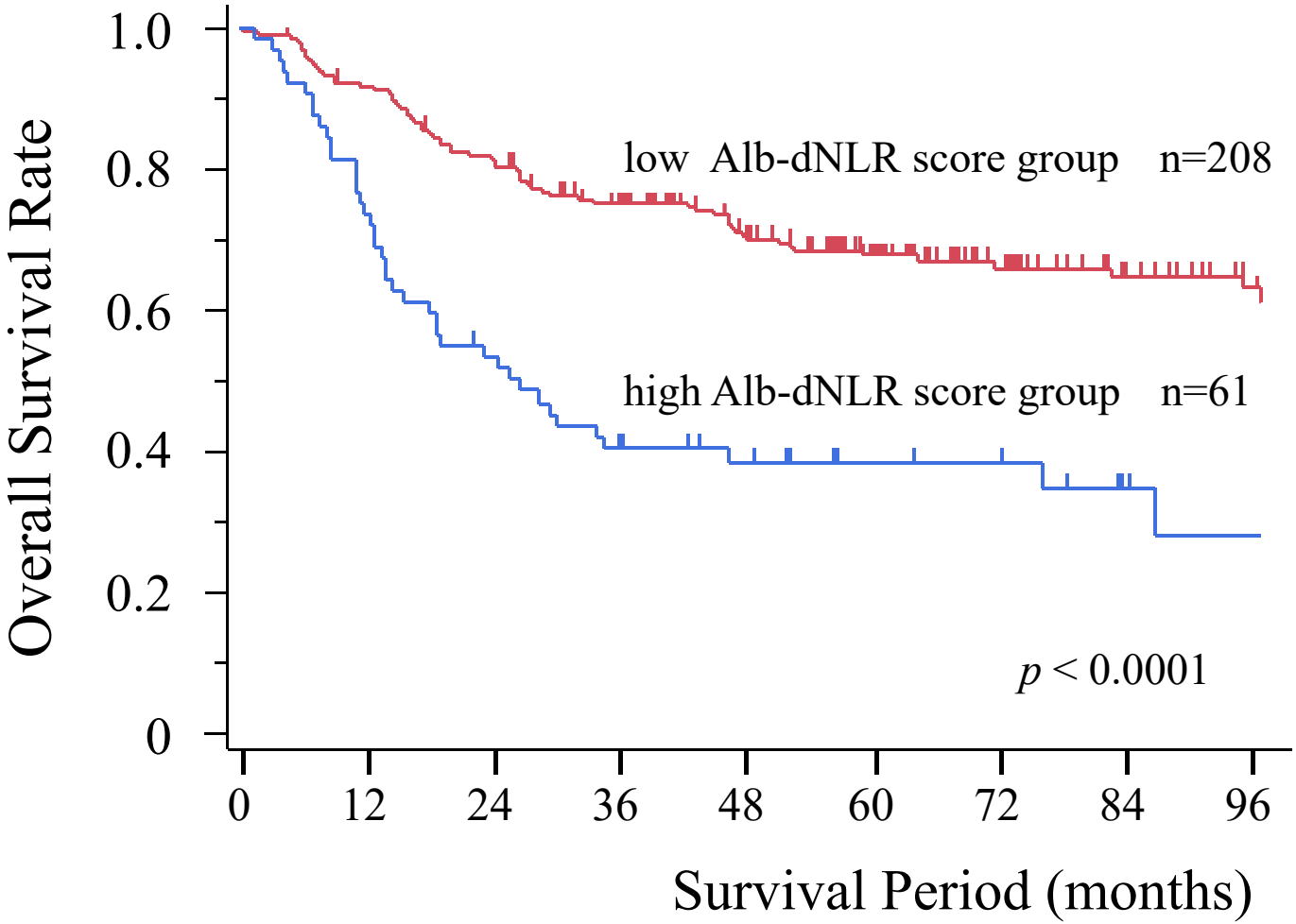
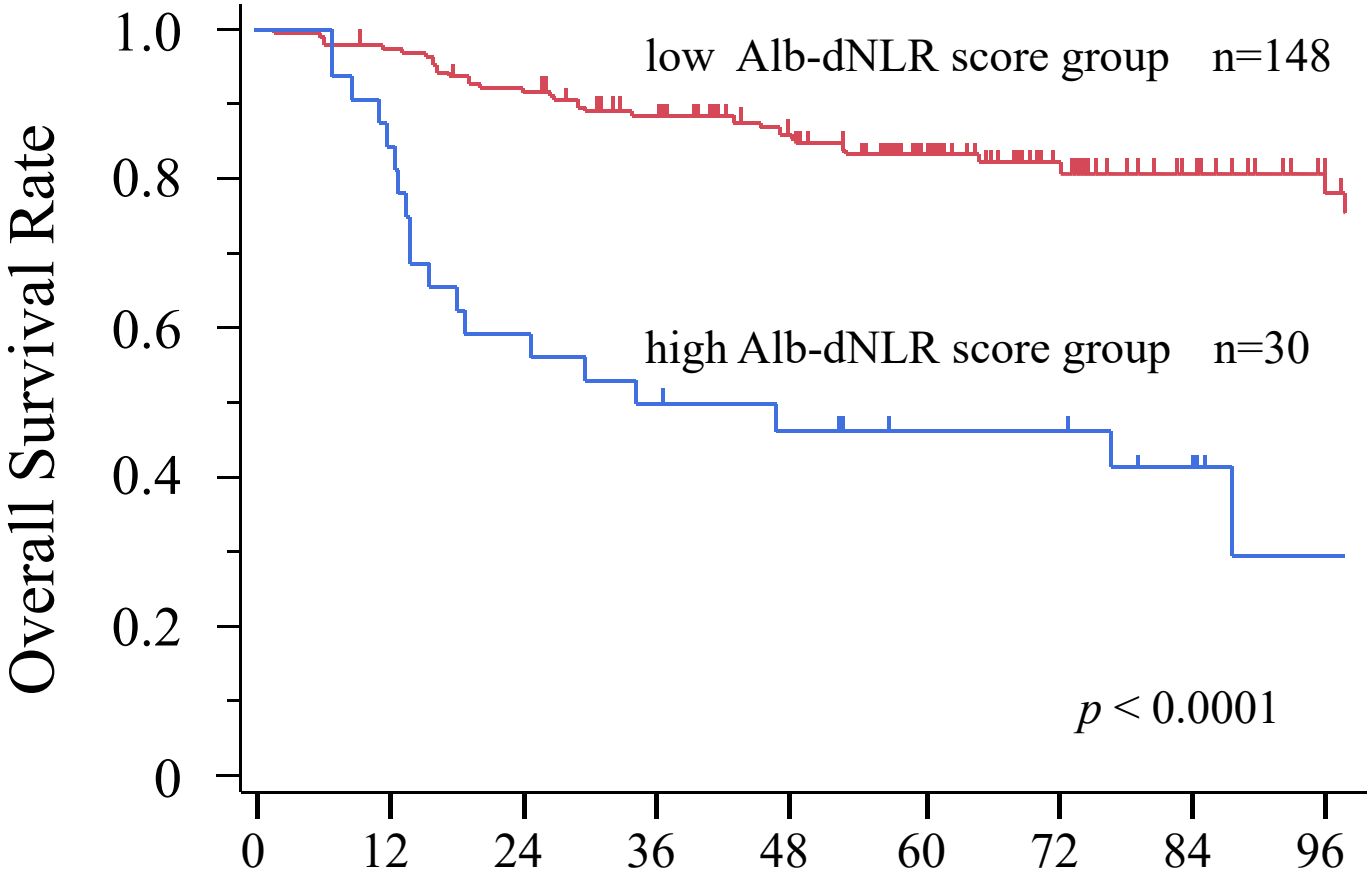


Number at risk

low Alb-dNLR score group	208	189	166	144	123	96	65	50	37
high Alb-dNLR score group	61	45	30	22	17	12	11	8	4

b



Number at risk

low Alb-dNLR score group	148	144	135	122	109	86	58	43	32
high Alb-dNLR score group	30	27	18	15	13	10	10	7	3

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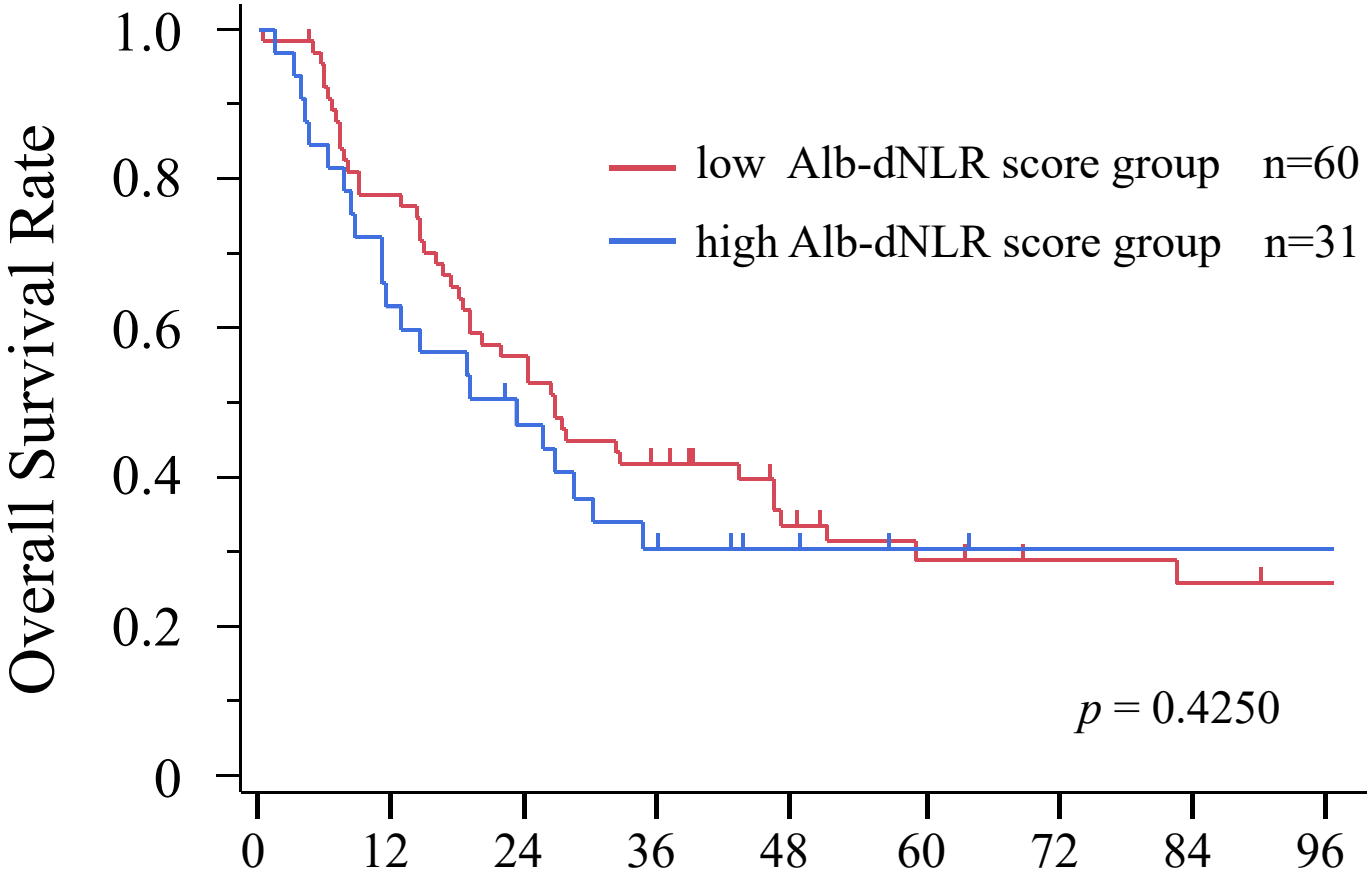
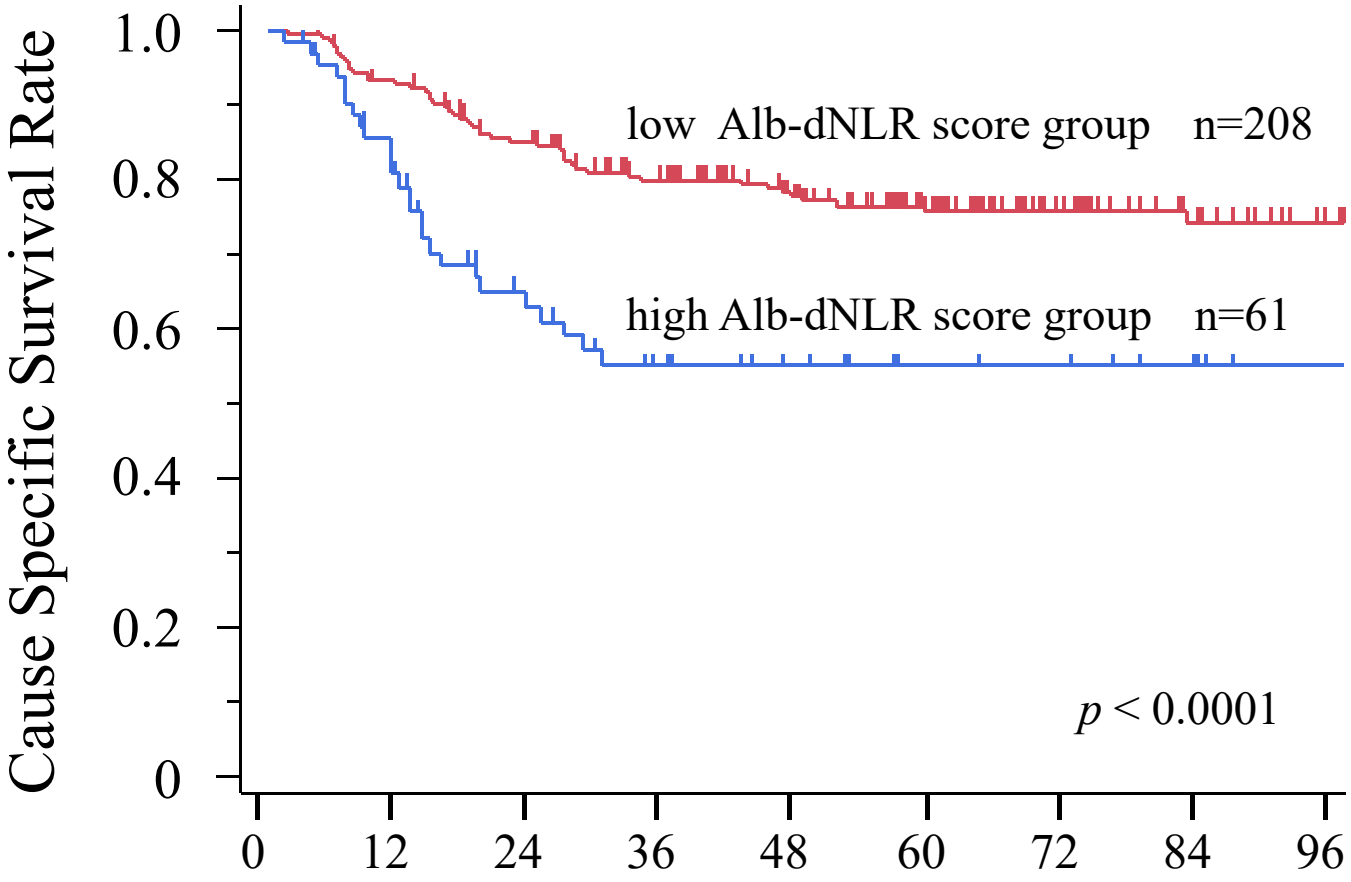


Number at risk

low Alb-dNLR score group	60	47	32	23	15	11	8	8	6
high Alb-dNLR score group	31	19	13	8	5	3	2	2	2

a



Number at risk

low Alb-dNLR score group	208	189	166	144	123	96	65	50	37
high Alb-dNLR score group	61	45	30	22	17	12	11	8	4

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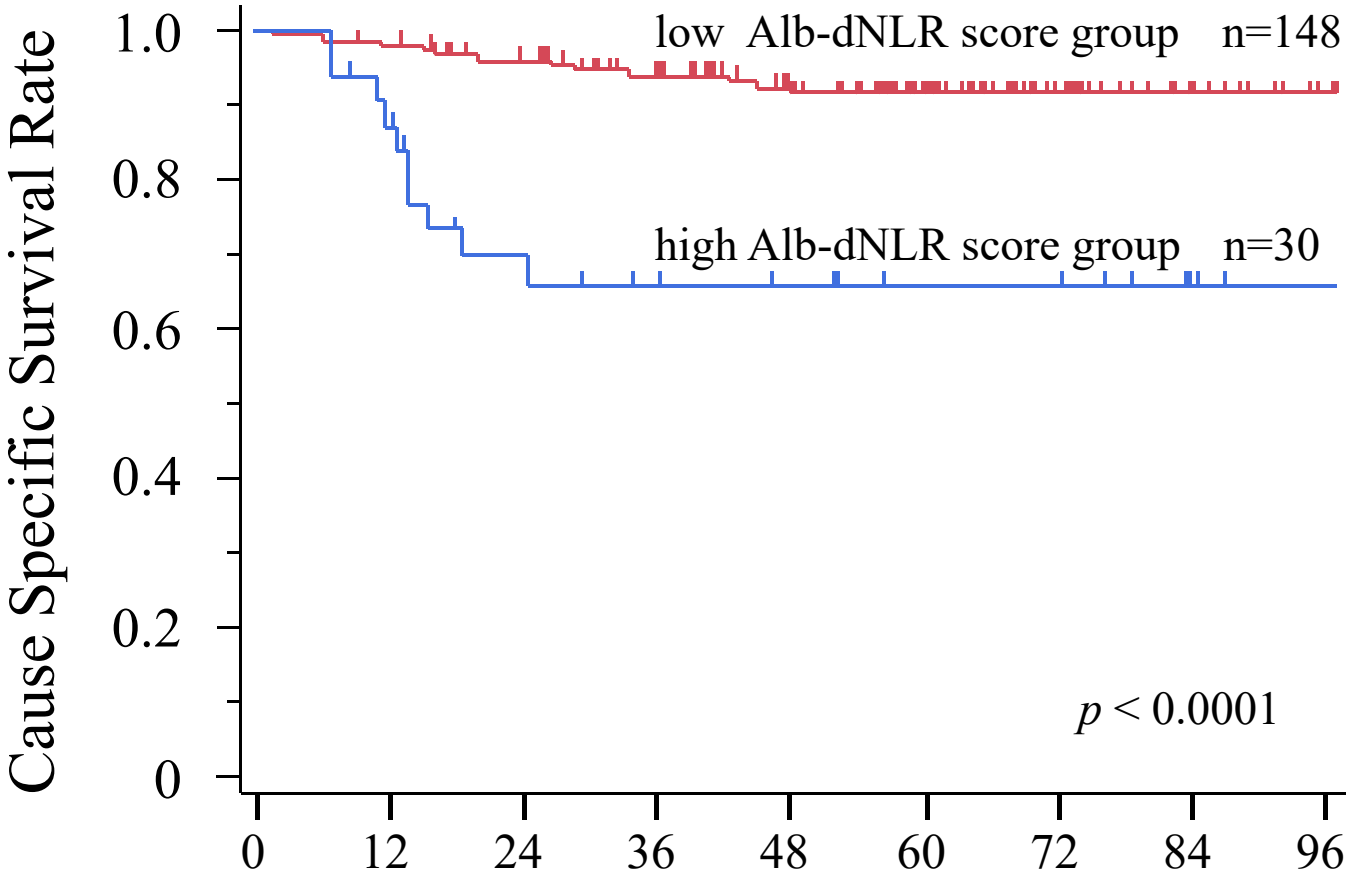

Number at risk

low Alb-dNLR score group	148	144	135	122	109	86	58	43	32
high Alb-dNLR score group	30	27	18	15	13	10	10	7	3

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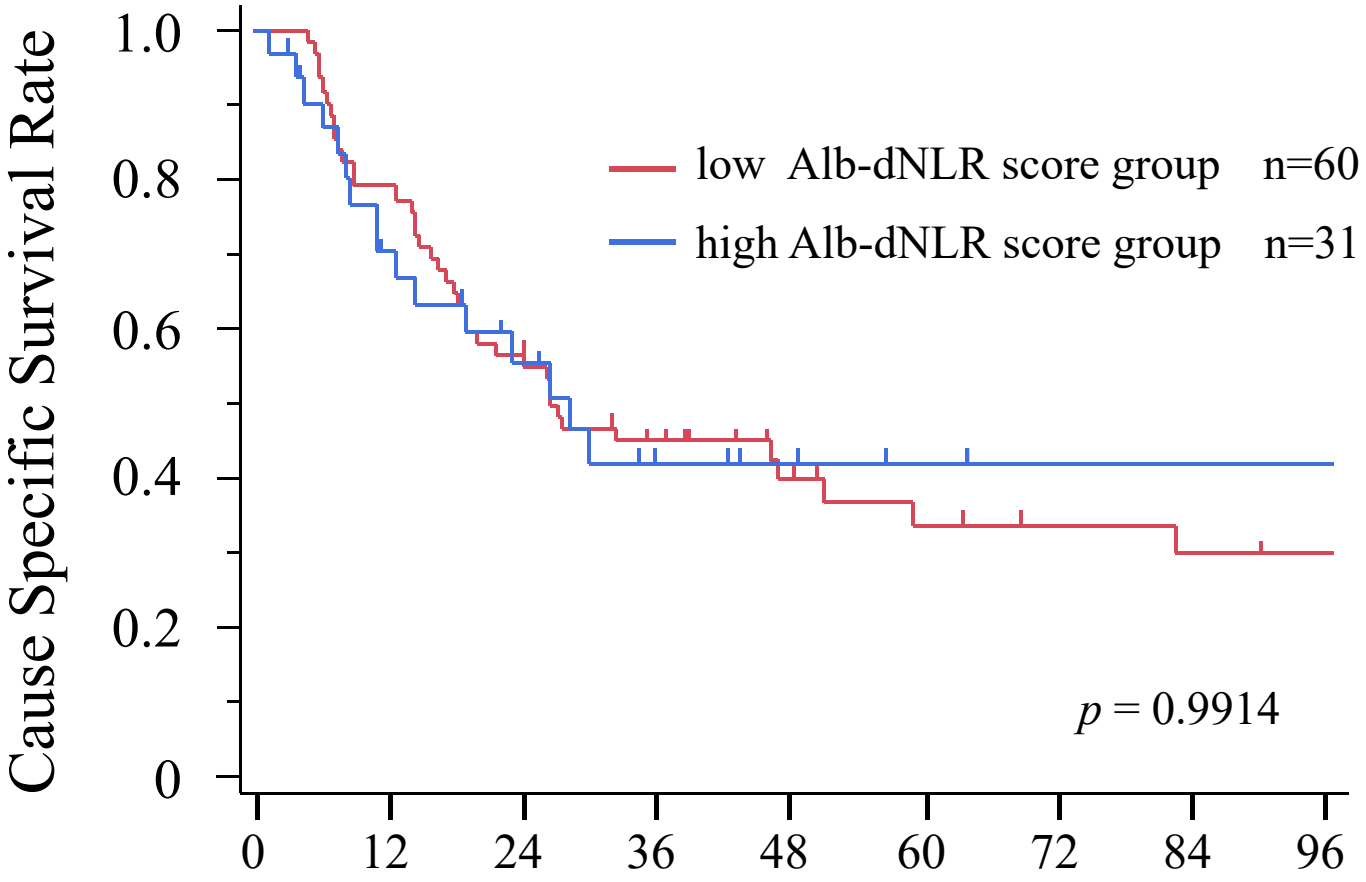

Number at risk									
low Alb-dNLR score group	60	47	32	23	15	11	8	8	6
high Alb-dNLR score group	31	19	13	8	5	3	2	2	2