# Impact of change in the Naples prognostic score after neoadjuvant chemoradiotherapy on survival in esophageal squamous cell carcinoma patients

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## ABSTRACT

**الأهداف**: تقييم الأهمية السريرية والقيم الاستشرافية للتغير في مؤشر NPS بعد العلاج الكيميا‌عقاعدة المسبق (NACR) في مرضى سرطان المريء الخلايا القرنية المتقدم محليًا (ESCC).

**الأساليب**: قمنا بتحليل 232 مريضًا مصابًا بـ ESCC محلياً متقدمًا أجريوا NACR تلاه استئصال المريء. استنادًا إلى التغير في NPS بعد NACR (ΔNPS ≤ 0 أو ΔNPS > 0)، تم تقسيم جميع المشاركين إلى مجموعة NPS المرتفعة ومجموعة NPS غير المرتفعة (ΔNPS = post–NACR NPS – pre–NACR NPS). قمنا بمقارنة السمات السريرية والمرضية والبقاء والمضاعفات ما بعد العملية الجراحية بين المجموعتين.

**النتائج**: تم انتقاء 232 مريضًا، بما في ذلك 105 مريضًا في مجموعة NPS المرتفعة و 127 مريضًا في مجموعة NPS غير المرتفعة. أظهرت نتائج تحليل البقاء أن المرضى في مجموعة NPS المرتفعة كان لديهم بقاء عام أسوأ (P = 0.024) وبقاء خاليًا من العودة ($p$=0.047) مقارنة بالمرضى في مجموعة NPS غير المرتفعة. أظهرت تحليلات خطر كوكس أحادية المتغير ومتعددة المتغيرات أن تغيير NPS بعد NACR كان عاملاً مستقلاً للخطر للبقاء العام ($p$=0.036) وبقاء خاليًا من العودة ($p$=0.029).

**الخلاصة**: كانت مؤشر NPS المرتفع بعد NACR عامل استشرافي مستقل لمرضى ESCC المتقدمين محلياً الذين أجروا NACR. تحمل هذه النتيجة إمكانية كبيرة للاستفادة منها في التعرف على مرضى ESCC ذوي المخاطر العالية الذين أجروا NACR واتخاذ قرارات علاج فردية في الممارسة السريرية

**Objectives:** To assess the clinical relevance and prognostic value of changes in the Naples prognostic score (NPS) after neoadjuvant chemoradiotherapy (NACR) among esophageal squamous cell carcinoma (ESCC) patients.

**Methods:** We studied 232 locally advanced ESCC patients who received NACR before undergoing esophagectomy retrospectively. Categorizing individuals into the elevated NPS group and the non-elevated NPS group based on the change in NPS after NACR (ΔNPS > 0 or ΔNPS ≤ 0), we examined and compared the clinicopathological characteristics, survival rates, and postoperative complications between these 2 groups (ΔNPS = post-NACR NPS - pre-NACR NPS).

**Results:** Out of the 232 patients enrolled, 105 exhibited elevated NPS levels, while 127 showed non-elevated NPS levels. Survival analyses indicated inferior overall survival (OS) ($p$=0.024) and recurrence-free survival (RFS) ($p$=0.047) in the elevated NPS cohort compared to the non-elevated NPS cohort. Subsequent cox regression analyses identified the post-NACR change in NPS as an independent prognostic indicator for RFS ($p$=0.029) and OS ($p$=0.036).

**Conclusion:** Elevated NPS post-NACR emerged as a significant indicator of worse prognosis for locally advanced ESCC patients who underwent NACR. This finding has great potential to be useful for recognizing high-risk ESCC patients who received NACR before undergoing esophagectomy and making individualized subsequent therapeutic decisions in clinical practice.


**Keywords:** esophageal cancer, Naples prognostic score, Neoadjuvant therapy, prognosis

***Saudi Med J 2024; Vol. 45 (5): 481-489***
***doi: 10.15537/smj.2024.45.5.20230908***

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*Received 17th March 2024. Accepted 21st April 2024.*

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Esophageal cancer (EC) presents a considerable health challenge owing to its aggressive characteristics. Remarkably, more than half of the worldwide incidences and mortalities are concentrated in China, where esophageal squamous cell carcinoma (ESCC) predominates among all EC subtypes.[1] Recent studies in managing EC have focused on neoadjuvant chemoradiotherapy (NACR) administered before surgery to enhance treatment success.[2,3] Importantly, the nutritional and immune statuses of individuals with EC are crucial factors affecting treatment efficacy and long-term prognosis. Malnutrition and immune dysfunction are prevalent in these patients and can result in treatment-related complications and increased mortality.[4,5] Therefore, the evaluation of the prognostic relevance of nutritional and immune markers in EC patients who received NACR is of utmost importance in clinical practice.

In the realm of EC research, there is a growing focus on blood-based biomarkers and scoring systems due to their potential to predict treatment response and prognosis. Over the past few years, there has been a notable upsurge in investigations concentrating on blood-related biomarkers, encompassing the platelet-to-lymphocyte ratio, neutrophil-to-lymphocyte ratio (NLR), and systemic immune-inflammatory index, across numerous studies evaluating the clinical outcomes of neoadjuvant therapy in EC patients.[6-8] Furthermore, there has been a proliferation of scoring systems introduced for assessing both the nutritional and inflammatory profiles of patients, as well as predicting their prognosis. These systems encompass a range of indices, such as the modified Glasgow prognostic score, controlling nutritional status score, as well as prognostic nutritional index. They serve as valuable tools in comprehensively evaluating patient health and anticipating their clinical outcomes.[6-8]

Recently, the Naples prognostic score (NPS) has risen to prominence as a significant prognostic indicator across various cancer types. It encompasses the albumin (ALB), total cholesterol (TC), lymphocyte-to-monocyte ratio (LMR), and NLR, where elevated scores correlate with poorer patient prognoses.[9] In a retrospective study involving 165 Japanese ESCC patients, the pre-neoadjuvant NPS emerged as an independent prognostic factor.[10] However, considering that neoadjuvant therapy is a continuous process, patients might experience a sustained decline in nutritional and immune statuses during treatment, potentially altering the NPS. These changes could also influence prognosis. Additionally, studies emphasize the significance of closely monitoring the fluctuating trends in nutritional and immune-related parameters during NACR.[11,12] Therefore, we hypothesize that patients experiencing an elevation in NPS following NACR might exhibit poorer nutritional and immune statuses, resulting in a lack of significant treatment benefits after surgery. The primary objective of the study is to assess the clinical relevance and prognostic value of changes in the NPS after NACR among ESCC patients.

**Disclosure.** This study was supported in part by the National Natural Science Foundation of China (Grant No. 81970481) and Sichuan Science and Technology Program (Grant No. 2022YFS0048).

**Methods.** Figure 1A presents the detailed flow diagram outlining the study procedures. Between May 2016 and March 2021, 232 ESCC patients meeting the criteria were enrolled. This study received approval from the Institutional Review Board of West China Hospital, Sichuan University (IRB number: 2022-853). Every procedure in the study followed the Declaration of Helsinki.

The subsequent criteria were employed for inclusion: i) patients with histologically confirmed ESCC, ii) patients with clinical stages of cTis-2 N1-3 M0 or cT3-4a Nany M0, and iii) patients who underwent NACR and McKeown esophagectomy. The following criteria were used for exlusion: i) individuals who underwent immunotherapy, prior gastric resection, or salvage esophagectomy, ii) individuals with gastric or gastroesophageal cancer, iii) patients with missing pathological information data, and iv) patients had cervical ECs.

The Naples prognostic score was computed using data on TC, ALB, LMR, and NLR collected before and after NACR. (Table 1). The first NPS assessment was based on the routine examination results taken before the initiation of the first round of chemotherapy or radiotherapy. The second NPS assessment was based on the routine examination results taken 5 days before surgery. Figure 1B outlines the distribution of patients with varying NPSs before and after NACR. Based on the change in NPS after NACR (ΔNPS >0 or ΔNPS ≤0), all patients with locally advanced ESCC were stratified into either an elevated NPS group or a non-elevated NPS group (ΔNPS = post-NACR NPS - pre-NACR NPS).

All patients underwent a treatment regimen involving two cycles of chemotherapy concurrently with intensity-

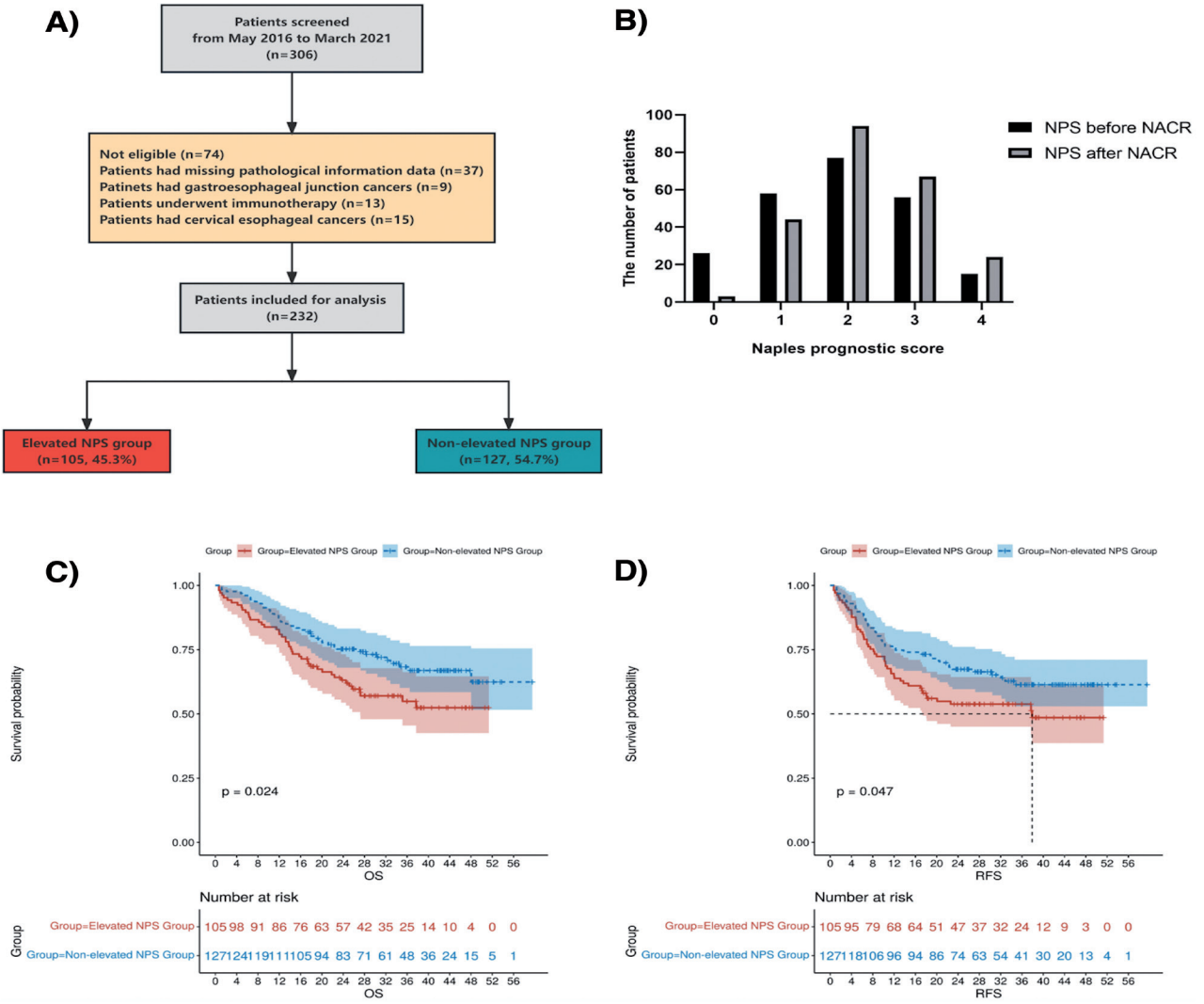


**Figure 1 -** (**A**) Flow diagram of the study. (**B**) The number of patients with different Naples prognostic scores (NPSs) before and after neoadjuvant chemoradiotherapy. (**C**) Kaplan–Meier curves for overall survival (**OS**) in the elevated NPS and non-elevated NPS groups. (**D**) Kaplan–Meier curves for recurrence-free survival (RFS) in the elevated NPS and non-elevated NPS groups.

**Table 1 -** The grading standard of the Naples prognostic score.

| Grade (Points) | Serum albumin (g/dL) | Total cholesterol (mg/dL) | NLR | LMR |
|---|---|---|---|---|
| 0 | ≥4.0 | >180 | ≤2.96 | >4.44 |
| 1 | <4.0 | ≤180 | >2.96 | ≤4.44 |

LMR: lymphocyte-to-monocyte ratio, NLR: neutrophil-to-lymphocyte ratio

modulated radiation therapy. Each patient received 2 cycles of cisplatin and paclitaxel. Furthermore, in addition to the 2 chemotherapy cycles, each patient underwent 23-28 fractions of radiation therapy, with doses ranging from 1.8-2.0 Gray per fraction, resulting in a cumulative radiation dose of 40-50.4 Gray.

The esophagectomy was planned to take place 8–10 weeks subsequent to the conclusion of NACR. The procedure involved employing the McKeown minimally invasive surgery technique, which entails 3 incisions made in the left neck, upper abdomen, and chest. Additionally, a 2-field lymphadenectomy was performed.

Nutrition was provided via total parenteral nutrition for the initial 5 days after surgery. On postoperative day (POD) 5, a chest radiograph was conducted to assess the patient's condition. Subsequently, oral intake of water was initiated provided there were no signs of anastomotic leakage detected during the examination. By POD 9, a systematic transition from a semi-liquid

to a soft dietary regimen was instituted. By POD 10, the patient experienced an uneventful recovery and was released from the hospital. Upon discharge on POD 21, the patient transitioned to a regular diet with complete oral feeding. Chest radiography was performed a month after surgery, guiding the administration of adjuvant treatment based on their post-operative pathology.

***Statistical analysis.*** The data analysis was conducted utilizing R (R Development Core Team), and the Statistical Package for the Social Sciences, version 27.0 (IBM Corp., Armonk, N.Y., USA). Variables underwent analysis utilizing either the Student's t-test or chi-square test. Cox regression analyses were employed to ascertain independent prognostic indicators for both OS and RFS. Continuous variables were presented as the median and standard deviation/interquartile range (IQR), whereas count data were typically represented as percentages and absolute numbers. $P<0.05$ was deemed significant.

**Results.** The study included 232 individuals, consisting of 105 individuals categorized in elevated NPS group and 127 in non-elevated NPS group. Table 2 outlines the patients' age, gender, tumor type, tumor location, tumor length, body mass index, ypTNM, pre-treatment clinical stage of the disease, tumor regression score, and pathologic complete response. A median tumor length of 3 cm was set as the

**Table 2 -** Baseline characteristics of the patients (N=232).

| Variables | Elevated NPS group (n=105) n (%) | Non-elevated NPS group (n=127) n (%) | *P*-value |
|---|---|---|---|
| Age (year), median (±SD) | 61.6 ± 7.5 | 62.1 ± 7.7 | 0.606 |
| BMI, median (±SD) | | | |
| Before NAT | 22.6 ± 3.2 | 22.3 ± 2.9 | 0.414 |
| Before surgery | 22.5 ± 3.3 | 22.5 ± 3.0 | 0.947 |
| ***Gender*** | | | 0.125 |
| Male | 84 (80.0) | 111 (87.4) | |
| Female | 21(20.0) | 16 (12.6) | |
| ***Tumor type*** | | | NA |
| SCC | 105 (100) | 127 (100) | |
| ***Tumor location*** | | | 0.458 |
| Upper | 12 (11.4) | 9 (7.1) | |
| Middle | 66 (62.9) | 80 (63.0) | |
| Lower | 27 (25.7) | 38 (29.9) | |
| ***Tumor length*** | | | 0.819 |
| >3 cm | 27 (25.7) | 31 (24.4) | |
| ≤3 cm | 78 (74.3) | 96 (75.6) | |
| ***ypTNM stage*** | | | 0.864 |
| I | 59 (56.2) | 68 (53.5) | |
| II | 12 (11.4) | 17 (13.4) | |
| III | 29 (27.6) | 38 (29.9) | |
| IV | 5 (4.8) | 4 (3.1) | |
| ***cTNM stage*** | | | 0.211 |
| II | 19 (18.1) | 13 (10.2) | |
| III | 66 (62.9) | 85 (66.9) | |
| IV | 20 (19.0) | 29 (22.8) | |
| ***Tumor regression score*** | | | 0.386 |
| 0 | 46 (43.8) | 53 (41.7) | |
| 1 | 12 (11.4) | 23 (18.1) | |
| 2 | 42 (40.0) | 42* (33.1) | |
| 3 | 5 (4.8) | 9 (7.1) | |
| pCR | 41 (39.0) | 50 (39.4) | 0.960 |
| Number of days in hospital, median (IQR), days | 15 (13-17) | 14 (13-15) | 0.671 |
| Time between NACR and surgery, median (IQR), days | 70 (63-81) | 68 (60-87) | 0.230 |

BMI: body mass index, IQR: interquartile range, LOS: length of stay, NAT: neoadjuvant therapy, pCR: pathological complete regression, SD: standard deviation, SCC: Squamous cell carcinoma

threshold. The statistical analysis revealed no notable variances in baseline characteristics between 2 groups.

***Survival analyses.*** Following a median follow-up duration of 25.17 months (IQR: 14.33–35.13) in the elevated NPS group and 30.43 months (IQR: 19.33–42.13) in the non-elevated NPS group, notable discrepancies in OS were noted between these cohorts ($p$=0.024), as depicted in **Figure 1C**. Patients in the non-elevated NPS group exhibited superior OS compared to those in the elevated NPS group. The cumulative rates of OS at 1 and 3 years were 81% (95% CI: 73.8–88.8%) and 54.9% (95% CI: 45.5–66.3%) in the elevated NPS group versus 87.4% (95% CI: 81.8–93.4%) and 66.9% (95% CI: 58.5–76.4%) in the non-elevated NPS group. Likewise, notable distinctions in RFS were noted between the elevated NPS and non-elevated NPS groups ($p$=0.047), as illustrated in **Figure 1D**. Patients within the non-elevated NPS group exhibited improved RFS compared to those within the elevated NPS group. The cumulative rates of RFS at 1 and 3 years were 63.8% (95% CI: 55.2–73.7%) and 51.3% (95% CI: 41.8–62.8%) in the elevated NPS group versus 74.8% (95% CI: 67.6–82.7%) and 61.4% (95% CI: 53.0–71.1%) in the non-elevated NPS group.

**Table 3 -** Univariate and multivariate analyses of clinicopathological factors linked to overall survival

| Variables | Univariate analysis | | Multivariate analysis | |
|---|---|---|---|---|
| | HR (95% CI) | *P*-value | HR (95% CI) | *P*-value |
| ***Change in NPS after NACR*** | | | | |
| Elevated NPS group versus non-elevated NPS group | 1.631(1.061-2.507) | 0.026 | 1.868 (1.063-2.646) | 0.036 |
| ***Pre-NACR NPS*** | | | | |
| ≥3 versus <3 | 0.940 (0.589-1.501) | 0.796 | | |
| ***Post-NACR NPS*** | | | | |
| ≥3 versus <3 | 1.750 (1.140-2.687) | 0.010 | 1.072 (0.622-1.848) | 0.803 |
| ***Pre-NACR serum albumin (g/dL)*** | | | | |
| <4 versus ≥4 | 1.088(0.658-1.797) | 0.742 | | |
| ***Pre-NACR total cholesterol (mg/dL)*** | | | | |
| ≤180 versus >180 | 1.010(0.657-1.533) | 0.963 | | |
| ***Pre-NACR NLR*** | | | | |
| >2.96 versus ≤2.96 | 0.806(0.505-1.287) | 0.366 | | |
| ***Pre-NACR LMR*** | | | | |
| ≤4.44 versus <4.44 | 1.057(0.639-1.746) | 0.830 | | |
| ***Post-NACR serum albumin (g/dL)*** | | | | |
| <4 versus ≥4 | 1.154(0.858-1.897) | 0.527 | | |
| ***Post-NACR total cholesterol (mg/dL)*** | | | | |
| ≤180 versus >180 | 1.284(0.837-1.804) | 0.253 | | |
| ***Post-NACR NLR*** | | | | |
| >2.96 versus ≤2.96 | 1.162(0.749-1.84) | 0.502 | | |
| ***Post-NACR LMR*** | | | | |
| ≤4.44 versus <4.44 | 0.541(0.171-1.715) | 0.497 | | |
| ***Age (year)*** | | | | |
| ≥60 versus <60 | 1.093 (0.700-1.708) | 0.696 | | |
| ***Gender*** | | | | |
| Male versus female | 1.962 (0.947-4.067) | 0.07 | | |
| ***Tumor length*** | | | | |
| >3 cm versus ≤3 cm | 1.861 (1.190-2.910) | 0.006 | 1.636 (1.013-2.641) | 0.044 |
| ***BMI (kg/m² )*** | | | | |
| Before NAT (≤22 versus >22) | 1.483 (0.966-2.277) | 0.072 | | |
| Before surgery (≤22 versus >22) | 1.439 (0.938-2.208) | 0.096 | | |
| ***Tumor location*** | | | | |
| Ut versus Mt/Lt | 1.034 (0.499-2.144) | 0.927 | | |
| ***ypTNM stage*** | | | | |
| III-IV versus I-II | 4.127 (2.666-6.391) | <0.001 | 3.89 (2.475-6.115) | <0.001 |
| ***cTNM stage*** | | | | |
| III-IV versus II | 1.010 (0.547-1.867) | 0.974 | | |

HR: hazard ratio, LMR: lymphocyte-to-monocyte ratio, NPS: naples prognostic score, NACR: neoadjuvant chemoradiotherapy, NLR: neutrophil-to-lymphocyte ratio, CI: confidence interval

***Cox regression analysis.*** The clinicopathological factors' correlations with OS and RFS were scrutinized to identify independent prognostic determinants. Within the univariate Cox regression model, 18 variables underwent evaluation. Univariate analyses of OS unveiled notable associations between OS and the change in NPS after NACR ($p$=0.026), Post-NACR therapy NPS ($p$=0.010), tumor length ($p$=0.006), as well as ypTNM stage ($p$<0.001). And these significant associations were subsequently integrated into the multivariate Cox regression analysis (**Table 3**). Correspondingly, univariate analyses of RFS exhibited significant associations between RFS and the change in NPS after NACR, tumor length, and ypTNM stage, warranting their inclusion in the multivariable Cox regression analysis (**Table 4**). The conclusive multivariable analysis confirmed that the change in NPS after NACR was a significant valuable indicator for OS (HR: 1.868, $p$=0.036) and RFS (HR: 1.709, $p$=0.029).

***Postoperative complications.*** The mortality and morbidity profiles following esophagectomy in the

**Table 4 -** Univariate and multivariate analyses of clinicopathological factors linked to recurrence-free survival

| Variables | Univariate analysis | | Multivariate analysis | |
|---|---|---|---|---|
| | HR (95% CI) | P-value | HR (95% CI) | *P* value |
| ***Change in NPS after NACR*** | | | | |
| Elevated NPS group versus non-elevated NPS group | 1.497 (1.002-2.235) | 0.049 | 1.709 (1.291-2.854) | 0.029 |
| ***Pre-NACR NPS*** | | | | |
| ≥3 versus <3 | 0.855 (0.548-1.334) | 0.490 | | |
| ***Post-NACR NPS*** | | | | |
| ≥3 versus <3 | 1.475 (0.986-2.205) | 0.058 | | |
| ***Pre-NACR serum albumin (g/dL)*** | | | | |
| <4 versus ≥4 | 1.121(0.702-1.792) | 0.632 | | |
| ***Pre-NACR total cholesterol (mg/dL)*** | | | | |
| ≤180 versus >180 | 0.980(0.656-1.464) | 0.920 | | |
| ***Pre-NACR NLR*** | | | | |
| >2.96 versus ≤2.96 | 0.892(0.579-1.374) | 0.605 | | |
| ***Pre-NACR LMR*** | | | | |
| ≤4.44 versus <4.44 | 0.932(0.587-1.479) | 0.764 | | |
| ***Post-NACR serum albumin (g/dL)*** | | | | |
| <4 versus ≥4 | 1.038(0.655-1.589) | 0.720 | | |
| ***Post-NACR total cholesterol (mg/dL)*** | | | | |
| ≤180 versus >180 | 1.055(0.707-1.575) | 0.793 | | |
| ***Post-NACR NLR*** | | | | |
| >2.96 versus ≤2.96 | 1.102(0.732-1.659) | 0.641 | | |
| ***Post-NACR LMR*** | | | | |
| ≤4.44 versus <4.44 | 0.615(0.195-1.943) | 0.408 | | |
| ***Age (year)*** | | | | |
| ≥60 versus >60 | 0.929 (0.616-1.402) | 0.726 | | |
| ***Gender*** | | | | |
| Male versus female | 1.582 (0.844-2.965) | 0.153 | | |
| ***Tumor length*** | | | | |
| >3 cm versus ≤3 cm | 2.016 (1.326-3.064) | 0.001 | 1.96 (1.247-3.08) | 0.004 |
| ***BMI (kg/m$^2$ )*** | | | | |
| Before NAT (≤22 versus >22) | 1.406 (0.941-2.099) | 0.096 | | |
| Before surgery (≤22 versus >22) | 1.452 (0.973-2.166) | 0.068 | | |
| ***Tumour location*** | | | | |
| Ut versus Mt/Lt | 1.052 (0.530-2.090) | 0.885 | | |
| ***ypTNM stage*** | | | | |
| III-IV versus I-II | 3.529 (2.351-5.298) | 0<0.001 | 3.361 (2.2-5.135) | <0.001 |
| ***cTNM stage*** | | | | |
| III-IV versus II | 1.200 (0.654-2.200) | 0.556 | | |

HR: hazard ratio, LMR: lymphocyte-to-monocyte ratio, NPS: naples prognostic score, NACR: neoadjuvant chemoradiotherapy, NLR: neutrophil-to-lymphocyte ratio

**Table 5 -** Morbidity and mortality in elevated Naples prognostic score (NPS) and non-elevated NPS groups.

| Variables | Elevated NPS group (n=105) n (%) | Non-elevated NPS group (n=127) n (%) | *P*-value |
|---|---|---|---|
| Anastomotic leakage | 8 (7.6) | 7 (5.5) | 0.516 |
| Anastomotic stricture (CD grade 2) | 6 (5.7) | 1 (0.8) | 0.029 |
| Vocal cord injury (CD type 1) | 9 (8.5) | 10 (7.8) | 0.811 |
| Pneumonia | 30 (28.6) | 34 (26.8) | 0.212 |
| Respiratory failure (CD grades 3–4) | 3 (2.9) | 3 (2.4) | 0.813 |
| Cardiac complications (CD grades 1–2) | 1 (1.0) | 3 (2.4) | 0.412 |
| ICU stay | 7 (6.7) | 6 (4.7) | 0.789 |
| ***Clavien–Dindo grade*** | | | |
| CD I–II | 17 (16.2) | 12 (9.5) | 0.122 |
| CD III–V | 10 (9.5) | 12 (9.5) | 0.985 |
| Postoperative LOS, median (IQR), days | 11 (9-13) | 10 (9-12) | 0.528 |
| 30-Day mortality | 3 (2.9) | 1 (0.8) | 0.228 |
| 30-Day readmissions | 2 (1.9) | 1 (0.8) | 0.528 |

CD: Clavien–Dindo classification system, ICU: intensive care unit, IQR: interquartile range, LOS: length of stay

groups with elevated and non-elevated NPS are detailed in Table 5. Comparisons between 2 groups revealed no statistically significant disparities across various parameters including respiratory failure, pneumonia, cardiac complications, vocal cord injury, anastomotic leakage, duration of intensive care unit stay, 30-day mortality, 30-day readmissions, Clavien-Dindo grade, and postoperative length of stay. However, anastomotic stricture manifested in 6 (5.7%) patients within the elevated NPS group compared to one (0.8%) patient in the non-elevated NPS group, signifying a noteworthy distinction ($p$=0.029).

**Discussion.** Previous studies have evidenced the association between patients' prognosis in various malignant tumors and their nutritional immune status alongside inflammatory response levels. Systemic inflammation, malnutrition, and immune system disorders have been linked to tumor cell angiogenesis, metastasis, proliferation, and resistance to anticancer therapies.[13,14] Within patients with ESCC, the absence of early-stage symptoms and limitations in diagnostic methods often result in pre-treatment malnutrition and immune system disorders, diminishing anti-inflammatory and anti-tumor effects.[15] Therefore, monitoring and evaluating the nutritional immune status and inflammatory response levels hold significant implications for treatment efficacy and prognosis in patients with ESCC. However, prevailing studies in ESCC primarily focus on individual nutritional or inflammatory indices' effects on prognosis, offering limited guidance to clinicians.[16,17] Establishing a reliable prognostic assessment approach that incorporates various factors is essential for more accurate prognostic insights.

Recent evidence has highlighted the NPS as a novel and reliable prognostic system reflecting inflammatory response levels and nutritional immune status in cancer patients.[9,18-20] Hypoalbuminemia within NPS indicates systemic inflammation, liver dysfunction, and malnutrition.[21] Additionally, hypocholesterolemia affects cell membrane fluidity, compromising immunocompetent cell function.[22] Furthermore, LMR and NLR, indicative of cancer-associated inflammation and cellular immune response levels, have been associated with cancer development and progression.[23] The NPS, initially proposed for colorectal cancer, has been validated across various cancers.[9,19,20,24,25] Within the realm of ESCC, a retrospective study carried out by Kano et al. revealed NPS as a crucial independent prognostic factor.[10] However, dynamic changes in immune-related and nutritional parameters during neoadjuvant therapy highlight the need to evaluate the prognostic value of NPS changes among ESCC patients undergoing treatment.[11,12] Therefore, we evaluated the prognostic value of NPS changes among ESCC patients enderwent NACR, aiming to complement the conventional NPS assessment at a single time point.

In this investigation, we assessed the prognostic implications and clinical relevance of alterations in the NPS subsequent to NACR within 232 locally advanced ESCC patients. Analysis of baseline characteristics between 2 cohorts revealed no statistically significant differences. Notably, anastomotic stricture (AS) emerged as a noteworthy post-esophagectomy complication that affects oral intake, increases the risk of aspiration pneumonia, and compromises patient well-being.[26] Previous research has highlighted the importance of maintaining optimal blood supply to the proximal end of the gastric conduit and ensuring

an adequate anastomosis size to reduce AS risk.[27] Our study identified a significant association between elevated NPS after NACR and AS incidence ($p$=0.029). This finding suggests that an elevated NPS after NACR might serve as an indicator necessitating prophylactic measures against AS. Additionally, an elevated NPS after NACR could aid in early AS detection, enabling timely interventions that might improve esophagectomy outcomes.

Regarding long-term survival outcomes, survival analyses demonstrated poorer OS and RFS in the elevated NPS group compared to non-elevated NPS group. The cumulative rates of OS at 1 and 3 years were 81.0% and 54.9% in the elevated NPS group versus 87.4% and 66.9% in the non-elevated NPS group. Furthermore, the cumulative rates of RFS at 1 and 3 years were 63.8% and 51.3% in the elevated NPS group versus 74.8% and 61.4% in the non-elevated NPS group. Further Cox regression analyses highlighted the change in NPS after NACR as a significant independent risk indicator for RFS and OS. Therefore, an elevated NPS after NACR might serve as a valuable indicator for considering more active immunonutritional interventions.

Overall, our study demonstrated that NPS changes after NACR constitute a valuable prognostic indicator in ESCC patients. The increased NPS after NACR might predict an unfavorable prognosis. Given that neoadjuvant therapy followed by esophagectomy continues to be the routine protocol for ESCC patients (radiotherapy, chemotherapy, or their combination before surgery), monitoring and evaluating NPS changes after NACR could aid in identifying high-risk patients and making individualized therapeutic decisions in clinical practice.

The study's primary strength lies in pioneering the suggestion to monitor and evaluate NPS changes after NACR in patients with ESCC, offering significant potential in identifying high-risk individuals who have undergone NACR and tailoring subsequent therapeutic approaches in clinical practice. Furthermore, exploring the value of this novel and promising independent prognostic indicator in other cancer patients undergone NACR holds promise for future investigations.

***Study limitations.*** This study presents several limitations. Primarily, its retrospective nature constitutes a limitation. Additionally, the absence of an external validation cohort restricts the generalizability of the findings. Furthermore, it is imperative to exercise prudence concerning the utilization of NPS predicated on these variables, owing to plausible influences on serum markers like TC, LMR, NLR, and ALB induced by diverse conditions.

In conclusion, our results suggest that an elevated NPS following NACR functions as a significant indicator of worse prognosis in locally advanced ESCC patients. This discovery holds significant promise for identifying high-risk ESCC patients who have undergone NACR and for tailoring personalized therapeutic interventions in clinical settings.

**Acknowledgment.** *We thank Bullet Edits Limited for the linguistic editing and proofreading of the manuscript.*

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