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ORIGINAL ARTICLE – THORACIC ONCOLOGY

The Influence of the Perioperative Nutritional Status on the Survival Outcomes for Esophageal Cancer Patients with Neoadjuvant Chemotherapy

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ABSTRACT

Background. Studies have shown a variety of nutritional indices to be prognostic predictors for esophageal cancer patients. However, which nutritional index should be used and when it should be measured during the perioperative period remain unclear. This study attempted to clarify the details surrounding predictive nutritional evaluation by assessing the longitudinal data of serologic indices in perioperative esophageal cancer patients.

Methods. The study included 141 esophageal cancer patients who underwent neoadjuvant chemotherapy after radical esophagectomy at Tohoku University Hospital from April 2008 to December 2017. The nutritional status was retrospectively assessed during the perioperative period, and the prognostic factors related to survival were analyzed.

Results. Use of the controlling nutritional status (CONUT) score showed that malnutrition occurred only from 14 days after surgery in most cases. Use of the prognostic nutritional index (PNI) showed that the ratio of malnutrition increased gradually from presurgery to 14 days after surgery. The timing of malnutrition that affected survival was 14 days after surgery with the CONUT score and presurgery and 4 months after surgery with the PNI. A multivariable analysis of independent prognostic factors predicting survival identified malnutrition 14 days after surgery with the CONUT score and a low PNI before surgery, invasion depth of the primary lesion, and node metastasis.

Conclusions. Malnutrition occurring during the perioperative state of esophageal cancer was shown to be a survival prognostic factor. Development of an optimal nutritional intervention is recommended for esophageal cancer patients to prevent malnutrition both before and after surgery.

Nutritional management is an important task that can determine the success or failure of treatment for cancer.[1] The mainstay of treatment for resectable esophageal cancer is radical resection with neoadjuvant therapy, which is regarded as a standard course.[2,3] A number of risk factors can make nutrition maintenance difficult in esophageal cancer treatment, including tract obstruction,[4] dyscrasia,[5] gastrointestinal adverse events induced by neoadjuvant therapy,[6] and dysfunction of the digestive organ after surgery.[7]

In recent years, studies have shown several nutritional indices conveniently calculated from peripheral blood data such as the controlling nutritional status (CONUT) score[8] and the prognostic nutritional index (PNI)[9] to be prognostic predictors for either the safety or efficacy of perioperative management of upper gastrointestinal cancers.[10–14] However, previous studies have neglected to examine which assessment is the most relevant to the survival outcome. In addition, when the nutritional index should be measured in the perioperative period remains unclear. The current study

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therefore attempted to clarify the details surrounding predictive nutritional evaluation by assessing the longitudinal data of these serologic indices in perioperative esophageal cancer patients.

METHODS

The participants in this study were 154 consecutive esophageal cancer patients who underwent neoadjuvant chemotherapy (NAC) consisting of intravenous cisplatin and 5-fluorouracil after radical esophagectomy at a single institution (Department of Surgery, Tohoku University Hospital) from April 2008 to December 2017. We retrospectively collected the clinical, surgical, and pathologic data of patients from our prospective database together with the medical records for each patient. We excluded 13 patients as follows: 4 patients who received chemotherapy other than the 5-fluorouracil plus cisplatin regimen, 1 patient with systemic metastasis from breast cancer, 1 patient with a history of total gastrectomy for gastric cancer, 6 patients who received palliative esophagectomy defined as R1 or R2 resection, and 1 patient who died by suicide within 4 months after surgery. Accordingly, 141 patients were eligible and analyzed retrospectively (Fig. 1).

The Institutional Review Board of Tohoku University Hospital approved the current study. Written informed consent was obtained from all the patients.

Treatment Strategy

The patients underwent all necessary routine investigations for esophageal surgery according to the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology: Esophageal and Esophagogastric Junction Cancers,[15] which consisted of a medical interview; physical examinations; upper gastrointestinal endoscopy and biopsy; computed tomography (CT) of the chest, abdomen, and pelvis; positron emission tomography-CT; blood testing; endoscopic ultrasonography; and bronchoscopy based on their cancer stage.

For the patients with node-negative cT1 tumors, we performed esophagectomy without neoadjuvant treatment. For the remaining patients with advanced cancer, we administered neoadjuvant chemotherapy comprising two cycles of intravenous cisplatin and 5-fluorouracil in addition to esophagectomy.[2] The patients with distant metastasis were excluded from surgical application, although the patients with only supraclavicular lymph node metastasis were included.

In the current study, the pretreatment tumor stage was classified according to the Union for International Cancer Control TNM Staging, Version 8.[16]

Surgical Procedure

The operations consisted of three stages: thoracoscopic esophageal mobilization with radical mediastinal lymphadenectomy, laparoscopic or open gastric mobilization, and cervical esophagogastrostomy or esophagoileostomy. All the patients underwent thoracoscopic esophagectomy in either the left lateral decubitus position or the prone position.[17,18] The thoracic nodes including the paraesophageal nodes, bilateral recurrent laryngeal nerve (RLN) nodes, subcarinal nodes, and bilateral pulmonary hilar

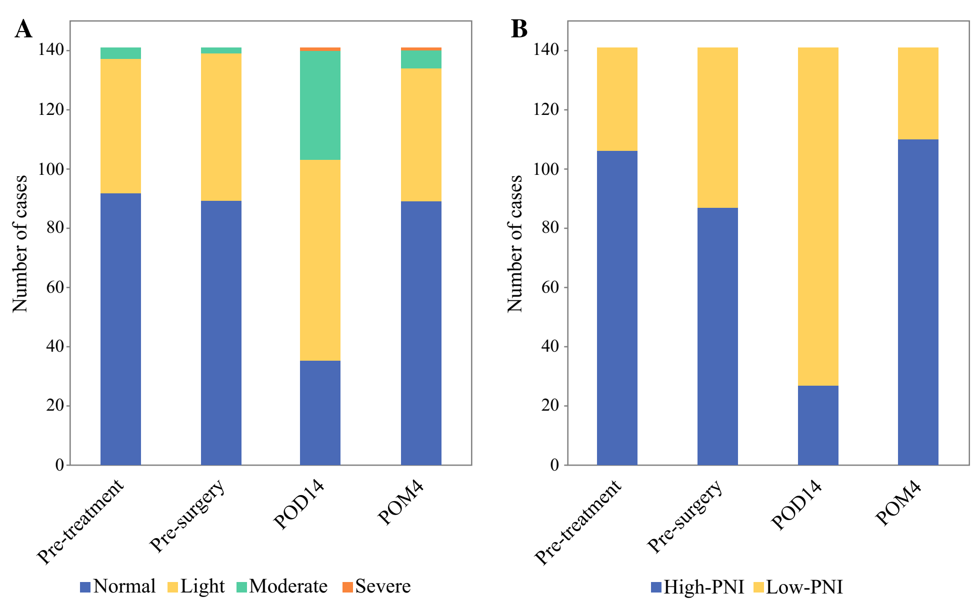

FIG. 1 Longitudinal data of the nutritional score before treatment, before surgery, 14 days after surgery, and 4 months after surgery. **a** Controlling Nutrition Status (CONUT) score, **b** Prognostic nutritional index (PNI). POD14, postoperative 14 days; POM4, postoperative 4 months

TABLE 1 Patient characteristics

Variables		Patients (n = 141)
Sex	Male/female	116/25
Age	Years (range)	67 (47–84)
Pretreatment BMI (kg/m^2)	< 18.5/18.5–25/> 25	14/103/24
Brinkman Index	0–399/400–799/≥ 800	38/44/59
ECOG-PS	0/1:2	82/55/4
Respiratory impairment	Yes/no	45/96
NAC		
Response	PR/SD/PD	65/68/8
Adverse event (CTCAE)		
Myelosuppression	≤G1/G2/G3/G4	53/46/38/4
Renal impairment	≤G1/G2	130/11
Gastrointestinal damage	≤G2/G3	110/31
Clinical T	T1/T2/T3/T4	21/27/92/1
Clinical N	N0/N1/N2/N3	17/82/41/1
Clinical stage	1/2/3/4	17/35/78/11
Surgery		
Position of thoracic operation	Left decubitus/prone	57/84
Conduit	Stomach/colon	140/1
Reconstruction route	Posterior mediastinal/retrosternal/ante-thoracic	133/3/5
Operative time	Min (range)	619 (363–895)
EBL	ml (range)	240 (26–7035)
Morbidity (CDc)		
Respiratory morbidity	≤ 1/2/≥ 3	89/38/14
RLNP	≤ 1/2/≥ 3	119/18/4
Anastomotic leakage	≤ 1/2/≥ 3	124/12/5
Any morbidity (worst)	≤ 1/2/≥ 3	63/55/23
Reoperation	Yes/no	7/134
Pathologic T	T0/T1/T2/T3/T4	5/44/24/63/5
Pathological N	N0/N1/N2/N3	60/45/27/9
Pathologic stage	0/1/2/3/4	5/22/45/52/17

Data are expressed as the number of cases or median number (range)

BMI, body mass index; ECOG-PS, Eastern Cooperative Oncology Group Performance Status; NAC, neoadjuvant chemotherapy; CTCAE, Common Terminology Criteria for Adverse Events; EBL, estimated blood loss; CDc, Clavien–Dindo classification; RLNP, recurrent laryngeal nerve palsy

nodes were dissected in all cases. Through an upper midline laparotomy or laparoscopic procedure, the paracardiac nodes, celiac nodes, and nodes along the left gastric artery were dissected, and the stomach tube was made. All anastomoses were performed cervically. Through a horizontal neck incision, the bilateral RLNs were identified in order to remove the cervical paraesophageal nodes. Supraclavicular lymphadenectomy was routinely performed for upper esophageal tumors. The gastric conduit usually was pulled through the posterior mediastinum for subsequent hand-sewn anastomosis. A jejunostomy tube also was routinely placed.

Definition of Outcomes

The clinicopathologic, surgical, and pathologic findings were collected from a prospectively maintained database, as well as from individual patient medical records when necessary. The clinical response to chemotherapy was categorized based on the Response Evaluation Criteria in Solid Tumors guidelines and the criteria of the Japanese Society for Esophageal Diseases.[19] Adverse events were evaluated each day of chemotherapy and scored by the most severe event based on the toxicity grading criteria from the Common Terminology Criteria for Adverse

Events (CTCAE) Version 4.0 by each primary physician.[20] Complications were graded according to the Clavien–Dindo classification (CDc) system.[21] Postoperative complications in this study were defined as any adverse event occurring within 30 days after esophagectomy.

Follow-up visits were scheduled according to our protocol. In brief, patients were required to attend an outpatient clinic every 4 months for 2 years, then every 6 months thereafter for up to 5 years. The follow-up data were updated in January 2019.

Nutrition Assessment

With the data from blood tests, assessment of nutritional status was performed according to both the CONUT score and the PNI in all cases. These scores were calculated after each of four examinations: before treatment, before surgery, 14 days after surgery, and 4 months after surgery.

For the CONUT score, the serum albumin level, total lymphocyte count, and cholesterol level were classified and scored according to their values. The total score of the three parameters was categorized as normal, light malnutrition, moderate malnutrition, or severe malnutrition and applied to subsequent analyses (Table S1).[8]

The PNI was calculated as follows:

$$10 \times \text{serum albumin}(\text{g/dl}) + 0.005 \times \text{total lymphocyte count}\left(/\text{mm}^3\right).$$

.

The cutoff value of the PNI was set at 45 because a PNI lower than 45 was defined as moderate to severe malnutrition.[9]

Statistical Analyses

All continuous variables are presented as median (range). Survival curves were estimated by the Kaplan–Meier method, and the log-rank test was used to assess differences. Uni- and multivariable analyses of prognostic factors related to survival were performed using the Cox proportional hazards model.

All P values lower than 0.05 were considered statistically significant. All statistical analyses were performed using the JMP software program (version 11; SAS Institute, Cary, NC, USA).

RESULTS

The patient characteristics are summarized in Table 1. The patient cohort included 116 male patients (82.3%) with a mean age of 67 years (range, 47–84 years). Grade 3 adverse events from the NAC were observed in 59 patients (41.8%). Left decubitus thoracoscopic esophagectomy was performed for 57 patients and prone esophagectomy for 84 patients. The median operative time was 619 min (range, 363–895 min), and the median estimated blood loss was 240 ml (range, 26–7035 ml). Grade 3 or greater postoperative complications occurred for 23 of the patients (16.3%). The mortality rate was 0% in the study cohort. The pathologic stage was 0 for 5 patients (3.5%), 1 for 22 patients (15.6%), 2 for 45 patients (31.9%), 3 for 52 patients (36.9%), and 4 for 17 patients (12.1%).

Figure 1 shows the longitudinal data of the nutritional score before treatment, before surgery, 14 days after surgery, and 4 months after surgery. According to the malnutrition degree based on the CONUT score, the numbers of patients assigned to the moderate and severe malnutrition groups were respectively 4, 2, 38, and 7 (Fig. 1a). For the PNI score, the numbers of patients assigned to the low PNI group were respectively 35, 54, 114, and 31 (Fig. 1b).

Figure 2 shows the Kaplan–Meier curves for overall survival (OS) and relapse-free survival (RFS) according to the nutrition score-based malnutrition groups. According to the CONUT score, the OS and RFS were significantly reduced for the patients with moderate or severe malnutrition only 14 days after surgery versus patients with normal or light malnutrition (Fig. 2a, $P < 0.001$; Fig. 2b, $P < 0.001$). According to the PNI score, the RFS was significantly reduced for the patients with a low PNI before surgery and 4 months after surgery (Fig. 2c, $P = 0.013$; Fig. 2d, $P = 0.007$), although the OS was not reduced at these points (Fig. S1A, $P = 0.066$; Fig. S1B, $P = 0.069$). Furthermore, malnutrition 14 days after surgery according to the CONUT score significantly reduced the OS irrespective of the nutritional score before treatment (Fig. 3a, $P = 0.004$; Fig. 3b, $P = 0.004$), but not in the malnutrition cases before surgery (Fig. 3c, $P < 0.001$; Fig. 3d, $P = 0.177$).

The multivariable analysis showed that moderate or severe malnutrition 14 days after surgery according to the CONUT score ($P = 0.005$) and node metastasis ($P < 0.001$) were independent prognostic factors for OS (Table 2), and that moderate or severe malnutrition 14 days after surgery according to the CONUT score ($P = 0.044$), a low PNI before surgery ($P = 0.043$), invasion depth of the primary lesion ($P = 0.004$), and node metastasis ($P = 0.001$) were independent prognostic factors for RFS (Table 3). The adjusted OS curves for the pathologic node status also showed a poor survival for the malnutrition patients according to the CONUT score 14 days after surgery (Fig. 2e, $P = 0.027$; Fig. 2f, $P = 0.006$).

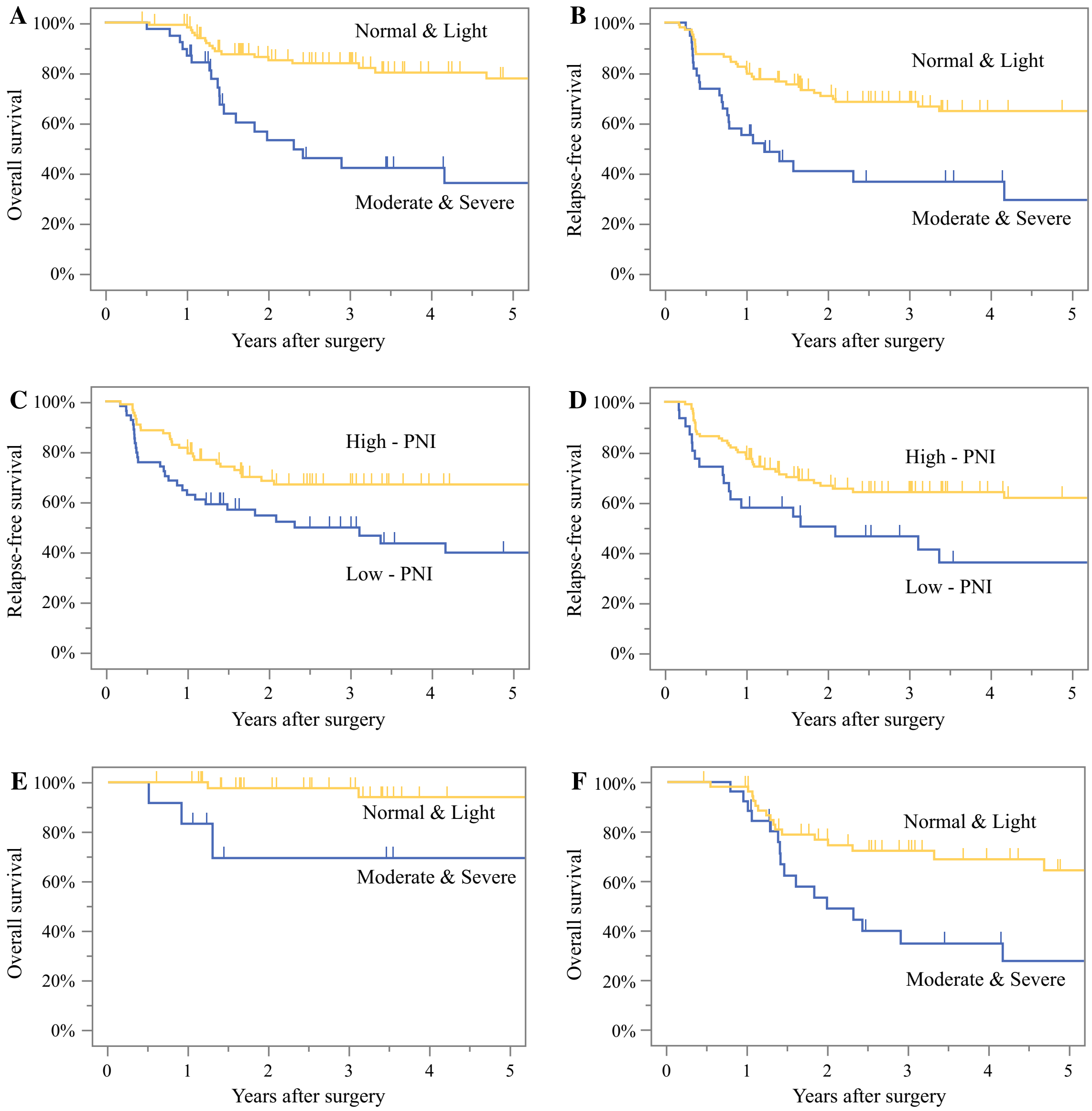

FIG. 2 Survival curves according to the nutrition score-based malnutrition groups derived using the Kaplan–Meier method. **a** Overall survival (OS) according to the Controlling Nutrition Status (CONUT) score 14 days after surgery. **b** Relapse-free survival (RFS) according to the CONUT score 14 days after surgery. **c** Recurrence-free survival (RFS) according to the Prognostic Nutritional Index (PNI) before surgery. **d** The RFS according to the PNI 4 months after surgery. **e** The OS of the pathologic node-negative group according to the CONUT score 14 days after surgery. **f** The OS of the pathologic node-positive group according to the CONUT score 14 days after surgery

DISCUSSION

In this study, malnutrition was shown to be an independent prognostic factor in the perioperative treatment of esophageal cancer patients. Interestingly, the multivariable analysis identified malnutrition at different time points as an independent prognostic factor in both nutrition indices. To our knowledge, this is the first study to provide evidence that malnutrition occurring at different time points in the perioperative period is a critical factor for the prognosis of esophageal cancer patients.

With the CONUT score, the proportion of malnutrition was unchanged from pretreatment to presurgery or 4 months after surgery, but a large proportion of moderate or severe malnutrition was noted 14 days after surgery. With the PNI, the ratio of malnutrition was the same between pretreatment and 4 months after surgery, but the ratio of malnutrition increased gradually from presurgery to 14 days after surgery. The timing of malnutrition that affected survival was 14 days after surgery with the CONUT score and presurgery or 4 months after surgery with the PNI. The CONUT score has four values,[8] whereas

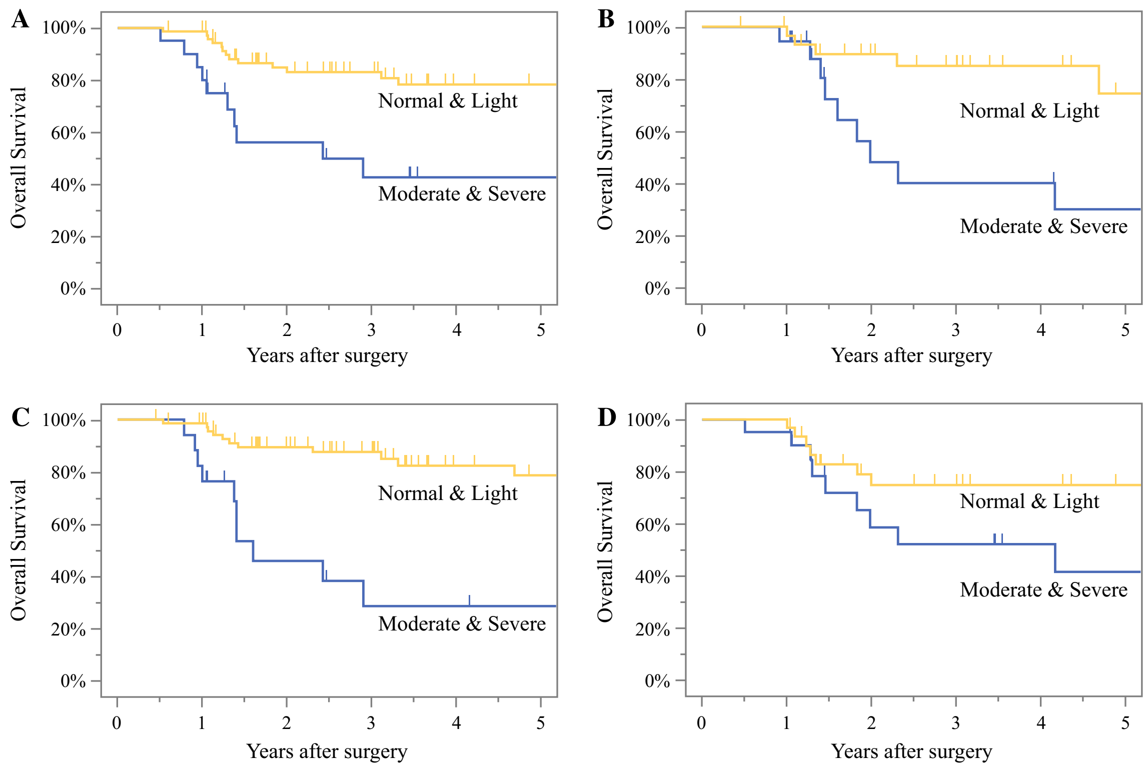

FIG. 3 Overall survival curves according to the Controlling Nutrition Status (CONUT) score 14 days after surgery derived using the Kaplan–Meier method by the nutritional status based on the CONUT score before treatment or before surgery. **a** Group with normal nutrition before treatment. **b** Group with any malnutrition before treatment. **c** Group with normal nutrition before surgery. **d** Group with any malnutrition before surgery

the PNI has two values.[9] The total cholesterol level is included only in the CONUT score. Cholesterol reportedly reflects not only nutritional status but also cancer malignancy[22,23] and surgical stress.[24]

In the current study cohort 14 days after surgery, the number of patients assigned to the moderate or severe malnutrition group according to the CONUT score was 38 (27%), whereas 114 patients (80.9%) were assigned to the low-PNI group. Regarding the cholesterol level, a total of 34 hypocholesterolemia patients (< 180 mg/dL) (89.5%) were in the moderate or severe malnutrition group according to the CONUT score, but only 44 (38.6%) were assigned to the low-PNI group (data not shown). Thus, the CONUT score might have high sensitivity for detecting hypocholesterolemia patients. Therefore, 14 days after surgery, when the ratio of malnutrition markedly increases, the CONUT score might more accurately predict prognosis than the PNI. At other times, when the proportion of malnutrition is relatively small, the PNI might be more convenient and useful. For proper assessment of the ever-changing nutritional status in the perioperative period, use of both indices according to the situation might be the most efficient and effective approach.

The nutritional status was shown to be an independent predictor of survival, such as the OS and RFS, and nutritional management was found to be important for cancer treatment. Because findings also have shown oncologic factors to be risk factors, we thought this analysis result was valid.

Survival after esophageal cancer surgery reportedly worsens with postoperative respiratory complications.[25,26] An inflammatory response, which suppresses the immune response, can be caused by postoperative pneumonia. On the other hand, Kanekiyo et al.[27] showed that perioperative immunonutrition, reported to have a pharmacologic effect on the immune system, improved the early postoperative nutritional status and reduced the risk of postoperative pneumonia in esophageal cancer patients. Whereas the incidence of postoperative complications was not shown to be an independent prognostic factor for a survival outcome in this study, respiratory complications were shown to have a significant correlation with malnutrition 14 days after surgery, which our survival analyses identified as an important time point (Table S2). Okadome et al.[14] hypothesized a relationship between nutritional status and local immune competence with the PNI and immunohistologic features in esophageal cancer patients. The way that

TABLE 2 Uni- and multivariable analyses for overall survival by the Cox proportional hazards model

Variable		Univariable analysis			Multivariable analysis		
		HR	95% CI	*P* value	HR	95% CI	*P* value
A CONUT							
CONUT	Malnutrition (moderate or severe)						
Pretreatment		1.165	0.066–5.388	0.883			
Presurgery		1.969	0.111–9.133	0.547			
POD14		3.316	1.800–6.058	< 0.001	2.484	1.327–4.620	0.005
POM4		2.006	0.687–4.674	0.183			
BMI (kg/m^2)	< 18.5						
Pretreatment		1.222	0.420–2.829	0.682			
Presurgery		1.682	0.726–3.439	0.209			
POM4		1.647	0.868–3.021	0.123			
Gender	Male	1.117	0.508–2.947	0.799			
Age (years)	≥ 75	0.746	0.180–2.066	0.611			
ECOG-PS score	≥ 2	< 0.001	1.736–1.736	0.135			
Respiratory impairment	Yes	1.790	0.968–3.263	0.063			
Operative time (h)	≥ 10	1.523	0.825–2.905	0.180			
EBL (ml)	≥ 400	2.119	1.128–3.875	0.020	1.406	0.726–2.663	0.305
Morbidity	CDc						
Respiratory (grade)	≥ Grade 2	1.397	0.769–2.540	0.272			
RLNP (grade)	≥ 2	1.758	0.791–3.521	0.156			
Anastomotic leakage (grade)	≥ 2	1.913	0.714–4.324	0.181			
Any morbidity (worst) (grade)	≥ 2	1.765	0.960–3.384	0.068			
Pathologic T	≥ pT2	2.362	1.185–5.236	0.013	1.743	0.847–3.955	0.136
Pathologic N	≥ pN1	3.837	1.876–8.903	< 0.001	2.896	1.394–6.796	< 0.001
B PNI							
PNI	< 45						
Pretreatment		1.249	0.601–2.401	0.532			
Presurgery		1.744	0.955–3.194	0.070			
POD14		1.836	0.835–4.846	0.139			
POM4		1.789	0.920–3.312	0.084			

HR, hazard ratio; 95% CI, 95% confidence interval; CONUT, Controlling Nutrition Status; POD14, postoperative 14 days; POM4, postoperative 4 months; BMI, body mass index; ECOG-PS, Eastern Cooperative Oncology Group Performance Status; CDc, Clavien–Dindo classification; RLNP, recurrent laryngeal nerve palsy; PNI, Prognostic Nutritional Index

malnutrition exerts a significant negative impact on prognosis is poorly understood, but nutritional status is suspected to affect systemic immune competence and consequently interfere with the oncologic circumstances.

We selected the CONUT score and the PNI as the nutritional indices in this study due to their convenience because they can be calculated using only peripheral blood data and have acceptable individual variability regardless of the patient physique.[11,14] Many parameters, such as the blood albumin level,[28,29] body mass index,[30–32] and sarcopenia,[33–36] are reported to be reliable nutrition indices related to the outcome of cancer treatment. However, although these factors should definitely be integrated into the nutritional assessment tool for esophageal cancer patients, robust evidence needs to be accumulated regarding both surgical outcomes and long-term survival.

Our finding that nutritional status is related to survival outcome strongly suggests the need for nutritional intervention during the perioperative management of esophageal cancer. Pretreatment malnutrition was not shown to be an independent prognostic factor, but malnutrition at both time points after preoperative chemotherapy (in the early and later postoperative periods) was found to be associated with survival. Furthermore, patients with any degree of malnutrition before surgery could not have achieved a significantly better survival outcome even if

TABLE 3 Uni- and multivariable analyses for the relapse-free survival by the Cox proportional hazards model

Variable		Univariable analysis			Multivariable analysis		
		HR	95% CI	*P* value	HR	95% CI	*P* value
A CONUT							
CONUT	Malnutrition (moderate or severe)						
Pretreatment		0.625	0.035–2.838	0.614			
Presurgery		1.246	0.070–5.680	0.833			
POD14		2.121	1.230–3.589	0.008	2.025	1.200–3.418	0.008
POM4		1.521	0.524–3.492	0.403			
BMI (kg/m^2)	< 18.5						
Pretreatment		1.286	0.533–2.624	0.545			
Presurgery		1.229	0.565–2.374	0.578			
POM4		1.226	0.697–2.075	0.467			
Gender	Male	1.221	0.632–2.654	0.572			
Age (years)	≥ 75	0.578	0.175–1.409	0.252			
ECOG-PS score	≥ 2	0.598	0.034–2.720	0.579			
Respiratory impairment	Yes	1.340	0.784–2.242	0.279			
Operative time (h)	≥ 10	1.361	0.815–2.324	0.242			
EBL (ml)	≥ 400	1.621	0.930–2.732	0.087			
Morbidity (grade)	≥ CDc 2						
Respiratory		1.051	0.628–1.761	0.849			
RLNP		1.438	0.709–2.663	0.296			
Anastomotic leakage		1.192	0.492–2.466	0.672			
Any morbidity (worst)		1.312	0.793–2.206	0.292			
Pathologic T	≥ pT2	2.615	1.462–5.030	0.001	2.140	1.155–3.968	0.016
Pathologic N	≥ pN1	3.146	1.780–5.934	< 0.001	2.542	1.387–4.657	0.003
B PNI							
PNI	< 45						
Pretreatment		1.473	0.830–2.510	0.180			
Presurgery		1.868	1.126–3.094	0.016	1.862	1.112–3.118	0.018
POD14		1.490	0.790–3.119	0.229			
POM4		2.048	1.177–3.446	0.012	1.628	0.938–2.826	0.083
Pathologic T	≥ pT2	2.615	1.462–5.030	0.001	2.509	1.349–4.665	0.004
Pathologic N	≥ pN1	3.146	1.780–5.934	< 0.001	2.715	1.488–4.955	0.001

HR, hazard ratio; 95% CI, 95% confidence interval; CONUT, Controlling Nutrition Status; POD14, postoperative 14 days; POM4, postoperative 4 months; BMI, body mass index; ECOG-PS, Eastern Cooperative Oncology Group Performance Status; EBL, estimated blood loss; CDc, Clavien–Dindo classification; RLNP, recurrent laryngeal nerve palsy; PNI, Prognostic Nutritional Index

they had improved their nutritional status 14 days after surgery. Therefore, malnutrition accompanying preoperative chemotherapy and surgery was shown to be a risk factor for survival.

Reported measures against malnutrition caused by perioperative cancer treatment include nutrition management during neoadjuvant therapy[37] and enhanced recovery programs for early after-surgery care.[38] The current results suggest that these efforts have the effect of improving survival. Further efforts should be made to develop nutritional intervention methods suitable for preventing the onset of malnutrition throughout perioperative treatment.

Several limitations associated with the current study warrant mention. First, this was a retrospective study conducted at a single institution, although the oncologic factors, which are robust predictive indicators for the prognosis, were not identified as independent factors associated with malnutrition (Tables S2 and S3). Second, our study lacked an evaluation of perioperative quality of life due to the difficulty of establishing a fixed methodology.

CONCLUSIONS

Malnutrition occurring during the perioperative state of esophageal cancer was shown to be a survival prognostic factor using two types of nutritional indices calculated from peripheral blood data. Development of an optimal nutritional intervention is recommended for esophageal cancer patients to prevent malnutrition both before and after surgery.

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DISCLOSURE There are no conflicts of interest.

REFERENCES

1. Arends J, Baracos V, Bertz H, et al. ESPEN expert group recommendations for action against cancer-related malnutrition. *Clin Nutr.* 2017;36:1187–96.
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. Gebski V, Burmeister B, Smithers BM, Foo K, Zalcberg J, Simes J. Australasian Gastro-Intestinal Trials Group. Survival benefits from neoadjuvant chemoradiotherapy or chemotherapy in oesophageal carcinoma: a meta-analysis. *Lancet Oncol.* 2007;8:226–34.
4. Nagaraja V, Cox MR, Eslick GD. Safety and efficacy of esophageal stents preceding or during neoadjuvant chemotherapy for esophageal cancer: a systematic review and meta-analysis. *J Gastrointest Oncol.* 2014;5:119–26.
5. Weimann A, Braga M, Carli F, et al. ESPEN guideline: clinical nutrition in surgery. *Clin Nutr.* 2017;36:623–50.
6. Capra S, Ferguson M, Ried K. Cancer: impact of nutrition intervention outcome: nutrition issues for patients. *Nutrition.* 2001;17:769–72.
7. Lanuti M, DeDelva P, Morse CR, et al. Management of delayed gastric emptying after esophagectomy with endoscopic balloon dilatation of the pylorus. *Ann Thorac Surg.* 2011;91:1019–24.
8. Ignacio de Ulíbarri J, González-Madroño A, de Villar NG, et al. CONUT: a tool for controlling nutritional status: first validation in a hospital population. *Nutr Hosp.* 2005;20:38–45.
9. Onodera T, Goseki N, Kosakim G. Prognostic nutritional index in gastrointestinal surgery of malnourished cancer patients. *Nihon Geka Zasshi.* 1984;85:1001–5.
10. Yoshida N, Baba Y, Shigaki H, et al. Preoperative nutritional assessment by controlling nutritional status (CONUT) is useful to estimate postoperative morbidity after esophagectomy for esophageal cancer. *World J Surg.* 2016;40:1910–7.
11. Yoshida N, Harada K, Baba Y, et al. Preoperative controlling nutritional status (CONUT) is useful to estimate the prognosis after esophagectomy for esophageal cancer. *Langenbecks Arch Surg.* 2017;402:333–41.
12. Nakatani M, Migita K, Matsumoto S, et al. Prognostic significance of the prognostic nutritional index in esophageal cancer patients undergoing neoadjuvant chemotherapy. *Dis Esophagus.* 2017;30:1–7.
13. Matsumoto H, Okamoto Y, Kawai A, et al. Prognosis prediction for postoperative esophageal cancer patients using Onodera's Prognostic Nutritional Index. *Nutr Cancer.* 2017;69:849–54.
14. Okadome K, Baba Y, Yagi T, et al. Prognostic nutritional index, tumor-infiltrating lymphocytes, and prognosis in patients with esophageal cancer. *Ann Surg.* 2018. https://doi.org/10.1097/SLA.0000000000002985.
15. NCCN guidelines: esophageal and esophagogastric junction cancers. Retrieved 23 Jan 2019 at http://www.nccn.org/professionals/physician_gls/f_guidelines.asp#site.
16. Brierley JD, Gospodarowicz MK, Wittekind C. *TNM classification of malignant tumours.* 8th ed. Wiley, Oxford; 2017.
17. Ichikawa H, Miyata G, Miyazaki S, et al. Esophagectomy using a thoracoscopic approach with an open laparotomic or hand-assisted laparoscopic abdominal stage for esophageal cancer: analysis of survival and prognostic factors in 315 patients. *Ann Surg.* 2013;257:873–85.
18. Teshima J, Miyata G, Kamei T, et al. Comparison of short-term outcomes between prone and lateral decubitus positions for thoracoscopic esophagectomy. *Surg Endosc.* 2015;29:2756–62.
19. Japan Esophageal Society. Japanese Classification of Esophageal Cancer, 11th edition: parts II and III. *Esophagus.* 2017;14:37–65.
20. National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE), version 4.0. U.S. Department of Health and Human Services, National Institutes of Health, Bethesda, MD, 2010. Retrieved 23 Jan 2019 at https://cabig-kc.nci.nih.gov/Vocab/KC/index.php/CTCAE.
21. Clavien PA, Barkun J, de Oliveira ML, et al. The Clavien–Dindo classification of surgical complications: five-year experience. *Ann Surg.* 2009;250:187–96.
22. Chen P, Han L, Wang C, et al. Preoperative serum lipids as prognostic predictors in esophageal squamous cell carcinoma patients with esophagectomy. *Oncotarget.* 2017;8:41605–19.
23. Lee H, Jeong CW, Kwak C, et al. Preoperative cholesterol level is associated with worse pathological outcomes and postoperative survival in localized renal cell carcinoma patients: a propensity score-matched study. *Clin Genitourin Cancer.* 2017;15:e935–41.
24. Lee SH, Lee JY, Hong TH, Kim BO, Lee YJ, Lee JG. Severe persistent hypocholesterolemia after emergency gastrointestinal surgery predicts in-hospital mortality in critically ill patients with diffuse peritonitis. *PLoS ONE.* 2018;13:e0200187.
25. Baba Y, Yoshida N, Shigaki H, et al. Prognostic impact of postoperative complications in 502 patients with surgically resected esophageal squamous cell carcinoma: a retrospective single-institution study. *Ann Surg.* 2016;264:305–11.
26. Goense L, Meziani J, Ruurda JP, van Hillegersberg R. Impact of postoperative complications on outcomes after oesophagectomy for cancer. *Br J Surg.* 2019;106:111–9.
27. Kanekiyo S, Takeda S, Iida M, et al. Efficacy of perioperative immunonutrition in esophageal cancer patients undergoing esophagectomy. *Nutrition.* 2019;59:96–102.
28. Wu N, Chen G, Hu H, Pang L, Chen Z. Low pretherapeutic serum albumin as a risk factor for poor outcome in esophageal squamous cell carcinomas. *Nutr Cancer.* 2015;67:481–5.
29. Tan Z, Zhang M, Han Q, et al. A novel blood tool of cancer prognosis in esophageal squamous cell carcinoma: the fibrinogen/albumin ratio. *J Cancer.* 2017;8:1025–9.
30. Yamana I, Takeno S, Shimaoka H, et al. Geriatric Nutritional Risk Index as a prognostic factor in patients with esophageal

squamous cell carcinoma: retrospective cohort study. *Int J Surg.* 2018;56:44–8.
31. Mitzman B, Schipper PH, Edwards MA, Kim S, Ferguson MK. Complications after esophagectomy are associated with extremes of body mass index. *Ann Thorac Surg.* 2018;106:973–80.
32. Wightman SC, Posner MC, Patti MG, et al. Extremes of body mass index and postoperative complications after esophagectomy. *Dis Esophagus.* 2017;30:1–6.
33. Ida S, Watanabe M, Karashima R, et al. Changes in body composition secondary to neoadjuvant chemotherapy for advanced esophageal cancer are related to the occurrence of postoperative complications after esophagectomy. *Ann Surg Oncol.* 2014;21:3675–9.
34. Reisinger KW, Bosmans JW, Uittenbogaart M, et al. Loss of skeletal muscle mass during neoadjuvant chemoradiotherapy predicts postoperative mortality in esophageal cancer surgery. *Ann Surg Oncol.* 2015;22:4445–52.
35. Ida S, Watanabe M, Yoshida N, et al. Sarcopenia is a predictor of postoperative respiratory complications in patients with esophageal cancer. *Ann Surg Oncol.* 2015;22:4432–7.
36. Paireder M, Asari R, Kristo I, et al. Impact of sarcopenia on outcome in patients with esophageal resection following neoadjuvant chemotherapy for esophageal cancer. *Eur J Surg Oncol.* 2017;43:478–84.
37. Miyata H, Yano M, Yasuda T, et al. Randomized study of clinical effect of enteral nutrition support during neoadjuvant chemotherapy on chemotherapy-related toxicity in patients with esophageal cancer. *Clin Nutr.* 2012;31:330–6.
38. Taniguchi H, Sasaki T, Fujita H, et al. Effects of goal-directed fluid therapy on enhanced postoperative recovery: an interventional comparative observational study with a historical control group on oesophagectomy combined with ERAS program. *Clin Nutr ESPEN.* 2018;23:184–93.