



Patient-reported outcomes of the prognostic nutritional index for resectable esophageal squamous cell carcinoma

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Background: The prognostic nutritional index (PNI) involves both the nutritional status and immune function as crucial factors linked to the prognosis of various gastrointestinal cancers. The relationship between the PNI and postoperative quality of life (QOL) in patients with esophageal cancer (EC) has not been examined. This study sought to examine the effects of the PNI on the postoperative patient-reported outcomes (PROs) of patients with esophageal squamous cell carcinoma (ESCC).

Methods: Consecutive ESCC patients undergoing minimally invasive McKeown esophagectomy at a single center from April 2019 to December 2020 were enrolled in this study. The patients were allocated to the PNI-high group (PNI \geq 45) and PNI-low group (PNI $<$ 45). The longitudinal PROs were handled to compare the functions and symptoms using a linear mixed-effect models. The M.D. Anderson Symptom Inventory (MDASI) and the European Organization for Research and Treatment of Cancer (EORTC) questionnaires were used to assess patients' symptoms and QOL.

Results: A total of 274 patients were included in the study. Patients with esophageal cancer experienced a decline in functional status and significant esophageal cancer-related symptoms shortly after surgery. When PNI was less than 45, a higher PNI might be associated with improved functional status and more obvious symptoms such as pain, problems with taste, sadness, shortness of breath, and drowsiness ($P < 0.05$)

Conclusions: There might be a non-linear association between PNI and the postoperative health-related QOL of ESCC patients. It was emphasized that individualized nutritional intervention should be provided for patients with PNI lower than 45.

Keywords: Prognostic nutritional index (PNI); esophageal squamous cell carcinoma (ESCC); patient-reported outcomes (PROs); esophagectomy

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Introduction

Esophageal cancer (EC) is the 11th most common cancer and the seventh leading cause of cancer-related death worldwide (1,2). Malnutrition is a complication of EC, and is influenced by various factors, including local factors, such as swallowing obstruction, swallowing pain, gastroesophageal reflux, and coughing, and systemic metabolic factors, such as anorexia, satiety, an increased basal metabolic rate, and tumor-induced disorders in glucose, protein, and fat metabolism. Consequently, many patients with advanced upper-gastrointestinal tumors frequently present with hypoproteinemia, dehydration, and electrolyte abnormalities (3). Evidence suggests that perioperative protein malnutrition, particularly baseline nutritional status, significantly affects the outcomes of EC treatments (4,5). This implies that for surgical patients, successful recovery relies not only on surgical expertise, but also on the management of patients' metabolic load and the provision of appropriate nutritional support. Thus, perioperative nutritional assessment plays a crucial role in patient recovery (6).

The immune system of tumor patients is mainly

composed of T lymphocytes, B cells, and natural killer cells. Wang *et al.* reported that neutrophil and lymphocyte counts are associated with the survival and quality of life (QOL) of EC patients, and that severe inflammatory responses are associated with a poor prognosis in patients with EC (7). The prognostic nutritional index (PNI) involves both the nutritional status and immune function as crucial factors linked to the prognosis of various gastrointestinal cancers (8-10).

Numerous studies have used QOL as an outcome measure, and the PNI has been reported to be a predictor of QOL (11-13). However, the relationship between the PNI and postoperative QOL in patients with EC has not been examined, especially in research with greater continuity and long-term follow-up. Therefore, the primary objective of this study was to assess the relationship between the preoperative PNI and changes in QOL over time in ESCC patients undergoing McKeown esophagectomy using the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core-30 (QLQ-C30), the EORTC Quality of Life Esophagus-specific Questionnaire (QLQ-OES18), and M.D. Anderson Symptom Inventory in Esophageal Cancer (MDASI-Eso) (14-17). We present this article in accordance with the REMARK reporting checklist (available at <https://jtd.amegroups.com/article/view/10.21037/jtd-2025-1229/rc>).

Highlight box

Key findings

- The preoperative prognostic nutritional index (PNI) was associated with the health-related quality of life (QOL) of esophageal squamous cell carcinoma (ESCC) patients.
- The study showed that a higher PNI might be associated with improved functional status and more obvious symptoms in patients with PNI <45.

What is known, and what is new?

- QOL is considered an outcome measure, and PNI has been reported to be a predictor of QOL.
- This study found that the relationship between the preoperative PNI and QOL changed over time in ESCC patients who underwent McKeown esophagectomy.

What is the implication, and what should change now?

- The PNI may serve as a new potential factor for predicting the QOL and symptoms of ESCC patients undergoing McKeown esophagectomy.

Methods

Patients

This single-center retrospective study used prospective patient-reported outcome (PRO) data. Patients with esophageal squamous cell carcinoma (ESCC) who underwent minimally invasive McKeown esophagectomy at Sichuan Cancer Hospital & Institute from April 2019 to December 2020 were consecutively enrolled in this study. The baseline information of the patients, including age, sex, body mass index (BMI), comorbidities (diabetes, hypertension, and coronary disease), education, smoking history, drinking history, tumor location, clinical stage, Eastern Cooperative Oncology Group (ECOG) performance status scores, neoadjuvant therapy (NT), and adjuvant therapy, post-surgery hospital staying

days, preoperative nutritional optimization, nasogastric feeding tube, complications were collected. Clinical stage was assessed using the Cancer Staging Manual (8th edition) of the American Joint Commission on Cancer by ultrasonic endoscopy and computed tomography (CT) (18). Complications are classified according to the Clavien-Dindo grade. The MDASI and EORTC-QOLs were used to assess symptoms and QOL.

To be eligible for inclusion in the study, the patients had to meet the following inclusion criteria: (I) have squamous cell carcinoma; (II) have EC located in the thorax; (III) have undergone fully minimally invasive McKeown esophagectomy; (IV) have a fully mechanical anastomosis; and (V) be aged from 18 to 80 years. Patients were excluded from the study if they met any of the following exclusion criteria: (I) had metastasis or recurrence within 6 months of surgery, or other malignant tumors; (II) had less than 6 months of follow-up, or died within 6 months of surgery; (III) had perioperative complications caused by secondary surgery; (IV) had a non-tubular stomach substitute for the esophagus; (V) not had nasogastric feeding tube after surgery; and/or (VI) had a lack of complete clinical data. The “secondary surgery” referred to a non-anticipated open surgery or invasive procedure that needs to be performed again in the operating room due to severe acute complications after the surgery. “Non-tubular stomach substitute” referred to the reconstruction of the esophagus using non-gastric tissues (such as the colon or jejunum). NT included neoadjuvant chemoradiotherapy, chemotherapy, and radiotherapy received before surgery. The enrolled patients were allocated to the PNI-high group (PNI \geq 45) or the PNI-low group (PNI <45). Preoperative nutritional optimization refers to a standardized nutritional intervention protocol for patients with nutritional risk (Nutritional Risk Screening 2002 score \geq 3). This involves providing 7–10 days of preoperative nutrition via enteral (oral/tube feeding) or parenteral routes to achieve: protein intake: 1.2–2.0 g/(kg·d); energy intake: 25–30 kcal/(kg·d). For patients with normal gastrointestinal function, oral nutritional supplements are prioritized. If enteral nutrition alone fails to meet the target requirements, combined enteral and parenteral nutrition is used. For those with digestive/absorptive impairments, parenteral nutrition is directly employed. The study was authorized by the Ethics Committee of the Medical Research and New Medical Technology of Sichuan Cancer Hospital & Institute (No. SCCHEC-02-2023-090). Informed consent was taken from all the patients. This study was conducted in accordance

with the Declaration of Helsinki and its subsequent amendments.

PNI calculation

The PNI was calculated as follows: PNI = serum albumin (g/L) + 5*total lymphocyte count (10^9 /L). For clarity, an example calculation using both International System of Units (SI) and US common units is provided: A patient with serum albumin of 4.5 g/dL (equivalent to 45 g/L) and a total lymphocyte count of 1,500 cells/mm³ (equivalent to 1.5×10^9 /L) would have a PNI = 45+(5×1.5)=45+7.5=52.5. Based on previous reports (8,9,19–21), patients with a PNI \geq 45 were allocated to the PNI-high group, and those with a PNI <45 were allocated to the PNI-low group. Blood samples were collected from the patients after they were admitted to the hospital when they were fasting before esophagectomy. Serum albumin and the total lymphocyte count were assessed by flow cytometry.

Symptom measurements

The MDASI is a comprehensive set of screening tools developed by the M.D. Anderson Cancer Center in Texas, USA that seeks to capture cancer patients’ symptoms in a concise and comprehensive manner. The MDASI-Eso questionnaire is divided into two distinct sections. The initial section assesses the symptoms associated with cancer, including pain, fatigue, nausea, and disrupted sleep. While the second section gauges the effects of general activity, mood, work relationships, walking, and enjoyment of life on daily life on a scale of 0 to 10 (where 0 represents asymptomatic status and 10 represents the most severe imaginable state). The more severe the symptoms and the greater the disruption to life, the higher the total score in each section (14).

Health-related QOL measurements

The EORTC-QLQ-C30, a tool developed by the EORTC, is a reliable and effective means of assessing the QOL of cancer patients across diverse cultural and clinical research settings. The Chinese version of the EORTC-QLQ-OES18, designed as a supplement for the EORTC-QLQ-C30, has been shown to be a dependable, effective, and well-accepted tool for assessing health-related QOL among patients with ESCC in mainland China (16). The EORTC-QLQ-C30 has a total of 30 entries divided into

15 dimensions: five functional dimensions (physical, role, cognitive, emotional, and social functions); three symptom dimensions (fatigue, pain, and nausea and vomiting); one general health/QOL dimension; and six single entries. The EORTC-QLQ-OES18 comprises 18 items, organized into four multi-item scales addressing dysphagia (three items), eating (four items), reflux (two items), and pain (three items). Additionally, it features six single-item scales that evaluate trouble swallowing saliva, choking, dry mouth, taste, cough, and speech. The raw scores for each dimension were initially computed using a specific formula. Subsequently, the polarization method was applied to linearly transform these raw scores into standardized scores (16,17).

Data collection

The PRO data were obtained from the Prospective Sichuan Cancer Hospital & Institute's Case Management Registration Database based on REDCap (<http://125.71.214.100:888/redcap>). The data collection was conducted independently by the researchers, who interpreted the questionnaire items using unified guidelines to identify patients with ESCC who met the inclusion criteria. With the patients' informed consent, the researchers gathered general data by consulting them and reviewing their medical records during hospitalization. Patients' symptoms and QOL were evaluated at the time of enrollment (the preoperative baseline) and within half a year of surgery. The symptom survey time points were the day before esophagectomy, and 1, 3, 5, 7, 14, 21, 30, 90, and 180 days after esophagectomy. The health-related QOL survey time points were the day before esophagectomy, and 7, 30, 90, and 180 days after esophagectomy.

Statistical analysis

All the statistical analyses were conducted using statistical package SPSS (25.0 SPSS Inc., Chicago, IL, USA) or GraphPad Prism 9 (GraphPad Software Inc., San Diego, CA, USA). The continuous variables with a normal distribution are presented as the mean (standard deviation), and otherwise as the median and interquartile range (IQR). The categorical variables are presented as the number, percentage, or proportion. The Chi-squared test or Fisher's exact test was used to compare the categorical variables, and the student *t*-test or the Wilcoxon Mann-Whitney test was used to compare the continuous variables. The estimated

values (β , when PNI was involved as continuous variable) and the mean score difference (MD, scores of the scales, when PNI were grouped in PNI-high and PNI-low) in the pre- and postoperative health-related QOL and symptoms between the two groups and differences in changes over time between different groups were assessed using linear mixed-effects models in which group, time (the survey time points for the health-related QOL and symptoms), and the interaction between the patient groups and time were set as the fixed effects, and the patients and time were set as the random effects. The missing data and fixed effects and random effects were estimated using the maximum likelihood estimation method. A two-sided *P* value <0.05 was considered statistically significant. MD >10 in EORTC QLQ-C30/OES 18 and MD >1 in MDASI-Eso were considered clinically significant. The β value was adjusted for PNI (continuous variable), time and the interaction effect of PNI (continuous variable) and time, age, sex, BMI, comorbidity, education, smoking history, drinking history, tumor location, clinical stage, ECOG performance status scores, adjuvant therapy, post-surgery hospital staying days, preoperative nutritional optimization, nasoenteral feeding tube, complications.

Results

PNI and clinical features

Figure 1 provides a flow chart showing the study selection process. The clinical characteristics of all the patients are summarized in Table 1. The PNI-low group comprised 130 (of the 274 patients) with a PNI <45, and the PNI-high group comprised 144 patients. The patients in the PNI-low group were older ($P=0.04$), had a higher proportion of smokers ($P=0.045$), and a significantly higher proportion of patients in stage III of the clinical assessment (57.7% *vs.* 34.7%). In contrast, the proportion of stage I patients was higher in the PNI-high group (11.8% *vs.* 3.1%, $P<0.001$). There was a significant difference in treatment strategies—the proportion of patients receiving NT was higher in the PNI-high group (79.2% *vs.* 43.8%, $P<0.001$), but the rate of adjuvant therapy was higher in the PNI-low group (84.6% *vs.* 68.1%, $P=0.001$). The physical status assessment showed that the proportion of patients with ECOG score of 2–3 in the PNI-low group significantly increased (20.0% *vs.* 10.4%, $P=0.03$). No significant differences were observed between the groups in terms of gender, BMI, comorbidities, tumor location, and postoperative recovery indicators

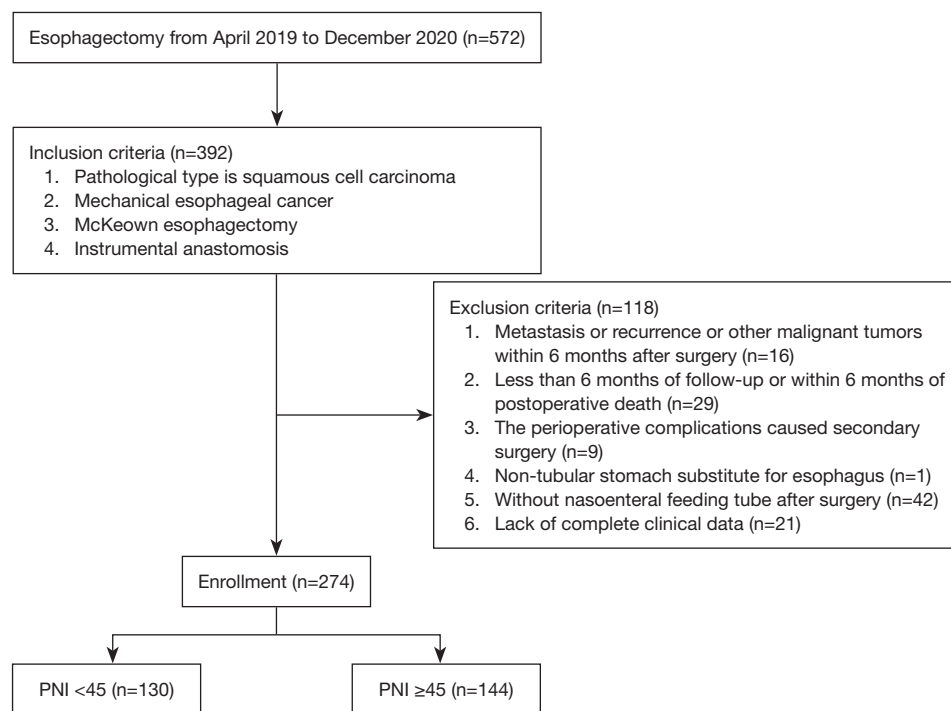


Figure 1 The flow chart of enrollment. PNI, prognostic nutritional index.

(length of hospital stay, days of nasogastric tube use, Clavien-Dindo grade \geq II complications) ($P>0.05$).

Table S1 shows the distribution of the incidence rate of the complications. The completion status of the scales was presented in Tables 2,3.

Longitudinal changes in health-related QOL and symptoms

In the EORTC-QLQ-C30 and EORTC-QLQ-OES18, on the 7th day after surgery, the most significant decreases among the survey time points were observed in the global QOL [$P<0.001$; the change of MD from the baseline to the 7th day after surgery: 28.98 (13.11)], physical function [$P<0.001$; 18.78 (19.87)], role function [$P<0.001$; 18.78 (19.87)], and cognitive function [$P<0.001$; 10.57 (11.37)] but these gradually returned to the baseline level in the 180 days after surgery. Additionally, the symptoms of fatigue [$P<0.001$; -29.52 (13.37)], pain [$P<0.001$; -32.90 (15.19)], dyspnea [$P<0.001$; -18.91 (19.76)], sleep disturbance [$P<0.001$; -29.85 (24.40)], appetite loss [$P<0.001$; -15.55 (21.07)], diarrhea [$P<0.001$; -9.74 (18.87)], dysphagia [$P<0.001$; -81.72 (24.92)] dry mouth [$P<0.001$; -28.36 (23.97)], and sense of taste problems [$P<0.001$; -15.55

(27.72)] increased by varying amounts 7 days after surgery. In the MDASI-Eso, increases in severity of pain [$P<0.001$; -4.69 (1.45)], fatigue [$P<0.001$; -5.06 (1.90)], disturbed sleep [$P<0.001$; -3.03 (2.55)], distress [$P<0.001$; -1.14 (1.47)], lack of appetite [$P<0.001$; scores: -1.98 (2.37)], drowsiness [$P<0.001$; 0.40 (0.87) to 3.43 (1.43)], dry mouth [$P<0.001$; -5.05 (2.31)], sadness [$P<0.001$; -0.85 (1.42)], dysphagia [$P<0.001$; -6.02 (1.85)], difficulties eating [$P<0.001$; -1.70 (1.63)], reflux [$P<0.001$; -7.89 (2.34)], sore throat [$P<0.001$; -8.84 (1.38)], and hoarseness [$P<0.001$; -3.80 (3.03)] were observed 1 day after surgery, but returned to the baseline levels over time.

Health related QOL and PNI

When using the mixed-effects model to analyze the relationship between PNI (a continuous variable) and QOL (complete data in Table S2), a higher PNI was associated with better global QOL (unadjusted $\beta=0.28$, $P=0.03$), cognitive Function (unadjusted $\beta=0.20$, $P=0.02$) and social function (unadjusted $\beta=0.33$, $P=0.02$; adjusted $\beta=0.41$, $P=0.006$), and was correlated with more symptoms such as pain (OES18, unadjusted $\beta=0.25$, $P<0.001$; adjusted $\beta=0.22$, $P<0.001$), problems with tasting (unadjusted

Table 1 Clinical characteristics of the patients

Characteristic	Total (N=274)	PNI <45 (N=130)	PNI ≥45 (N=144)	P value
PNI, mean [SD]	45.6 [5.5]	41.1 [3.4]	49.6 [3.6]	<0.001 [†]
Age (years), median [range]	63 [41–80]	63.5 [45–80]	62 [41–77]	0.04 [†]
Sex				
Male	232 (84.7)	115 (88.5)	117 (81.3)	0.13 [‡]
Female	42 (15.3)	15 (11.5)	27 (18.8)	
BMI (kg/m ²), median (IQR)	23.1 (20.7, 24.8)	22.7 [20.5, 24.6]	23.4 [21.2, 24.9]	0.05 [†]
Comorbidity (diabetes, hypertension, and coronary disease)				0.89 [‡]
Yes	64 (23.4)	31 (23.8)	33 (22.9)	
No	210 (75.6)	99 (76.2)	111 (77.1)	
Education				0.16 [‡]
≤ middle school	236 (86.1)	116 (89.2)	120 (83.3)	
≥ high school	38 (13.9)	14 (10.8)	24 (16.7)	
Smoking history				0.045 [‡]
Yes	175 (63.9)	91 (70.0)	84 (58.3)	
No	99 (36.1)	39 (30.0)	60 (41.7)	
Drinking history				0.07 [‡]
Yes	155 (56.6)	81 (62.3)	74 (51.4)	
No	119 (43.4)	49 (37.7)	70 (48.6)	
Tumor location				0.80 [‡]
Upper	26 (9.5)	12 (9.2)	14 (9.7)	
Middle	163 (59.5)	80 (61.5)	83 (57.6)	
Lower	85 (31.0)	38 (29.2)	47 (32.6)	
Clinical stage				<0.001 [†]
I	21 (7.7)	4 (3.1)	17 (11.8)	
II	90 (32.8)	37 (28.5)	53 (36.8)	
III	125 (45.6)	75 (57.7)	50 (34.7)	
IV	38 (13.9)	14 (10.8)	24 (16.7)	
ECOG performance status scores				0.03 [‡]
0–1	233 (85.0)	104 (80.0)	129 (89.6)	
2–3	41 (15.0)	26 (20.0)	15 (10.4)	
Neoadjuvant therapy				<0.001 [†]
Yes	171 (62.4)	57 (43.8)	114 (79.2)	
No	103 (37.6)	73 (56.2)	30 (20.8)	
Adjuvant therapy				0.001 [†]
Yes	208 (75.9)	110 (84.6)	98 (68.1)	
No	66 (24.1)	20 (15.4)	46 (31.9)	

Table 1 (continued)

Table 1 (continued)

Characteristic	Total (N=274)	PNI <45 (N=130)	PNI ≥45 (N=144)	P value
Post-surgery hospital stays (days), mean [SD]	11.1 [7.5]	10.8 [6.7]	11.5 [8.2]	0.49 [†]
Preoperative nutritional optimization				0.50 [‡]
Yes	108 (39.4)	54 (41.5)	54 (37.5)	
No	166 (60.6)	76 (58.5)	90 (62.5)	
Nasoenteral feeding tube (days), mean [SD]	19.4 [20.8]	20.1 [21.1]	18.8 [20.6]	0.61 [†]
Complications (CD ≥II)				0.36 [‡]
Yes	147 (53.6)	66 (50.8)	63 (43.8)	
No	127 (46.4)	64 (49.2)	81 (56.3)	

Data are expressed as n (%), unless otherwise noted. [†], Mann-Whitney *U* test or independent-sample *t*-test; [‡], χ^2 test or Fisher's exact test. BMI, body mass index; CD, Clavien-Dindo; IQR, interquartile range; PNI, prognostic nutritional index; SD, standard deviation.

Table 2 Completion of the QOL questionnaire

Status	Before surgery	Days after surgery			
		7	30	90	180
EORTC QLQ-C30 /OES18					
Eligible	274	274	274	274	274
Missing/other	2	4	0	0	0
Returned total (% of eligible)	272 (99.3)	270 (98.5)	274 (100.0)	274 (100.0)	274 (100.0)
PNI-high	142	143	144	144	144
PNI-low	130	127	130	130	130

ECOG, Eastern Cooperative Oncology Group; EORTC QLQ-C30, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire; OES-18, EORTC Quality of Life Esophagus-specific Questionnaire; PNI, prognostic nutritional index; QOL, quality of life.

Table 3 Completion of the QOL questionnaire (MDASI-Eso)

Status	Before surgery	Days after surgery								
		1	3	5	7	14	21	30	90	180
MDASI-Eso										
Eligible	274	274	274	274	274	274	274	274	274	274
Missing/other	2	20	11	8	4	2	1	1	1	0
Returned total (% of eligible)	272 (99.3)	254 (92.7)	263 (96.0)	266 (97.1)	270 (98.5)	272 (99.3)	273 (99.6)	273 (99.6)	273 (99.6)	274 (100)
PNI-high	142	136	137	140	143	143	144	144	144	144
PNI-low	130	118	126	126	127	129	129	129	129	130

MDASI-Eso, M.D. Anderson Symptom Inventory in Esophageal Cancer; PNI, prognostic nutritional index; QOL, quality of life.

$\beta=0.52$, $P=0.002$; adjusted $\beta=0.54$, $P=0.004$), short breath (adjusted $\beta=0.02$, $P=0.03$), appetite loss (unadjusted $\beta=0.03$, $P<0.001$), drowsiness (unadjusted $\beta=0.02$, $P=0.03$; adjusted

$\beta=0.03$, $P=0.01$), sadness (unadjusted $\beta=0.05$, $P<0.001$; adjusted $\beta=0.05$, $P<0.001$) and vomit (unadjusted $\beta=0.01$, $P=0.03$), less forgetfulness (unadjusted $\beta=-0.02$, $P=0.01$;

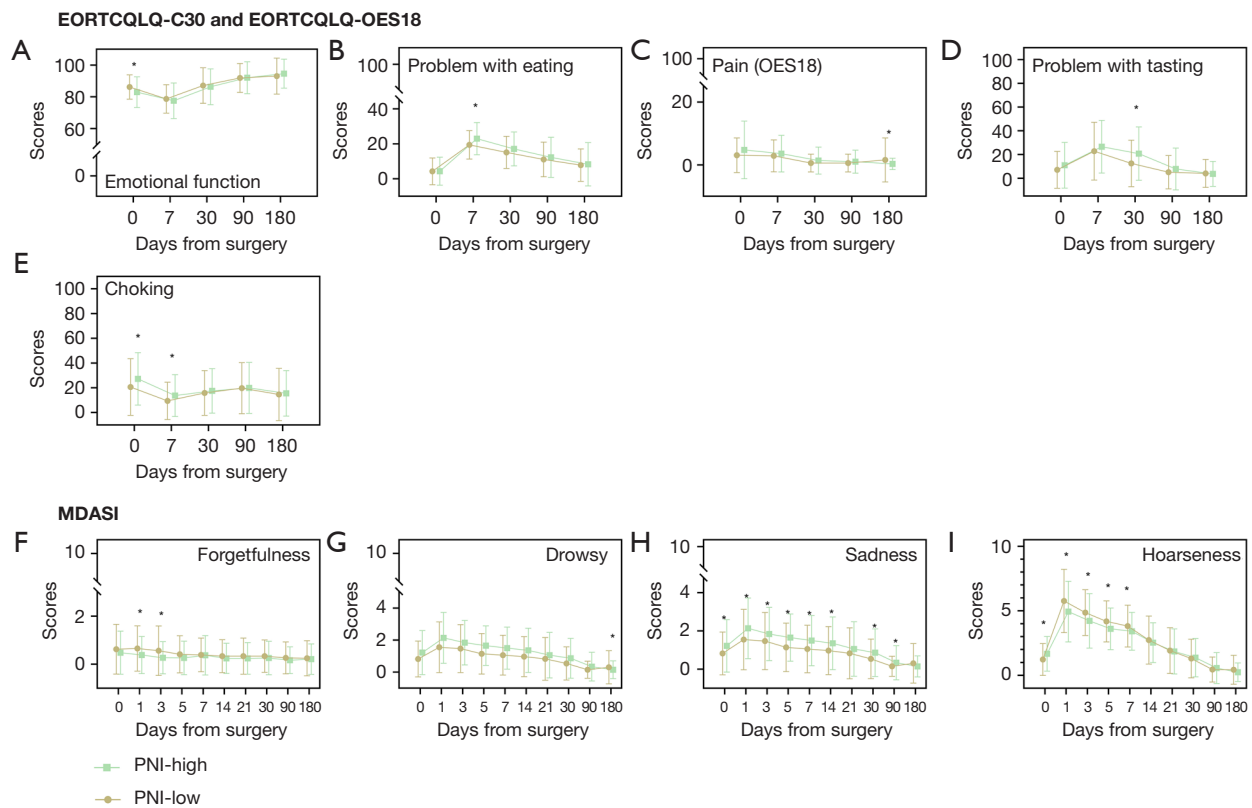


Figure 2 The quality-of-life scales of PNI-high group and PNI-low group. Each graph shows the mean symptom or function scores for the groups from pre-surgery to 6 months post-surgery. Higher scores reflect better function or worse symptom. *, $P<0.05$. MDASI-Eso, M.D. Anderson Symptom Inventory; PNI, prognostic nutritional index.

adjusted $\beta=-0.02$, $P<0.001$) and hoarseness (unadjusted $\beta=-0.04$, $P=0.01$; adjusted $\beta=-0.05$, $P=0.008$). Notably, after adjustment, the prolongation of postoperative hospital stay was significantly associated with global QOL ($\beta=-0.29$, $P<0.001$), physical function ($\beta=-0.37$, $P<0.001$), role function ($\beta=-0.31$, $P<0.001$), and emotional function ($\beta=-0.27$, $P<0.001$), and was also significantly correlated with more fatigue (C30, $\beta=0.38$, $P<0.001$; MDASI, $\beta=0.03$, $P<0.001$), pain (C30, $\beta=0.25$, $P<0.001$; OES18, $\beta=0.07$, $P=0.01$; MDASI-Eso, $\beta=0.01$, $P=0.04$), dyspnea ($\beta=0.28$, $P<0.001$), sleep disturbance (C30, $\beta=0.34$, $P<0.001$; MDASI, $\beta=0.05$, $P<0.001$), appetite loss ($\beta=0.26$, $P<0.001$), problems with tasting ($\beta=0.42$, $P<0.001$), choking ($\beta=0.14$, $P<0.001$), short breath ($\beta=0.04$, $P<0.001$), drowsiness ($\beta=0.04$, $P<0.001$), sadness ($\beta=0.05$, $P<0.001$), dysphagia ($\beta=0.05$, $P<0.001$), difficulty in eating ($\beta=0.03$, $P<0.001$), reflux ($\beta=0.05$, $P<0.001$), constipation ($\beta=0.01$, $P<0.001$), sore throat ($\beta=0.04$, $P<0.001$), hoarseness ($\beta=0.02$, $P<0.001$). Preoperative administration of NT was significantly associated with more fatigue (OES18, MD = -2.82,

$P<0.001$), pain (C30, MD = -2.21, $P=0.04$), dyspnea (MD = -3.53, $P=0.02$), less diarrhea (MD = 3.48, $P=0.02$) and choking (MD = 5.87, $P<0.001$).

When PNI was included in the adjusted model as a categorical variable [PNI-low and PNI-high group (Figure 2); The complete data are presented in Tables S3-S5], the PNI-high group (≥ 45) demonstrated worse emotional function (Figure 2A; adjusted MD = 2.41, $P=0.02$; at baseline.), more symptoms of problem with eating (Figure 2B; adjusted MD = -2.29, $P=0.04$; at 7 days after esophagectomy), pain (OES18, Figure 2C; adjusted MD = -1.35, $P=0.04$; at 180 days after esophagectomy), choking (Figure 2E, adjusted MD = -4.51, $P=0.02$; at baseline and 7 days after esophagectomy), problems with tasting (Figure 2D, adjusted MD = -5.05, $P=0.01$; at 60 days after esophagectomy) in the EORTCQLQ-C30/OES18 scales.

In MDASI scales, the PNI-high group demonstrated less symptom of forgetfulness (Figure 2F; adjusted MD = 0.19, $P<0.001$; at 1 day and 3 days after esophagectomy) and

hoarseness (*Figure 2I*; adjusted MD =0.40, P=0.04; from 1 day to 7 days after esophagectomy) and more symptoms of drowsiness (*Figure 2G*; adjusted MD =-0.26, P=0.008; at 180 days after esophagectomy), sadness (*Figure 2H*; adjusted MD =-0.51, P<0.001; from baseline to 90 days after esophagectomy) and vomit (adjusted MD =-0.09, P=0.03; no significant difference was observed at individual times), compared to the PNI-low group (<45).

The subgroup analysis showed that the correlation between PNI and the QOL of the patients was significantly different between the non-NT subgroup and the NT subgroup (the complete data is presented in [Table S6](#)). In the non-NT subgroup, a higher PNI was associated with worse role function ($\beta=-0.53$, P=0.01), more pain (OES18, $\beta=0.28$, P<0.01), problems with taste; ($\beta=0.61$, P=0.01), drowsiness ($\beta=0.03$, P=0.01), and sadness ($\beta=0.06$, P<0.01). At the same time, a higher PNI value was also significantly associated with less financial impact ($\beta=-0.47$, P=0.02) and forgetfulness ($\beta=-0.03$, P<0.01). In the NT subgroup, a higher PNI value was only significantly associated with more symptom of dry mouth (OES18, $\beta=0.55$, P=0.046).

Discussion

A decline in physical fitness and malnutrition resulting from EC are common complications that pose challenges to maintaining a high QOL (22). The currently available tools for assessing nutritional risk (e.g., micro-nutritional assessments, the nutritional risk screening 2002, and subject overall assessment) have significant clinical value. However, there is still a need for practical, precise, and cost-effective predictive factors that can help identify the patients who are most likely to benefit from esophagectomy. Due to Onodera's simplification based on serum albumin levels and the peripheral blood lymphocyte count, the PNI has emerged as one of the most straightforward routine indicators for assessing nutritional state. Multiple studies have reported a significant association between a low PNI and unfavorable prognosis, as well as a diminished QOL, in patients with diverse cancer types (23-25).

To the best of our knowledge, this was the first study to examine the correlation between the preoperative PNI and trends over time in the postoperative QOL and symptoms of ESCC patients. Our study focused on considering the temporal changes in different outcome indicators using mixed models to effectively reduce impact of various factors that could potentially affect patients' postoperative QOL and symptoms between the two groups. The

primary finding of this study was that the ESCC patients experienced a decline in their QOL, and encountered various symptoms related to both the disease itself and the surgery, which persisted after undergoing esophagectomy but gradually returned to baseline levels within 6 months. This study found that the preoperative PNI, as a continuous variable, showed a multi-dimensional association with the postoperative QOL of patients with resectable EC. Compared with patients who had a lower preoperative PNI score, those with a higher preoperative PNI score also experienced similar changes in QOL, but there were significant improvements in overall QOL, cognitive function, social function, and economic impact. This is consistent with the characteristic of PNI as a composite indicator of nutritional and immune status (19-21). PNI reflects the patient's nutritional reserves and anti-inflammatory capacity through serum albumin and lymphocyte counts. A high PNI indicates a good nutritional status and immune response capability, which may accelerate postoperative tissue repair and reduce the risk of infection, thereby supporting functional recovery (19-21). However, after adjusting for confounding factors, patients in the high PNI group reported more pain and taste problems, suggesting that improved nutritional status may be accompanied by the continuous activation of inflammatory responses. The local inflammatory microenvironment after EC surgery may exacerbate pain perception and reduce taste sensitivity by releasing cytokines [such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF- α)], counteracting some of the benefits of nutritional support (26).

Research suggests that the higher the level of negative emotions of patients, the more severe their symptom burden becomes (27,28). In this study, the PNI-high group had higher levels of sadness that persisted for up to 1 month postoperatively. It might be that patients with better preoperative nutritional status are more susceptible to experiencing pronounced psychological symptoms after surgery, but this needs to be further verified through a more comprehensive scale.

A common cause of hoarseness following surgery for EC is intraoperative injury to the recurrent laryngeal nerve or vocal cord injury resulting from endotracheal intubation. Obese patients present a challenge for surgeons due to their adipose tissue's tendency to obscure the surgical field. Moreover, malnourished patients are more prone to develop edema due to inflammation when the trachea is intubated, resulting in an increased risk of postoperative voice hoarseness lasting up to 7 days post-surgery while the

injury heals (29). Treatment-related fatigue is a frequently encountered adverse effect, and research has reported a positive association between postoperative fatigue and sleep symptoms, and pro-inflammatory cytokines such as interleukin-1, IL-6, TNF- α and interferon-alpha (30,31). This finding aligns with the observation that the drowsy symptoms were more pronounced in the patients in the PNI-high group. We also found that the prolonged postoperative hospital stay was significantly associated with the overall deterioration of the patients' functional-related QOL and the increased burden of postoperative symptoms. We speculate that the occurrence of intervention-requiring complications (anastomotic fistula, pulmonary infection, etc.) after surgery will delay the patients' discharge time, and the complications themselves will further exacerbate the deterioration of the QOL (32). The long-term bed rest during the patients' hospitalization leads to muscle atrophy, which also hinders the recovery of their functions (33). With the application of neoadjuvant treatment modalities, the survival rates of EC patients are on the rise, and there is a growing interest in strategies aimed at improving the QOL of cancer patients (34-36). Based on this, we intend to investigate the differences in QOL between patients who received NT and those who received conventional therapy. We found that EC patients in the study cohort who received NT had a certain degree of increased risk of fatigue and pain, which is consistent with the recent findings of Tsou's study about Cancer-Related Fatigue (37). The nutritional status of a patient is closely linked to their capacity to endure the entire treatment process (35,38,39). Thus, enhancing the nutritional status of patients before surgery plays a pivotal role in their postoperative recovery and even long-term survival, notwithstanding the potential challenges it may pose to their QOL.

Of note, although adjustments were made, the improvement in PNI showed marginal significance with enhanced overall QOL and cognitive function, and demonstrated persistent significant associations with improved social function. However, when analyzed using a threshold of PNI =45, the PNI-high group exhibited no significant advantage in functional domains (MD <10) (40). Within 30 days postoperatively, symptoms predominantly clustered in pain, problems with taste perception, sadness, and drowsiness. Although the clinical differences were modest (MD <10 in C30/OES18, MD <1 in MDASI), they became progressively more pronounced with increasing

PNI. This indicates that the relationship between PNI and QOL is likely not a simple linear association, and a tipping point may exist near PNI =45, beyond which higher improvements in functional HRQOL and global QOL may not be received by patients. These findings suggested that esophageal surgeons should develop individualized nutritional support strategies. For patients with PNI <45, nutritional intervention requires prioritized management to optimize PNI levels to a level beyond this threshold, thereby improving functional status. In terms of PNI >45, we suggest prioritizing symptom management rather than lowering nutritional intervention. Our future plan is to utilize machine learning to identify the interaction between PNI and other factors, thereby enhancing the precision of optimizing nutritional support.

This study had a number of limitations. Despite unifying the operation quality control and perioperative management of the patients, this was a single-center study, and the surgeries were performed by different surgical groups. Variations in the surgeons' experience, operation time, the patient's metabolic stress, psychological state during the perioperative period as well as unmeasured confounders might have affected the postoperative QOL of the patients. These limitations will be considered and optimized in our future studies.

Conclusions

The study found that there might be a non-linear association between PNI and the postoperative health-related QOL of ESCC patients. Our research indicates that when PNI is lower than 45, a higher PNI is associated with improved functional QOL in patients and more obvious symptoms. Therefore, it is emphasized that individualized nutritional intervention should be provided for patients with PNI lower than 45. And esophageal surgeons should pay close attention to postoperative symptom management for patients with a PNI more than 45.

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Footnote

Reporting Checklist: The authors have completed the REMARK reporting checklist. Available at <https://jtd.amegroups.com/article/view/10.21037/jtd-2025-1229/rc>

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was authorized by the Ethics Committee of the Medical Research and New Medical Technology of Sichuan Cancer Hospital & Institute (No. SCCHEC-02-2023-090). Informed consent was taken from all the patients. This study was conducted in accordance with the Declaration of Helsinki and its subsequent amendments.

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