Research Paper

Novel preoperative nutritional assessment tool and prognostic model for ESCC patients

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Abstract

Background: Esophageal squamous cell carcinoma (ESCC) is one of the most aggressive tumor types worldwide, and malnutrition prevails in these patients. However, there is no preoperative nutritional assessment tool specifically designed for patients with ESCC.

Methods: Patients who received esophagectomy from 2004 to 2016 were consecutively included. The preoperative nutritional risk factors for ESCC were screened by univariate and multivariate Cox regression analysis to construct a new nutritional scoring tool. A prognostic model of ESCC based on the new scoring tool was further proposed.

Results: A total of 510 ESCC patients were enrolled. A novel BLUT (BMI-lymphocyte-uric acid-triglyceride) scoring tool based on BMI, lymphocyte count, uric acid level, and triglyceride level was proposed, which could effectively predict the prognosis of ESCC patients (log rank P<0.001), and it was better than the traditional nutritional assessment tools. The C-index and 95% confidence interval (CI) of the nomogram based on the BLUT scoring tool was 0.735(0.698-0.772). It had good prognostic efficacy and was significantly better than the model based on T stage and N stage (P=0.038). The calibration curve of internal and external validation suggested a good fitting effect with the real situation in judging the 1-year, 3-year, and 5-year survival status.

Conclusions: The BULT scoring tool could distinguish the heterogeneity of preoperative nutritional status and the BLUT-based nomogram had good prognostic performance for ESCC patients.

Key words: esophageal squamous cell carcinoma; nutritional assessment tool; prognostic model

1. Introduction

Esophageal cancer is one of the most aggressive cancer types in China (1) and across the world (2), and esophageal squamous cell carcinoma (ESCC) is the most common pathological subtype. As the development of preoperative new adjuvant therapy, postoperative adjuvant therapy and enhanced recovery after surgery (ERAS), the surgery-based comprehensive treatment model has improved the prognosis of esophageal cancer in the past decades (3, 4). However, the 5-year survival rate was still not satisfied, which only ranged from 15% to 25% (5). It has been reported that weight loss, malnutrition and cachexia prevailed in most patients with esophageal cancer (6). Malnutrition could impact the short-term and long-term clinical outcomes of esophageal cancer patients, such as surgical complications and poor survival (7). Thus, nutritional management plays an important role in the treatment process (8).

Nutritional screening and assessment are indispensable to guide rational nutritional treatment. Nutrition risk screening (NRS 2002) was the first international evidence-based nutritional screening

tool (9). Since the 1970s, many nutritional assessment tools emerged, such as the patient generated-subjective global assessment (PG-SGA) tool (10), mini nutritional assessment (MNA) tool (11) and malnutrition universal screening tool (MUST) (12). However, these tools were limited to their inevitable subjective assessments. By contrast, nutritional assessment tools based on objective indexes could reflect the nutritional status more accurately, such as the prognostic nutritional index (PNI) (13), controlling nutritional status (CONUT) (14), and geriatric nutritional risk index (GNRI) (15) and so on.

So far, there is no preoperative nutritional assessment tool specifically designed for ESCC patients. Therefore, we designed a retrospective study to propose a novel nutritional scoring tool and a prognostic nomogram for ESCC patients.

2. Materials and methods

2.1. Study population

Patients who received esophagectomy from Jan. 1st, 2004 to Dec. 31, 2016 in the Department of Thoracic Surgery, the First Affiliated Hospital, Zhejiang University School of Medicine were consecutively included. The clinical and pathological information of these patients were collected. The inclusion and exclusion criteria were as follow: (1) more than 18 years old; (2) pathologically diagnosed as ESCC; (3) had no history of other malignancies; (4) had complete preoperative laboratory test information and height and weight information. The pathological staging of the tumor was conducted according to the American Joint Commission on Cancer/Union for International Cancer Control (AJCC/UICC 8th version) tumor-node-metastasis (TNM) staging manuals (16). All patients were enrolled with written informed consent under institutional review board-approved protocols of the First Affiliated Hospital, Zhejiang University School of Medicine. This study was performed in accordance with the principles of Declaration of Helsinki.

The follow-up information was collected from the outpatient clinical system, as well as the regular telephone follow-up. The last follow-up time was January 2018. The follow-up time ranged from 1.9 months to 134.0 months, and the mean follow-up time was 35.1 months.

2.2. Statistically analysis

The cohort was randomly divided into the training set and validation set in ratio 4:1 by SPSS software and the initial seed was 20180101. The cut-off values of continuous variables were determined by the X-tile software (http://www.tissuearray.org/rimmlab) and by the minimal P value approach (17).

Univariate and multivariate Cox regression analyses were conducted to screen potential risk indexes for ESCC, and the results were shown in the form of hazard ratios (HRs) and their 95% confidence intervals (CIs). The survival difference was assessed by the log rank tests and Kaplan-Meier curves. A new nutritional scoring tool was proposed, and the indexes were selected for both statistical and clinical consideration (18). A nutritional tool-based nomogram was further constructed. Harrell's concordance index (C-index), which ranged from 0.5 (denotes random splitting) to 1.0 (perfect prediction), was adopted to assess the discrimination efficacy (19). Besides, bootstrap technique with 1000 repetitions was used for internal and external validation and to calculate the 95% CIs (18, 20). Akaike information criterion (AIC) was used to assess the predictive efficacy, and smaller AIC values represent more accurate prognostic stratification (21). The detail definition of PNI, GNRI and CONUT assessment tools was shown in the Supplementary Methods.

All analyses were conducted using the SPSS 22.0 software (IBM SPSS Inc. United States), and R software version 3.2.2 (The R Foundation for Statistical Computing) with the rms, survival and hmisc statistical packages. Statistical significance was set at P < 0.05 (All P values presented were 2-sided).

3. Results

3.1. Characteristics of included patients

A total of 510 ESCC patients were enrolled in this study and there were 408 cases of training set and 102 cases of validation set. The baseline characteristics of included cases were shown in Table 1. The training set was selected to construct a new scoring tool, and the validation set was selected to test the prognostic model. Continuous variables were converted to categorical variables by X-tile software, as shown in Supplementary Figure 1.

3.2. Indexes selection by univariate and multivariate Cox regression analyses

Univariate Cox regression analysis was performed in the training set population, and the results suggested that gender (P=0.008), smoking (P=0.038), surgical approach (P=0.042), T stage (P<0.001), N stage (P<0.001), white blood cell (P=0.022), lymphocyte (P=0.036), triglyceride (P=0.004), uric acid (P=0.016) and BMI (P=0.016) were significantly associated with the prognosis of ESCC patients, as shown in Table 2. All these statistically significant indexes were further included in the multivariate Cox regression analysis. It suggested that gender (P=0.003), T stage (P=0.005), N stage (P<0.001),

white blood cell (P=0.015), lymphocyte (P=0.030) and uric acid (P=0.007) were independent prognostic factors for ESCC patients.

Table 1. Baseline characteristics of included ESCC patients.

Variable	Total cohort(n=510)		Training set(n=408)		Validation set(n=102)	
	number(percentage)		number(percentage)		number(percentage)	
Gender						
Male	444	87.06%	355	87.01%	89	87.25%
Female	66	12.94%	53	12.99%	13	12.75%
Age(years)						
≤59	157	30.78%	143	35.05%	14	13.73%
60-69	248	48.63%	192	47.06%	56	54.90%
≥70	105	20.59%	82	20.10%	23	22.55%
Alcohol						
No	178	34.90%	146	35.78%	32	31.37%
Yes	332	65.10%	262	64.22%	70	68.63%
Smoking						
No	164	32.16%	130	31.86%	34	33.33%
Yes	346	67.84%	278	68.14%	68	66.67%
Education						
Primary school and below	309	60.59%	242	59.31%	67	65.69%
Middle school and above	201	39.41%	166	40.69%	35	34.31%
Hypertension						
No	337	66.08%	309	75.74%	28	27.45%
Yes	133	26.08%	99	24.26%	34	33.33%
Surgical approach						
Sweet	236	46.27%	198	48.53%	38	37.25%
Ivor-Lewis	205	40.20%	153	37.50%	52	50.98%
Mckeown	69	13.53%	57	13.97%	12	11.76%
Margin						
Negative	487	95.49%	389	95.34%	98	96.08%
Positive	23	4.51%	19	4.66%	4	3.92%
Tumor location						
Upper	45	8.82%	38	9.31%	7	6.86%
Middle	355	69.61%	277	67.89%	78	76.47%
Lower	110	21.57%	93	22.79%	17	16.67%
Differentiation						
Well	49	9.61%	37	9.07%	12	11.76%
Moderate	288	56.47%	235	57.60%	53	51.96%
Poor	173	33.92%	136	33.33%	37	36.27%
T stage						
T1a	37	7.25%	31	30.39%	6	5.88%
T1b	66	12.94%	52	12.75%	14	13.73%
T2	111	21.76%	90	22.06%	21	20.59%
T3	255	50.00%	206	50.49%	49	48.04%
T4a	40	7.84%	28	6.86%	12	11.76%
T4b	1	0.20%	1	0.25%	0	0.00%
N stage						
N0	284	55.69%	221	54.17%	63	61.76%
N1	144	28.24%	120	29.41%	24	23.53%
N2	52	10.20%	42	10.29%	10	9.80%
N3	30	5.88%	25	6.13%	5	4.90%
AJCC-TNM stage						
IA	11	2.16%	8	1.96%	3	2.94%
IB	82	16.08%	67	16.42%	15	14.71%
IIA	100	19.61%	78	19.12%	22	21.57%
IIB	96	18.82%	76	18.63%	20	19.61%
IIIA	30	5.88%	24	5.88%	6	5.88%
IIIB	149	29.22%	121	29.66%	28	27.45%
IVA	42	8.24%	34	8.33%	8	7.84%
IVB	0	0.00%	0	0.00%	0	0.00%
Postoperative treatment						
None	315	61.76%	249	61.03%	66	64.71%
Radiation	36	7.06%	33	8.09%	3	2.94%
Chemotherapy	54	10.59%	45	11.03%	9	8.82%
Oral chemotherapy	28	5.49%	22	5.39%	6	5.88%
Chemoradiotherapy	51	10.00%	40	9.80%	11	10.78%
Traditional Chinese medicine	26	5.10%	19	4.66%	7	6.86%
Hospital day	24.17±14.62		24.02±12.87		24.75±20.23	
Postoperative hospital day	16.48±14.90		16.29±13.23		17.24±20.32	
Hemoglobin (HB)(g/L)	138.91±15.28		139.11±15.10		138.12±16.03	
White blood cell (WBC)(10^9/L)	6.02±1.81		6.08±1.89		5.74±1.43	

Variable	Total cohort(n=510)	Training set(n=408)	Validation set(n=102)
	number(percentage)	number(percentage)	number(percentage)
Lymphocyte (LY)(10⁹/L)	1.62±0.54	1.63±0.54	1.59±0.51
Total protein (TP)(g/L)	69.60±6.01	69.61±5.87	69.58±6.56
Albumin (ALB)(g/L)	43.81±4.47	43.92±4.44	43.36±4.58
Triglyceride (TG)(mmol/L)	1.28±0.65	1.30±0.67	1.21±0.55
Cholesterol (CH)(mmol/L)	4.59±0.95	4.60±0.91	4.55±1.11
Fasting glucose(mmol/L)	5.04±0.90	5.03±0.92	5.09±0.79
Uric acid (UA)(umol/L)	328.51±85.28	330.35±88.28	321.16±71.96
Height(cm)	166.77±6.35	166.65±6.31	167.24±6.50
Weight(kg)	61.06±9.13	60.61±9.14	62.84±8.94
BMI(kg/m²)	21.91±2.73	21.78±2.72	22.44±2.71
Maximum diameter of tumor (cm)	3.72±1.79	3.67±1.76	3.93±1.89

S.D.: standard deviation.

Table 2. Univariate and multivariate Cox regression analysis of the training set ESCC population.

Variable	Total	Event	Percentage	HR[1](95% CI)	*P* value[1]	HR[2](95% CI)	*P* value[2]
Gender							
Male	355	168	47.32%	1		1	
Female	53	11	20.75%	0.439(0.238-0.807)	0.008	0.357(0.179-0.712)	0.003
Age(years)					0.408		
≤59	134	67	50.00%	1			
60-69	192	80	41.67%	0.833(0.602-1.153)	0.271		
≥70	82	32	39.02%	0.780(0.512-1.189)	0.249		
Alcohol							
No	146	58	39.73%	1			
Yes	262	121	46.18%	1.163(0.850-1.590)	0.346		
Smoking							
No	130	44	33.85%	1		1	
Yes	278	135	48.56%	1.435(1.021-2.016)	0.038	1.093(0.742-1.611)	0.653
Education							
Primary school and below	242	97	40.08%	1			
Middle school and above	166	82	49.40%	1.232(0.918-1.654)	0.164		
Hypertension							
No	309	135	43.69%	1			
Yes	99	44	44.44%	1.017(0.724-1.430)	0.921		
Surgical approach					0.042		0.569
Sweet	198	99	50.00%	1		1	
Ivor-Lewis	153	66	43.14%	0.353(0.632-1.178)	0.353	0.880(0.630-1.230)	0.456
Mckeown	57	14	24.56%	0.491(0.281-0.860)	0.013	1.182(0.661-2.114)	0.573
Margin							
Negative	389	166	42.67%	1			
Positive	19	13	68.42%	1.603(0.912-2.820)	0.101		
Tumor location					0.485		
Upper	38	15	39.47%	1			
Middle	277	129	46.57%	1.180(0.691-2.014)	0.554		
Lower	93	35	37.63%	0.953(0.521-1.746)	0.877		
Differentiation					0.097		
Well	37	11	29.73%	1			
Moderate	235	96	40.85%	1.374(0.736-2.564)	0.318		
Poor	136	72	52.94%	1.781(0.944-3.359)	0.075		
T stage					<0.001		0.005
T1	83	16	19.28%	1		1	
T2	90	28	31.11%	2.027(1.097-3.748)	0.024	1.495(0.799-2.798)	0.209
T3	206	114	55.34%	3.622(2.146-6.155)	<0.001	2.197(1.250-3.861)	0.006
T4	29	21	72.41%	7.509(3.906-14.434)	<0.001	3.344(1.612-6.936)	0.001
N stage					<0.001		<0.001
N0	221	64	28.96%	1		1	
N1	120	60	50.00%	2.220(1.559-3.162)	<0.001	1.851(1.274-2.688)	0.001
N2	42	32	76.19%	4.674(3.045-7.174)	<0.001	3.208(1.999-5.149)	<0.001
N3	25	23	92.00%	7.514(4.623-12.212)	<0.001	4.958(2.930-8.389)	<0.001
Postoperative treatment							
No	249	114	45.78%	1			
Yes	159	65	40.88%	0.981(0.722-1.322)	0.903		
Hemoglobin (g/L)							
77-147	277	129	46.57%	1			
148-173	131	50	38.17%	0.822(0.593-1.139)	0.239		
White blood cell (10⁹/L)							
2.6-5.5	182	67	36.81%	1		1	
5.6-18.1	226	112	49.56%	1.424(1.052-1.928)	0.022	1.524(1.084-2.142)	0.015
Lymphocyte (10⁹/L)							
0.5-1.2	101	53	52.48%	1		1	

Variable	Total	Event	Percentage	HR[1](95% CI)	P value[1]	HR[2](95% CI)	P value[2]
1.3-4.0	307	126	41.04%	0.709(0.514-0.978)	0.036	0.676(0.475-0.962)	0.030
Total protein (g/L)							
54.7-66.0	124	60	48.39%	1			
66.1-92.1	284	119	41.90%	0.846(0.620-1.154)	0.291		
Albumin (g/L)							
30-49.5	362	167	46.13%	1			
49.6-56.4	46	12	26.09%	0.656(0.365-1.178)	0.158		
Triglyceride (mmol/L)							
0.43-1.33	262	130	49.62%	1		1	
1.34-6.05	146	49	33.56%	0.618(0.445-0.859)	0.004	0.826(0.581-1.173)	0.286
Cholesterol (mmol/L)							
1.68-3.63	172	82	47.67%	1			
3.64-8.58	236	97	41.10%	0.842(0.628-1.130)	0.253		
Fasting glucose (mmol/L)							
2.89-4.38	75	29	38.67%	1			
4.39-12.96	333	150	45.05%	1.482(0.995-2.208)	0.053		
Uric acid (umol/L)							
117-333	228	111	48.68%	1		1	
334-684	180	68	37.78%	0.691(0.510-0.934)	0.016	0.643(0.466-0.888)	0.007
BMI(kg/m²)							
15.79-20.70	143	71	49.65%	1		1	
20.76-32.60	265	108	40.75%	0.691(0.512-0.933)	0.016	0.908(0.661-1.247)	0.552

HR[1] and P[1]: univariate Cox regression results.
HR[2] and P[2]: multivariate Cox regression results.

For both statistical and clinical consideration, the indexes which were selected in the scoring tool had to meet the following criteria: (1) it should be statistically significant at least in the univariate Cox regression analysis; (2) it could reflect the patients' nutritional or metabolic status. Finally, BMI, lymphocyte count, uric acid level, and triglyceride level were selected to construct a new BLUT (BMI-lymphocyte-uric acid-triglyceride) nutritional assessment tool.

3.3. Definition and simplification of BLUT nutritional assessment tool

The weight of each index was assessed by the Cox regression model, which was based on the visualization of a nomogram, as shown in Figure 1A and Table 3. Indexes were given different risk scores and divided into the positive risk and negative risk categories. According to the weight scores of the four indexes, each patient was given a total score and a Kaplan-Meier curve was conducted, as shown in Supplementary Figure 2. The log rank test suggested the BLUT tool had significant prognostic performance in ESCC patients (P=0.049). However, this tool was complicated in this form and lacked of clinical practicability.

Thus, a simplified definition of BLUT tool was proposed based on the number of indexes in positive risk category, as shown in Table 4. If there was no index in the positive risk category, it was defined as normal. If there was 1 index, or there were 2 indexes or ≥3 indexes in the positive risk category, it was defined as low, moderate and high malnutrition risk, respectively. The Kaplan-Meier curve of the simplified tool was shown in Figure 1B, with a log rank P value <0.001. Subgroup analysis was further conducted in those patients with positive lymph nodes and BLUT showed significant prognostic value for those receiving post-surgery treatment, as shown in the Supplementary Table 1 and Supplementary Figure 3.

**Table 3.** Index categories and scores weighted by the nomogram model.

Variable	Category	Scores	Risk
BMI(kg/m²)	low(≤20.7)	7.23	Positive
	high(>20.7)	0	Negative
Lymphocyte (LY)(10⁹/L)	low (≤1.2)	7.45	Positive
	high (>1.2)	0	Negative
Uric acid (UA)(umol/L)	low (≤333)	6.24	Positive
	high (>333)	0	Negative
Triglyceride (TG)(mmol/L)	low(≤1.33)	10	Positive
	high(>1.33)	0	Negative

3.4. Comparison of PNI, GNRI, CONUT and BLUT assessment tools

The prognostic efficacy of PNI, GNRI, CONUT and BLUT assessment tools in ESCC patients was compared, as shown in Figure 2 and Table 5. The cut-off value of PNI was defined by the X-tile analysis, as shown in the Supplementary Figure 4. The log rank P values of PNI, CONUT and GNRI were 0.153, 0.098 and 0.174, respectively, indicating limited prognostic performance. The univariate analysis indicated that BLUT was significantly associated with the prognosis of ESCC (P<0.001). In addition, the multivariate Cox regression analysis also suggested that BLUT was an independent prognostic factor for ESCC patients (P=0.003), as shown in Table 6. Compared with PNI, CONUT and GNRI, the BLUT assessment tool had more rational population distribution in different malnutrition risk categories, and also suggested better predictive accuracy.
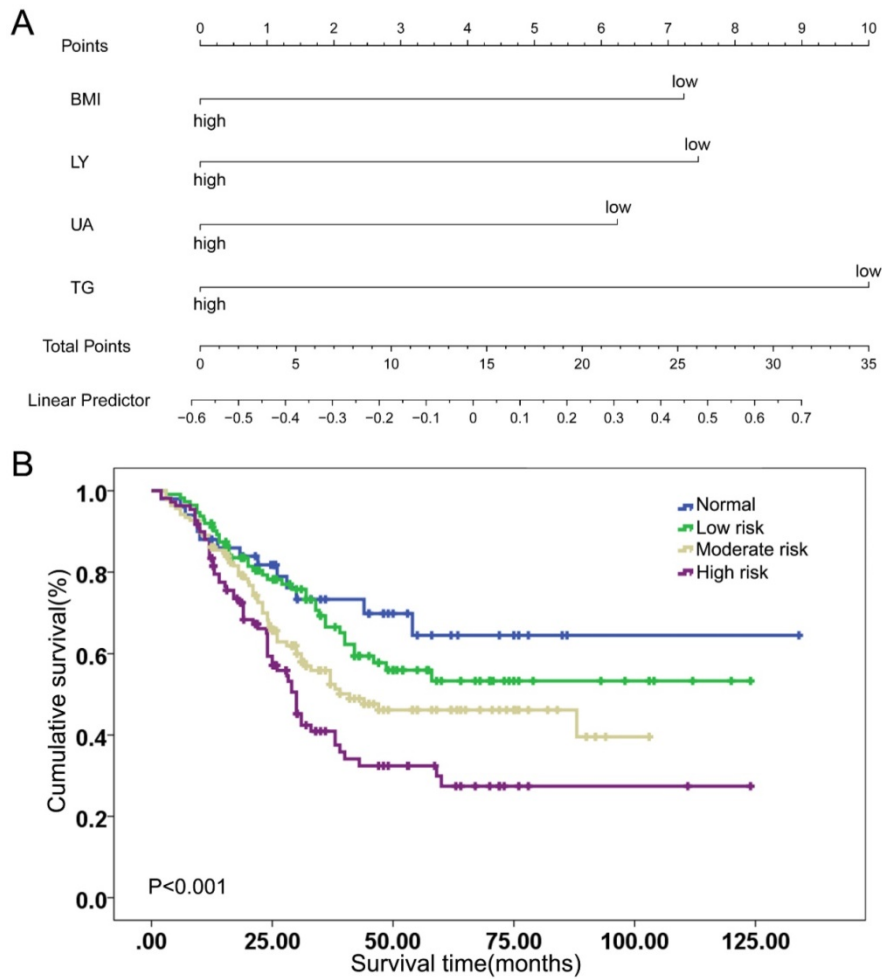
Figure 1. Indexes weight and simplification of BLUT nutritional assessment tool. (A) BMI, LY, UA and TG weight scores according to visualization of nomogram model, (B) Kaplan-Meier curve of simplified BLUT scoring tool (log rank P<0.001).
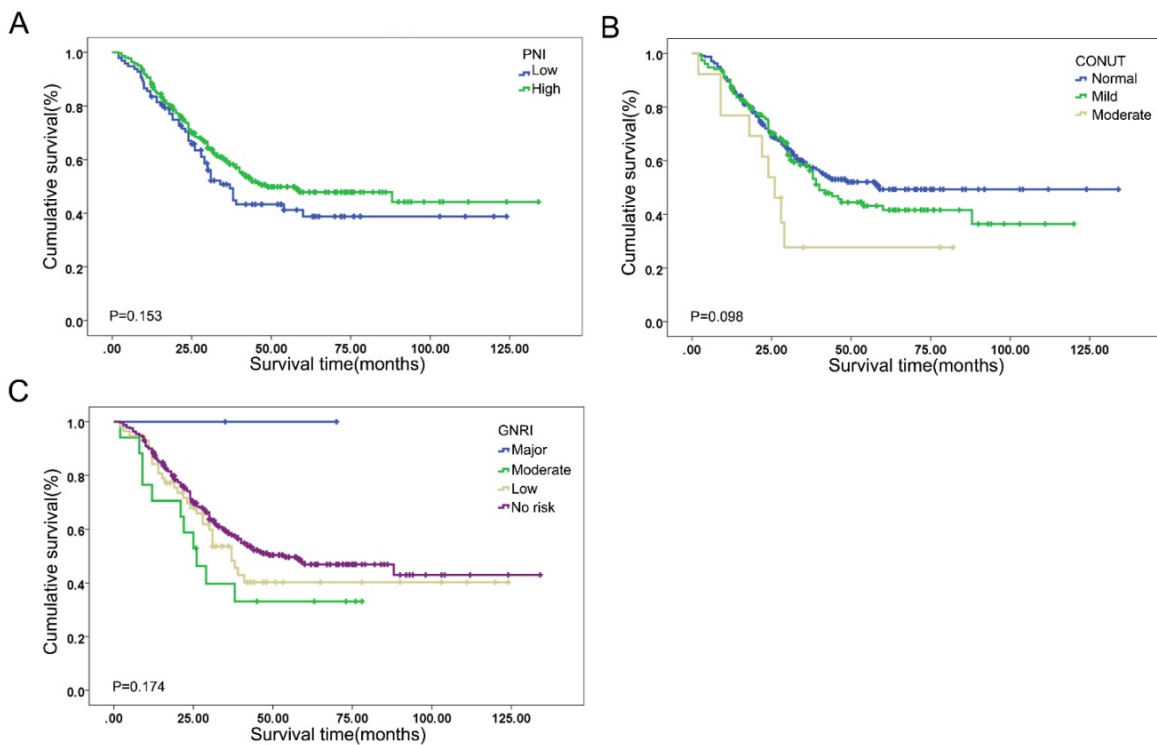
Figure 2. Kaplan-Meier curves of (A) PNI (log rank P=0.153), (B) CONUT (log rank P=0.098), and (C) GNRI (log rank P=0.174).

Table 4. Simplified definition of BLUT scoring tool.

BLUT category	Score interval	Status of BMI, LY, UA and TG
Normal	0.00	No index in the positive risk category
Low malnutrition risk	6.24-10.00	Any 1 index in the positive risk category
Moderate malnutrition risk	13.47-17.45	Any 2 indexes in the positive risk category
High malnutrition risk	20.92-30.92	Equal to or more than 3 indexes in the positive risk category

Table 5. Univariate Cox regression analysis of PNI, CONUT, GNRI and BLUT assessment tools in ESCC patients.

Assessment tool	Total	Event	Percentage	HR (95%CI)	P value[1]	P-value[2]
PNI						0.153
low	97	51	52.58%	1		
high	311	128	41.16%	0.791(0.571-1.094)	0.156	
CONUT					0.108	0.098
normal	241	98	40.66%	1		
mild malnutrition	154	72	46.75%	1.142(0.842-1.548)	0.393	
moderate malnutrition	13	9	69.23%	2.049(1.034-4.059)	0.040	
severe malnutrition	0	0	0	NA	NA	
GNRI					0.321	0.174
no risk	332	138	41.57%	1		
low risk	57	30	52.63%	1.237(0.833-1.837)	0.291	
moderate risk	17	11	64.71%	1.679(0.909-3.104)	0.098	
major risk	2	0	0.00%	NA	NA	
BLUT					<0.001	<0.001
Normal	50	14	28.00%	1		
Low malnutrition risk	112	40	35.71%	1.302(0.708-2.394)	0.395	
Moderate malnutrition risk	137	63	45.99%	1.849(1.036-3.300)	0.038	
High malnutrition risk	109	62	56.88%	2.699(1.510-4.826)	0.001	

P value[1]: univariate Cox regression analysis.

P value[2]: log rank test.

Table 6. Multivariate Cox regression analysis of BLUT assessment tool in ESCC patients.

Variable	HR (95%CI)	P value
Gender		
Male	1	
Female	0.348(0.188-0.644)	<0.001
T stage		0.007
T1	1	
T2	1.430(0.764-2.678)	0.264
T3	2.208(1.265-3.853)	0.005
T4	3.022(1.444-6.324)	0.003
N stage		<0.001
N0	1	
N1	1.724(1.188-2.502)	0.004
N2	3.270(2.020-5.293)	<0.001
N3	5.108(3.076-8.482)	<0.001
BLUT category		0.003
Normal	1	
Low malnutrition risk	1.211(0.655-2.240)	0.541
Moderate malnutrition risk	1.614(0.894-2.916)	0.112
High malnutrition risk	2.307(1.279-4.161)	0.006

3.5. A clinical nomogram based on preoperative nutritional assessment

In order to further analyze the prognostic value of the BLUT tool and to build a precise nutritional assessment-based model, a clinical nomogram based on gender, T stage, N stage and the BLUT tool was proposed, as shown in Figure 3A. The nomogram suggested good prognostic performance in both training set (log rank P<0.001) and validation set (log rank P=0.024), as shown in Figure 3B and 3C. The C-index and 95% CI of the nomogram was 0.735(0.698-0.772), and the AIC value was 1864.76. It had good prognostic efficacy and was significantly better than the model based on T stage and N stage (P=0.038), as shown in Table 7. Compared with other nutritional assessment based model, BLUT based nomogram had the highest C-index and the smallest AIC value, which further indicated that BLUT tool based model had more accurate discriminatory utility. The calibration curve of internal validation suggested that the BLUT based model had a high degree of similarity with the real situation in judging the 1-year, 3-year, and 5-year survival status, as shown in Supplementary Figure 5A, 5B and 5C. The external validation results also suggested good fitting effect (Supplementary Figure 5D, 5E and 5F), indicating that the BLUT score based ESCC prognosis model could be applied to other population cohorts.

Table 7. Comparison of different models based on different nutritional assessment tools.

| Model	C-index	AIC value
T stage+N stage	0.714(0.676-0.752)	1887.49
T stage+N stage+PNI	0.719(0.681-0.757)	1886.48
T stage+N stage+GNRI	0.721(0.683-0.759)	1889.00
T stage+N stage+CONUT	0.718(0.680-0.756)	1885.56
T stage+N stage+BLUT	0.728(0.691-0.765)	1878.35
T stage+N stage+PNI+Gender	0.726(0.688-0.764)	1875.03
T stage+N stage+GNRI+Gender	0.730(0.693-0.767)	1878.10
T stage+N stage+CONUT+Gender	0.726(0.689-0.763)	1874.77
T stage+N stage+BLUT+Gender	0.735(0.698-0.772)	1864.76

4. Discussion

The study proposed a new BLUT nutritional assessment tool by rigorous index selection and tool simplification, and also compared the prognostic performance between BLUT tool and traditional nutritional assessment tools, including PNI, CONUT and GNRI. In addition, a BLUT-based clinical nomogram was further proposed, which was significantly better than the T stage and N stage based model.

The prognostic value of PNI (log rank P=0.153), CONUT (log rank P=0.098) and GNRI (log rank P=0.174) in ESCC patients was limited. In contrast, BLUT assessment tool was an independent prognostic factor for ESCC patients, which had more rational population distribution in different malnutrition risk categories and better predictive accuracy. Besides, the simplification process enabled BLUT as a simple, convenient and efficient nutritional assessment tool, which could be easily applied in clinical practice.

Clinicians could quickly distinguish the preoperative malnutrition risk of ESCC patients by counting the number of indexes in positive risk intervals. On the other hand, a nutritional tool based clinical nomogram could help clinicians precisely predict the prognosis of ESCC patients. The complementarity of the two aspects can help to make quick and accurate clinical decisions.

PNI tool was firstly proposed by Onodera et al. (13) in 1984, which was based on 189 digestive tract cancer patients with malnutrition and received parenteral nutrition treatment. Although several studies have proved that PNI could predict the prognosis of ESCC patients who received surgery

(22-24), it should be noted that the cut-off value of PNI was controversial (24) and its independent prognostic role in ESCC patients was not determined (22). CONUT was proposed by Ignacio et al. (14), which included 53 patients from various clinical departments in the hospital. Toyokawa et al. (25) conducted a retrospective study based on 185 resectable thoracic ESCC patients and proved its independent prognostic value. However, the sample size of high-CONUT group and low-CONUT group was 17 and 168, respectively. Yoshida et al. (26, 27) suggested CONUT could be used to predict postoperative morbidity and long term survival of ESCC patients. The imbalanced population
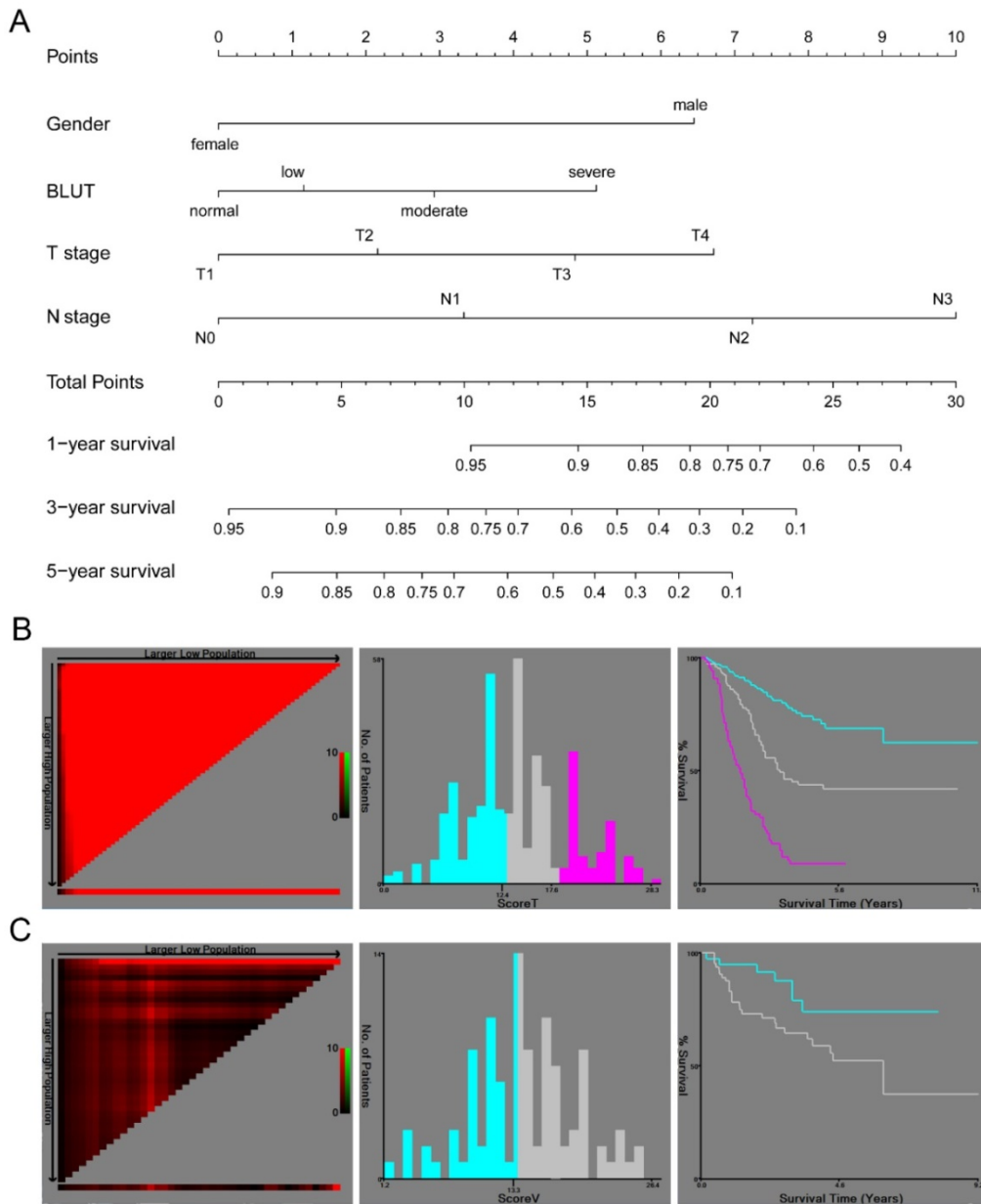
Figure 3. A clinical nomogram based on BLUT nutritional assessment tool. (A) Nomogram based on gender, BLUT, T stage and N stage, (B) Kaplan-Meier curve of the nomogram model by X-tile software in training set population (log rank P<0.001), (C) Kaplan-Meier curve of the nomogram model by X-tile software in validation set population (log rank P=0.024).

distribution in each category also emerged, with only 22 of total 373 cases in the moderate and severe risk category. GNRI was proposed by Yamada et al. (28), and the target population was 422 patients receiving continuous hemodialysis. This tool was popularized to 181 elderly hospitalized elderly people (age>65 years old) by Bouillanne et al. (15). It has been reported by Bo et al. (29) that GNRI was an independent prognostic factor for overall survival in elderly ESCC patients with radiotherapy. However, there is no study focusing on the prognostic value of GNRI in preoperative ESCC patients without age restriction. PNI, CONUT and GNRI had a common index of albumin level, while most of the preoperative ESCC patients included in the current study had a normal range of albumin level. 97.6% of the training set population had a normal range (35-55g/L), as shown in Supplementary Figure 6. The prognostic value of the albumin based scoring tool might be limited under this circumstance. Furthermore, in the univariate Cox analysis, the HRs and 95% Cis for Mckeown approach and Ivor-Lewis approach were 0.491(0.281-0.860) and 0.353(0.632-1.178) compared with Sweet approach, while there were no statistically significant results for these surgical approaches in the multivariate analysis. Many previous studies tried to find the optimal surgical approach for esophageal cancer, however, there was no definite conclusion for this question (30).

The current BLUT assessment tool adopted BMI, lymphocyte, uric acid and triglyceride as indexes, taking both general condition of the patients and laboratory tests into account. It has been reported that higher BMI was a protective factor for esophageal cancer (31, 32). Lymphocyte is one of the most commonly used nutritional markers (13, 14) and its metabolism and behavior could be impacted by nutritional status (33, 34). Besides, lymphopenia is an independent prognostic factor for ESCC patients (35). The association between uric acid and tumor was controversial. Kuhn et al. (36) reported there was a negative association between uric acid and cancer mortality. There were few studies on the relationship between preoperative triglyceride level and prognosis of ESCC, but it was proved as a protective factor in breast cancer patients (37). More well-designed prospective studies with large sample size were warranted in the future to further prove the prognostic role of uric acid and triglyceride in ESCC patients with surgery.

This single-center retrospective study also had some limitations. The BLUT tool was only applicable to ESCC patients who received cancer-directed surgery. The applicability was not yet clear for advanced stage patients who cannot undergo surgery, and for patients who received neoadjuvant therapy before surgery and the laboratory tests were severely impacted. In addition, more researches are required to further confirm whether the scoring system is suitable for continuous monitoring of nutritional status after surgery.

5. Conclusion

The BULT scoring tool could distinguish the heterogeneity of preoperative nutritional status for ESCC patients, especially for those with normal albumin level. Besides, the BLUT-based nomogram had good prognostic efficacy.

Supplementary Material

Supplementary methods, figures and table.
http://www.jcancer.org/v10p3883s1.pdf

Acknowledgements

Competing Interests

The authors have declared that no competing interest exists.

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