Original Article

Preoperative prognostic nutritional index shows no significant prognostic value for short-term outcomes of anastomosis-leakage patients after cancerous esophagectomy

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Background: The relationship between preoperative nutritional and immunological status and long-term outcome after cancerous esophagectomy has been investigated widely. Growing evidence also demonstrated preoperative nutritional and immunological status also affects short-term outcome after surgery for esophageal cancer. However, the relationship between preoperative nutritional and immunological status and short-term outcome of anastomosis-leakage patients after cancerous esophagectomy was scarce. The aim of this study was to evaluate the association between preoperative prognostic nutritional index (PNI) and short-term outcome of anastomosis-leakage patients after surgery.

Methods: In this study, we retrospectively enrolled 90 patients who were confirmed to be esophageal cancer by preoperative biopsy or postoperative pathological review and also suffered postoperative anastomotic leakage from January 2014 to June 2017 at the Department of Thoracic Surgery, West China Hospital. Then we evaluated the association between PNI and short-term surgical outcome. The endpoints included postoperative mortality, postoperative hospital duration, postoperative intensive care unit (ICU) duration, hospitalization cost.

Results: The cut-off value of PNI was set at 49.83 in our study, patients with a preoperative PNI ≥49.83 were divided into high-PNI group, while those with a preoperative PNI <49.83 were classified into low-PNI group. For the postoperative anastomosis-leakage patients in the two groups, baseline characteristics were all comparable, and analysis revealed no significantly statistical difference between the two groups regarding mortality, postoperative hospital duration and postoperative ICU duration. Though mean hospital-duration cost (144,791.08±87,312.87 *vs.* 127,364.25±69,233.16) was more in the low-PNI group, there was still no significant difference demonstrated (P=0.297). There was no significant difference revealed between the subgroups of non-death patients from the two original groups concerning the endpoints, while the hospital-duration cost of the high-PNI group tended to be lower than low-PNI group (125,262.80±71,304.12 *vs.* 136,421.60±77,052.49, P=0.503).

Conclusions: Although in-hospital cost of high-PNI group tended to be lower than low-PNI group, preoperative PNI showed no significant prognostic value for short-outcomes of anastomosis-leakage patients after cancerous esophagectomy. More prospective studies were badly needed to provide more evidence in the future.

Keywords: Prognostic nutritional index (PNI); cancerous esophagectomy; anastomosis leakage; short outcome

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Introduction

Esophageal cancer is the eighth most common cancer and one of the most aggressive malignancies which resulted in sixth cancer related death worldwide, the 5-year survival is just around 15–25% (1). However, as for the patients who underwent curative cancer surgery, the 5-year overall survival is significantly improved which increases to 40% (2). Owing to continuous improvements in surgery procedures and related auxiliary therapies, either short-term or long-term prognosis has been significantly improved in recent years (2-5). However, postoperative complications especially anastomosis leakage and other life-threatening complications still badly troubled surgeons, that results in unsatisfactory prognosis and giant economic burden (6-8).

Preoperative prognostic nutritional index (PNI) was originally developed to predict risk of perioperative and risk of postoperative morbidity and mortality for gastrointestinal surgery (9,10). The PNI which was simplified by Onodera *et al.* was defined based on the serum albumin level and peripheral blood lymphocyte count (11). PNI which directly represents the nutritional and immunological status of patients was usually low in esophageal cancer patients, resulting from difficulty in eating and chronic cost of the tumor. Increasing studies demonstrated that preoperative immunologic and nutritional status associated with either postoperative complications or long-term outcomes of cancer patients (12-14). With regard to esophageal cancer, it was showed that PNI was a significant and independent predictor of long-term outcomes of patients who received curative esophagectomy or neoadjuvant chemotherapy, and PNI could act as a marker of survival (10,15,16). What's more, recent studies also proved that preoperative PNI could provide predictive information for postoperative complications in patients with esophageal carcinoma (17,18).

On basis of the previous studies which demonstrated that PNI could be an independent predictor for both short-term and long-term outcomes of patients with esophagectomy. It is still unknown whether PNI could accurately predict the prognosis of anastomosis-leakage patients who were most concerned by surgeons. Thus, we hypothesize that preoperative PNI could provide predictive value for the anastomosis-leakage patients. Aiming to investigate the predictive value of preoperative PNI on the short-term outcomes of the patients suffered anastomotic leakage, including death rate, reoperation rate, costs and hospital duration.

Methods

For this retrospective observational study, a total of 97 consecutive patients who were diagnosed anastomosis leakage after undergoing curative esophagectomy and lymphadenectomy were retrieved from January 2014 to June 2017 in West China Hospital. Tumor stage of the patients were defined according to the seventh edition of the American Joint Committee on Cancer TNM classification system. The eligibility criteria for review were as follows: (I) underwent esophagectomy and regional lymphadenectomy (including abdominal and thoracic lymph nodes dissection, cervical lymph nodes of some patients were also dissected); (II) esophageal cancer proven by pathology; (III) underwent R0 resection regarding the surgical margin; (IV) no distant metastasis (M1) before surgery; (V) anastomotic leakage confirmed by endoscopy or methylene blue test postoperatively. The exclusion criteria were as follows: (I) suffered acute or chronic inflammatory disease; (II) diagnosed hematological or autoimmune disease; (III) with clinical data missing; (IV) suffered other malignancies other than esophageal cancer. All those patients received endoscopy, endoscopic ultrasound, chest computed tomography (CT), abdominal CT, cervical ultrasonography, and pulmonary function and blood testing routinely, evaluating as resectable esophageal cancer preoperatively. All the patients received open or minimally invasive esophagectomy and systematic lymph nodes dissection, surgery procedure included Ivor-Lewis or Sweet or McKeown procedure. Because this study was a retrospective prognostic analysis and analyzed anonymously, the Ethics Committee of West China Hospital, Sichuan University waived the need for informed consents from those patients, while an approval for the ethical committee was obtained (approval number: 20191022).

The end point parameters including secondary surgery, in-hospital mortality after anastomotic leakage, postoperative hospital duration, postoperative intensive care unit (ICU) duration and in-hospital cost. The clinical and pathological data including gender, age, smoking history, alcohol history, tumor location, tumor size, histological type, lymph node metastasis, TNM stage, and preoperative routine laboratory data including routine blood test and the hepatic function test before breakfast within 2 weeks before surgery were collected. The definitions of PNI was calculated as follows: PNI =10× serum albumin (g/dL) +0.005× total lymphocyte count (per mm3) (11).

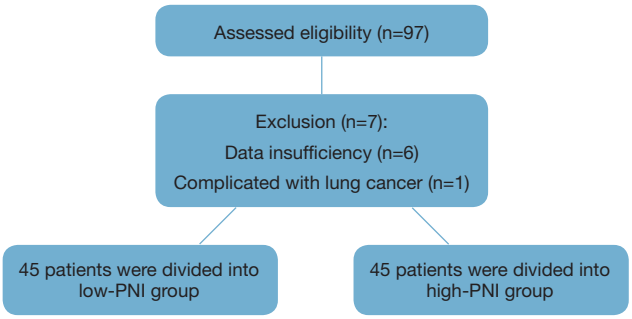

Figure 1 Flow chart showing patient recruitment. PNI, prognostic nutritional index.

One-sample Kolmogorov-Smirnov test

		PNI
N		90
Normal Parameters[a,b]	Mean	50.0650
	Std. deviation	5.10545
Most extreme differences	Absolute	0.112
	Positive	0.112
	Negative	−0.067
Test statistic		0.112
Asymp. Sig. (two-tailed)		0.007[c]

Figure 2 Normal distribution test of PNI. [a], test distribution is normal; [b], calculated from data; [c], Lilliefors significance correction. PNI, prognostic nutritional index.

Statistical analysis

All analyses were performed using Statistical Package for Social Science (SPSS for Windows, version 22.0, SPSS Inc., Chicago, IL, USA) program. Subject characteristics were compared using Chi-squared test or Fisher exact test for categorical variables and Student's t-test or Mann-Whitney U test for continuous variables. Kolmogorov-Smirnov test was applied to examine characteristics of PNI distribution. A P value of less than 0.05 was considered significant.

Results

A total of 97 patients with confirmed anastomotic leakage after cancerous esophagectomy were enrolled in this study primarily, preoperative PNI of three patients could not be gained owing to data of the hepatic function test was missing, postoperative pathological reports of three patients were missing, and diagnosis of 1 patient combined with lung cancer, then 90 patients were included in this study for analysis finally as demonstrated in *Figure 1*. Mean age of all the patients were 64.34 years old, the mean PNI value was 50.10, while the median value of PNI was 49.83.

As shown in *Figure 2*, characteristics of distribution of the PNI was skewed distribution examined by Kolmogorov-Smirnov test (P=0.007), we extracted the median value of the PNI values as cut-off value. The cut-off value of PNI was set at 49.83 in our study, then 45 patients with a preoperative PNI ≥49.83 were divided into high-PNI group, while another 45 patients with a preoperative PNI <49.83 were classified into low-PNI group.

With regard to relationship between different variables and PNI, analysis demonstrated that a strong positive correlation was detected between the level of albumin and lymphocyte count and PNI (P<0.001). Besides, it seemed that the preoperative PNI tended to be increased in low hospital-duration cost group compared with high hospital-duration cost group (51.00±5.20 *vs.* 49.13±4.89), no significant difference was observed (P=0.083). No significantly statistical differences of PNI were detected grouping by other variables as showed in *Table 1*. The demographics, pathological and other baseline characteristics of all the 90 patients included in this study were demonstrated in *Table 2*. Tumor size of the low-PNI group was significantly larger than high-PNI group which was measured by the longest diameter (4.73±2.30 *vs.* 3.88±1.69, P=0.047). Compared with low-PNI group, the level of albumin, lymphocyte count and PNI were both statistically significant higher in high-PNI group (P<0.001). While all the other baseline characteristics were comparable between the two groups. Comparison of the endpoints between low and high-PNI groups was showed in *Table 3*. Postoperative hospital duration, mortality in hospital and post-leakage hospital duration were all comparable between two groups. The reoperation ratio seemed higher in low-PNI group, while no significant difference was observed (P=0.266). What's more, the hospital-duration cost in high-PNI group inclined to be lower than in low-PNI group, even though it was statistically similar (127,364.25±69,233.16 *vs.* 144,791.08±87,312.87, P=0.297).

There were five hospital-duration deaths after anastomosis leakage in two groups respectively. Then subgroup analysis of the non-death patients in the two groups were conducted. As demonstrated in *Table 4*, the level of preoperative PNI, albumin and lymphocyte count

Table 1 Relationship between kinds of variables and the PNI

Variables	N	PNI	P value
Age (years old)			0.274
≤65	47	50.63±4.66	
>65	43	49.45±5.54	
Sex			0.295
Male	71	49.77±5.29	
Female	19	51.16±4.29	
Alcohol			0.743
Yes	41	49.87±4.53	
No	49	50.23±5.58	
Smoking			0.405
Yes	60	50.38±5.26	
No	30	49.43±4.81	
Albumin (g/L)			<0.001
≤40	30	45.49±3.33	
>40	60	52.35±4.23	
Lymphocyte count (10^9/L)			<0.001
≤1.64	45	47.43±4.12	
>1.64	45	52.70±4.65	
Tumor depth			0.544
T1–T2	35	50.48±5.43	
T3–T4	55	49.80±4.92	
Lymph node metastasis			0.775
Positive	38	50.25±5.69	
Negative	52	49.93±4.69	
Pathological stage			0.771
I–II	46	50.22±5.16	
III	44	49.90±5.10	
Differentiation degree			0.098
G1–G2	52	49.30±4.83	
G3	38	51.11±5.35	
Comorbidity			0.877
Yes	50	50.14±4.77	
No	40	49.97±5.56	
Cost (RMB)			0.083
≤115,600	45	51.00±5.20	
>115,600	45	49.13±4.89	
Postoperative hospital duration (days)			0.755
≤39	45	50.23±4.78	
>39	45	49.89±5.47	

PNI, prognostic nutritional index; RMB, renminbi.

Table 2 Baseline characteristics of the two groups

Variables	Low-PNI group	High-PNI group	P value
Age (years old)	65.38±9.45	63.31±8.57	0.280
Sex			0.438
Male	37	34	
Female	8	11	
Alcohol			0.832
Yes	21	20	
No	24	25	
Smoking			0.655
Yes	29	31	
No	16	14	
Albumin (g/L)	39.15±2.57	43.83±2.81	<0.001
Lymphocyte counts (10^9/L)	1.41±0.40	1.97±0.54	<0.001
PNI	46.20±2.95	53.93±3.67	<0.001
Neoadjuvant therapy			–
Yes	2	0	
No	43	45	
Surgery methods			0.833
MIE	23	24	
OE	22	21	
Surgery procedure			0.378
Sweet	11	16	
Ivor-Lewis	10	6	
McKeown	24	23	
Digestive tract reconstruction			0.434
Stomach	43	40	
Non-stomach	2	5	
Anastomotic methods			0.673
Sewn by hand	22	24	
Sewn by machine	23	21	
Anastomotic site			0.288
Neck	28	23	
Thorax	17	22	
Bleeding (mL)	170.22±132.52	179.89±108.54	0.706

Table 2 *(continued)*

Table 2 *(continued)*

Variables	Low-PNI group	High-PNI group	P value
Tumor site			0.500
Upper	6	7	
Medium	24	28	
Lower	15	10	
Tumor size (cm)	4.73±2.30	3.88±1.69	0.047
Tumor depth			0.123
T1	7	12	
T2	11	5	
T3	11	17	
T4	16	11	
Total lymph nodes	20.47±8.68	16.64±9.15	0.450
Positive lymph nodes	1.22±2.49	1.78±3.80	0.414
Pathological stage			0.200
I	7	12	
II	17	10	
III	21	23	
Lymph node metastasis			0.284
Positive	16	21	
Negative	29	24	
Lymph node stage			0.529
N0	29	23	
N1	8	13	
N2	6	6	
N3	2	3	
Differentiation degree			0.859
G1	3	5	
G2	23	21	
G3	19	19	

PNI, prognostic nutritional index; RMB, renminbi; MIE, minimally invasive esophagectomy; OE, open esophagectomy.

were significant lower in the low-PNI group than in high-PNI group (P<0.001). Besides, tumor size of the low-PNI group tended to be larger than high-PNI group, while it was not statistically significant (4.64±2.32 *vs.* 3.76±1.72, P=0.059). Other demographics and characteristics were all similar between the two groups in the subgroup analysis. Concerning the endpoints analysis between the subgroups illustrated in *Table 5*, reoperation ratio, postoperative hospital duration and post-leakage hospital duration were all comparable between the two groups in subgroup analysis. However, the mean in-hospital cost in high-PNI group tended to be lower than in low-PNI group more than 10,000 RMB, even though no significant differences was observed (125,262.80±71,304.12 *vs.* 136,421.60±77,052.49, P=0.503).

Discussion

To our knowledge, there have been a large quantity of studies exploring the relationship between preoperative PNI and long or short outcomes of patients undergoing esophagectomy for esophageal cancer (15,18), while this was the first study to investigate the prognostic value of preoperative PNI on short-term outcomes of anastomosis-leakage patients after receiving cancerous esophagectomy. As for anastomosis-leakage patients after undergoing cancerous esophagectomy, this study found there were no significant differences between high preoperative PNI group and low preoperative PNI group concerning short-term outcomes. Other than hospital-duration cost seemed to be higher in low preoperative PNI group both in original analysis and subgroup analysis, while it demonstrated no statistical significance. Besides, analysis revealed that tumor size of high-PNI group were significant smaller than in low-PNI group.

The PNI calculated from albumin and total lymphocyte count was initially designed to assess the nutritional and immunological status of patients undergoing surgery for gastrointestinal cancer (11). The cut-off value of preoperative PNI was defined to be 49.83 after analysis and calculation in this study, it was extracted from the median value of all the patients close to the mean value 50.065 after normal test. However, what's worth mentioning is that even though there have been a large number of studies relating to PNI, the cut-off value is still not reaching a consensus. Hirahara *et al.* in 2017 reported a cut-off value of 49.2 which was close to ours using receiver operating characteristics (ROC) curve and came to the conclusion that the PNI was a significant and independent predictor of cancer-specific survival and overall survival of esophageal squamous cell carcinoma (ESCC) patients after curative esophagectomy (10). In a study concerning the prognostic value of PNI on postoperative complications and survival in patients with resection of

Table 3 endpoints of the two groups

Variables	Low-PNI group	High-PNI group	P value
Reoperation			0.266
Yes	6	2	
No	39	43	
Postoperative hospital duration (days)	41.78±21.58	41.96±21.99	0.969
Post-leakage hospital duration (days)	33.31±20.76	31.96±22.74	0.768
Death			1.000
Yes	5	5	
No	40	40	
In-hospital cost (RMB)	144,791.08±87,312.87	127,364.25±69,233.16	0.297

PNI, prognostic nutritional index; RMB, renminbi.

colorectal cancer, Mohri *et al.* also defined a PNI value of ≥50 was locating in normal range (19). However, there still were other different cut-off values of PNI ranging from 45 to 55 (17,20-22). More robust trials and evidence are urgently performed to determine the accurate cut-off value of preoperative PNI in the future.

Our study demonstrated that the relationship between preoperative PNI and tumor size was negative. Similarly, previous studies have found enlarged tumor size, and higher TNM staging with preoperative PNI decreasing (17,19,23), which indicated low-PNI usually related with more progressive tumor. As for the short-term outcomes, Filip *et al.* showed that preoperative PNI acted as an independent risk factor for predicting major complications (grade III–V of Clavien-Dindo classification) after cancerous esophagectomy (18). Other studies also demonstrated that preoperative PNI represented a useful indicator of the occurrence of complications and length of hospital stay, and may influence overall survival at 6 months after surgery, and in which the result of high-PNI group were more favorable (17,24). On the contrary, Han-Geurts *et al.* concluded that preoperative nutritional parameters including PNI, Nutritional Risk Index (NRI), body mass index (BMI) and weight loss had no significant predictive value on postoperative complications in patients undergoing resection of esophageal cancer (25), which was analogous to this finding. Many studies have demonstrated that PNI was an independent prognostic factor for overall survival and advocated to act as a new maker of survival owing to cost-effective and readily available (10,26,27). Besides, the same result was found that high-PNI also act as an independent factor to predict better short- and long-term outcomes of gastric malignancy patients after surgery (28,29). Oshi *et al.* also reported patients with low preoperative PNI tended to suffer a higher risk for anastomotic leakage after laparoscopy-assisted total gastrectomy in 2016 (30). Concerning rectal cancer, Noh *et al.* concluded patients with anastomosis leakage were associated with poorer disease-free survival, and these anastomosis-leakage patients had a higher probability to suffer tumor recurrence while the PNI was decreasing to below 36 (31). What's interesting was increasing studies have demonstrated that systemic inflammation score and extended inflammation related factors were found to be novel and useful prognostic score for esophageal cancer patients after surgery, the prognosis was worsening with status of systemic inflammation decreasing (32-34). Absolutely, large, prospective studies of relationship between status of systemic inflammation and prognosis of esophageal patients are urgently needed in the future.

This study had several limitations. First, it was a retrospective study in nature which could limit the validity of our results. Second, this study still suffered from the limitation of 90 small sample size. Third, comparisons of long-term outcomes between high and low-PNI groups are badly needed for the patients with anastomosis leakage in the future. Finally, the adequacy of the cut-off value for the PNI was needed to be assessed.

Conclusions

In this retrospective study, it concluded that preoperative immunological and nutritional status established by PNI

Table 4 Subgroup analysis of baseline characteristics of non-death patients

Variables	Low-PNI group	High-PNI group	P value
Age (years old)	65.55±9.49	62.85±8.48	0.184
Sex			0.592
Male	32	30	
Female	8	10	
Alcohol			0.823
Yes	18	19	
No	22	21	
Smoking			0.348
Yes	24	28	
No	16	12	
Albumin (g/L)	39.20±2.69	43.93±2.81	<0.001
Lymphocyte counts (10^9/L)	1.41±0.40	2.00±0.54	<0.001
PNI	46.24±3.08	54.20±3.70	<0.001
Neoadjuvant therapy			–
Yes	2	0	
No	38	40	
Surgery methods			0.654
MIE	20	22	
OE	20	18	
Surgery procedure			0.345
Sweet	11	14	
Ivor-Lewis	10	5	
McKeown	19	21	
Digestive tract reconstruction			0.201
Stomach	39	35	
Non-stomach	1	5	
Anastomotic methods			0.654
Sewn by hand	18	20	
Sewn by machine	22	20	
Anastomotic site			0.653
Neck	23	21	
Thorax	17	19	
Bleeding (mL)	147.75±87.84	176.50±101.12	0.179
Tumor site			0.301
Upper	5	6	
Medium	22	27	
Lower	13	7	

Table 4 *(continued)*

Table 4 *(continued)*

Variables	Low-PNI group	High-PNI group	P value
Tumor depth			0.186
T1	7	11	
T2	10	4	
T3	11	16	
T4	12	9	
Tumor size (cm)	4.64±2.32	3.76±1.72	0.059
Total lymph nodes	20.75±8.97	17.08±9.39	0.077
Pathological stage			0.213
I	7	11	
II	16	9	
III	17	20	
Lymph node metastasis			0.108
Positive	12	19	
Negative	28	21	
Lymph node stage			0.350
N0	28	20	
N1	7	12	
N2	4	6	
N3	1	2	
Differentiation degree			0.357
G1	2	5	
G2	22	17	
G3	16	18	

PNI, prognostic nutritional index; RMB, Renminbi; MIE, minimally invasive esophagectomy; OE, open esophagectomy.

Table 5 Subgroup analysis of endpoints of non-death patients

Variables	Low-PNI group	High-PNI group	P value
Reoperation			0.359
Yes	4	1	
No	36	39	
Postoperative hospital duration (days)	43.20±21.26	44.35±21.96	0.813
Post-leakage hospital duration (days)	34.75±20.60	34.30±22.98	0.927
In-hospital cost (RMB)	136,421.60±77,052.49	125,262.80±71,304.12	0.503

PNI, prognostic nutritional index; RMB, renminbi.

has no significant predictive value on short-term outcomes in patients with anastomosis leakage after cancerous esophagectomy, while the in-hospital cost always tended to be lower in high-PNI group. And further studies conducted with larger cohorts were badly needed in the future to investigate significance of preoperative PNI for the patients.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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 Ethics Committee of West China Hospital, Sichuan University waived the need for informed consents from those patients, while an approval for the ethical committee was obtained (approval number: 20191022).

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