Original Article (Clinical Original)

The prognostic nutritional index is correlated negatively with the lung allocation score and predicts survival after both cadaveric and living-donor lobar lung transplantation

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Abstract

Purpose: The prognostic nutritional index (PNI), calculated based on the serum albumin levels and the total lymphocyte count, has been identified as a predictor of clinical outcomes in various fields of surgery. In the present study, we investigated the relationship between the PNI and the lung allocation score (LAS) as well as the impact of the PNI on the outcomes of both cadaveric lung transplantation (CLT) and living-donor lobar lung transplantation (LDLLT).

Methods: We reviewed retrospective data for 127 recipients of lung transplantation (LT), including 71 recipients of CLT and 56 recipients of LDLLT.

Results: The PNI was correlated significantly and negatively with the LAS (r = -0.40, P = 0.0000037). Multivariate analysis revealed that age (P = 0.00093), BMI (P = 0.00087), and PNI (P = 0.0046) were independent prognostic factors of a worse outcome after LT. In a subgroup analysis, survival after both CLT (P = 0.015) and LDLLT (P = 0.041) were significantly worse in the low PNI group than in the high PNI group.

Conclusion: Preoperative nutritional evaluations using the PNI can assist with the assessment of disease severity in LT recipients and may predict survival after both CLT and LDLLT.

Introduction

It is well known that preoperative nutritional status affects the clinical outcome of surgery; thus, an accurate assessment of the preoperative nutritional status is essential to prevent surgical complications and improve prognosis after surgery [1-4]. To evaluate the preoperative nutritional status appropriately, the prognostic nutritional index (PNI) was introduced. The PNI is calculated using only two preoperative parameters from a blood sample: serum albumin and the total lymphocyte count [5]. The PNI has been identified as a prognostic predictor in various fields of surgery [6-11], including lung cancer surgery and cadaveric lung transplantation (CLT) [6].

The lung allocation score (LAS) was established in the United States in 2005 to reduce the waiting time of lung transplantation (LT) candidates with serious conditions and to reduce the waitlist mortality rate [12-15]. Currently, the LAS is calculated using laboratory and physiological parameters of LT candidates, including age, body mass index (BMI), disease type, and respiratory, cardiac, and renal function. However, with the exception of BMI, the LAS calculator has not yet adopted factors assessing the nutritional status of LT candidates, such as the serum albumin level and the total lymphocyte count (which are used to calculate the PNI). Thus, the relationship between the PNI and the LAS remains unclear [16, 17].

As an alternative to CLT, living-donor lobar LT (LDLLT) can be life-saving for patients with end-stage lung disease and has a survival rate similar to that of CLT. LDLLT is a realistic option for patients requiring urgent LT who cannot wait for cadaveric lung donation because of the severe donor shortage in Japan [18]. Notably, the recipients of LDLLT have been shown to have a significantly higher LAS and a

significantly lower BMI than those of CLT [19-21], suggesting a more compromised condition in pretransplant recipients of LDLLT. Although the PNI has been shown to affect outcomes after CLT [6], there is limited information about the impact of PNI on outcomes after LDLLT. Thus, we investigated the relationship between the PNI and the LAS in recipients of LT as well as the impact of PNI on the outcomes of both CLT and LDLLT.

Methods

Patients

This was a single-center retrospective cohort study of patients undergoing LT for end-stage lung disease at Okayama University Hospital between June, 2003 and August, 2016. We assessed the patient characteristics and postoperative outcomes of 127 patients who underwent LT, including 71 recipients of CLT and 56 recipients of LDLLT. The study protocol (No. 2001-035) was approved, and each patient's written informed consent was waived by the institutional review board of Okayama University Hospital. All procedures were performed in accordance with the relevant guidelines and regulations.

Data management

The PNI was calculated using the following equation: **PNI = (10 × ALB (g/dL) + (0.005 × TLC[/mm^3])**. The LAS of each patient was calculated retrospectively at the time of registration with the LT waiting list using the LAS calculator published in November, 2015 on the OPTN website (https ://optn.transplant.hrsa.gov/resources/allocation-

calculators/lascalculator/) to establish the preoperative severity of the recipients. Chronic lung allograft dysfunction (CLAD) was diagnosed using the classification system proposed by the International Society for Heart and Lung Transplantation (ISHLT) [22].

The discriminative abilities of continuous variable factors such as age, BMI, supplemental oxygen concentration, serum creatinine level, LAS, and PNI were evaluated using a concordance index (c-index), which was identical to the area under a receiver operating characteristic (ROC) curve for overall mortality. Overall survival was evaluated using univariate analyses and a multivariate analysis of preoperative factors, including sex, age, BMI, diagnosis (interstitial lung disease vs. non-interstitial lung disease), supplemental oxygen concentration, mechanical ventilation, tracheostomy, extracorporeal membrane oxygenation support, use of glucocorticoids, serum creatinine level, diabetes mellitus, LAS, cytomegalovirus mismatch (recipient negative/ donor positive), total number of human leukocyte antigen (HLA)-A, HLA-B and HLA-DR mismatches, and PNI. The correlations between the PNI and LAS and between the PNI and BMI were evaluated. In a subgroup analysis, overall survival was analyzed separately for patients undergoing CLT and for those undergoing LDLLT.

Statistical analysis

Differences in the patient characteristics were tested using the Mann-Whitney U test for continuous variables and the Pearson chi-square test for categorical variables. Missing data were not replaced. The Pearson product-moment correlation coefficient was calculated in the correlation analysis. Overall survival after LT was analyzed using the

Kaplan–Meier method, and the log-rank test was used for statistical comparisons of differences between groups. The Cox proportional hazard regression model with the BIC stepwise method was used for the multivariate analysis. Differences were considered significant at P <0.05. All the statistical analyses except for the multivariate analysis were performed using GraphPad Prism 7.04 software program (San Diego, CA, USA). EZR version 1.40 (Saitama Medical Center, Jichi Medical University, Saitama, Japan) [23] was used for the multivariate analysis. EZR is a graphical user interface for R, version 3.5.2 (The R Foundation for Statistical Computing, Vienna, Austria). Specifically, the software is a modified version of R commander designed to add statistical functions frequently used in biostatistics.

Results

Table 1 summarizes the patient characteristics. Among the 127 patients, 71 (55.9%) underwent CLT and 56 (44.1%) underwent LDLLT. The PNI was correlated significantly and negatively with the LAS (**Fig. 1**, r = -0.40, P = 0.0000037), but not with the BMI (r = -0.042, P = 0.64). Using the ROC curve analysis, the cut-off values were defined as 28 years of age (c-index, 0.53), a BMI of 24.2 kg/m^2 (c-index, 0.53), an oxygen concentration of 32% (c-index, 0.53), a serum creatinine level of 0.61 mg/dL (c-index, 0.54), an LAS of 58.04 (c-index, 0.56), a total of six HLA mismatches (c-index, 0.61), and a PNI of 46.35 (c-index, 0.62). Univariate analysis revealed that the overall survival after LT was significantly worse in patients aged ≤28 years (P = 0.021), with a BMI ≥24.2 kg/m^2 (P = 0.0098), an LAS ≥58.04 (P = 0,00038), or a PNI ≤46.35 (P = 0.018) (**Table 2**). Multivariate analysis demonstrated that age (P = 0.00093), BMI (P = 0.00087)

and PNI (P = 0.0046) were independent prognostic factors of a worse survival outcome after LT (**Table. 3**).

The patients were divided into a high PNI group (N = 60) and a low-PNI group (N = 67), according to the PNI cut-off value, and the characteristics of the two groups are summarized in **Table 4**. Patient age, the number of cases of interstitial lung disease, and LAS were significantly higher in the low PNI group than in the high PNI group (age, P = 0.0058; interstitial lung disease, P = 0.0083; LAS, P = 0.0028). The percentages of preoperative glucocorticoid use (P = 0.058) and preoperative mechanical ventilation (P = 0.058) tended to be higher in the low PNI group, although the differences were not significant. Unsurprisingly, the low PNI group had a significantly worse overall survival after LT than the high PNI group (P = 0.018) (**Fig. 2**). In the subgroup analysis, the overall survival of the low PNI group was significantly worse than that of the high PNI group among both the CLT recipients (cut-off value = 49.50, c-index = 0.67, P = 0.015) (**Fig. 3a**) and the LDLLT recipients (cut-off value = 40.50, c-index = 0.59, P = 0.041) (**Fig. 3b**).

Discussion

In this study, the PNI was correlated significantly and negatively with the LAS, but not with the BMI. We also identified prognostic factors for survival after LT among the preoperative patient characteristics, including a low PNI of less than 46.35, a high BMI of more than 24.2 kg/m^2 and an age of younger than 28 years. Patients with a low PNI had a significantly worse survival outcome than those with a high PNI after CLT and after LDLLT. These findings suggest that the PNI could be an indicator of the severity of

the preoperative condition of LT recipients, and of their nutritional status, as well as a prognostic predictor not only after CLT, but also after LDLLT. Thus, the PNI could be a candidate parameter suitable for inclusion in the LAS calculator. To our knowledge, this is the first study to investigate the relationship between the PNI and the LAS, as well as the impact of the PNI on survival after LDLLT.

The negative correlation between the PNI and the LAS suggests that the PNI represents not only the nutritional status, but also the general status of the patient before LT. The LAS was developed originally to decrease a high waitlist mortality [14], with waitlist urgency calculated according to the patients' characteristics before LT using statistical models [13]. The LAS necessitates a considerable number of clinical and physiological factors for its calculation, such as the BMI, whereas the PNI requires only two factors, which is indicative of its simplicity and utility. Notably, the BMI, which is an indicator of obesity, was not correlated significantly with the PNI and did not differ between the low and high PNI groups in this study. Therefore, irrespective of the BMI, the PNI could be an indicator of the general status of the patient before LT.

Consistent with previously reported results of CLT [6], the PNI could be an independent prognostic predictor after both CLT and LDLLT. As malnutrition has been shown to affect survival after CLT [4, 6], the low PNI group had a significantly worse survival outcome than the high PNI group after both CLT and LDLLT. Generally, malnutrition is associated with impaired immune function, inflammatory processes, delayed or impaired wound healing, and a higher incidence of postoperative complications [24, 25]. Moreover, in patients with lung disease and limited respiratory reserve, malnutrition causes quantitative and functional changes in skeletal and

respiratory muscles to further compromise their condition, affecting quality of life and survival [26, 27]. Although malnourished recipients of LT could be more susceptible to postoperative complications, this study showed no difference in primary graft dysfunction, acute rejection, or CLAD after LT, between the two groups. Further study is needed to elucidate the detailed mechanism of how malnutrition affects mortality after LT.

Both high and low BMI before LT aids in the assessment of CLT patients [28-30], and BMI has been included in the LAS calculator, as described. Consistent with previously reported results [28-30], a BMI of more than 24.2 was identified as a preoperative prognostic factor, although the cut-off value for BMI in this study was much lower than previously reported values [28-30]. This deviation is because Japan has the lowest obesity rate among the countries of the Organization for Economic Co-operation and Development [31], and most LT patients in Japan have a low BMI. Among patients with a low BMI, those with a stable nutritional status, would have a normal PNI. Conversely, patients with a normal BMI who have progressive weight loss, would have low PNI resulting from a deteriorating nutritional status. Considering the differences in obesity rates among countries and races, the PNI, rather than the BMI, might be a more universal prognostic factor.

An age of younger than 28 years was identified as a prognostic factor in this study, which might reflect the poor survival rate of adolescent recipients, defined as 10 to 24 years of age [32]. In contrast, the age of the high PNI group, which had a better survival outcome after LT, was significantly lower than that of the low PNI group. Our results suggest that even in patients younger than 28 years with an improved nutritional status

might have a better survival outcome after LT. Thus, physicians should be cautious of nutritional status, in addition to an increased potential for non-adherence to treatment, especially in adolescent patients [32].

Some preoperative patient characteristics other than nutritional status might affect the PNI. In this study, the prevalence of interstitial lung disease and the preoperative use of glucocorticoids tended to be high in the low PNI group. Glucocorticoids, which are often used for interstitial lung disease and its underlying pathophysiology (such as autoimmune diseases), have been shown to reduce lymphocyte counts [33-35]. Reductions in lymphocyte counts could lead to a lower PNI, which is calculated based on the serum albumin level and the total lymphocyte count. Moreover, because the pretransplant use of glucocorticoids is associated with worse outcomes after LT [36], the high tendency for preoperative glucocorticoids administration in the low PNI group might have affected the outcomes after LT in this study.

The usefulness of the PNI as a prognostic predictor even after LDLLT simplifies the assessment of candidates for LDLLT in the clinical setting, as there is limited information on prognostic predictors after LDLLT. LDLLT is still a realistic option, especially for emergency LT, to solve the critical scarcity of lung donors in Japan [37]. In fact, the LAS of LDLLT recipients is higher than that of CLT recipients because of their severe conditions requiring emergency LT [18, 20]. Therefore, the lower cut-off value for the PNI in the LDLLT group than in the CLT group could reflect how critically ill the LDLLT recipients were in this study. Our results suggest that the PNI could provide a simple and essential assessment tool for LDLLT candidates.

This study had several limitations. First, it was a retrospective study conducted at a single transplant institution, and the number of LT recipients was relatively small. Second, longer follow-up periods are need to validate long-term survival after LT. Third, all of our subjects were Japanese, but the physical and nutritional characteristics of patients differ among countries. However, given the fact that studies focusing on LDLLT have been reported from Japan exclusively, our study could provide some practical information for the management of LDLLT patients.

In conclusion, the PNI of LT recipients was correlated significantly and negatively with the LAS, and the PNI could be an independent prognostic factor of outcome after both CLT and LDLLT. A pretransplant nutritional evaluation of LT recipients using the PNI could contribute to better assessment of the disease severity of LT recipients as well as the prediction of survival after CLT and LDLLT.

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Compliance with ethical standards

Conflict of Interest: Haruchika Yamamoto and his co-authors have no conflicts of interest to declare.

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Table 1

Patient characteristics

		N = 127
Preoperative variables		
Age, years, median (range)		34 (2-64)
Sex	Male	56 (44.1%)
	Female	71 (55.9%)
Body mass index, median (range)		17.84 (10.50-32.17)
Diagnoses	Interstitial lung disease	43 (33.9%)
	Pulmonary hypertension	26 (20.5%)
	Pulmonary graft-versus-host disease	23 (18.2%)
	Lymphangioleiomyomatosis	10 (7.9%)
	Bronchiectasis	8 (6.3%)
	Emphysema	7 (5.5%)
	Other diseases	10 (7.9%)
History of hematopoietic stem cell transplantation, yes		25 (19.7%)
Preoperative diabetes mellitus, yes		10 (7.9%)
Preoperative ECMO support, yes		3 (2.4%)
Preoperative use of glucocorticoids, yes		29 (22.8%)
Preoperative tracheostomy, yes		3 (2.4%)
Preoperative mechanical ventilation, yes		11 (8.7%)
Preoperative serum creatinine level, median (range), mg/dL		0.55 (0.1-1.72)
Preoperative oxygen concentration, median (range), %		28 (21-70)
Lung allocation score, median (range)		39.43 (30.23-89.94)
CMV mismatch (recipient negative/ donor positive), yes		22 (17.3%)
Lung donor		
	Deceased donor	71 (55.9%)
	Living donor	56 (44.1%)
Total number of HLA-A, HLA-B and HLA-DR mismatches, median (range)		5 (1-10)
Intraoperative variables		
Lung transplant procedure		
	Single	27 (21.3%)
	Double	100 (78.7%)
Operative time (min), median (range)		488 (233-845)
Ischemic time (min), median (range)		328.5 (74-787)
Cardiopulmonary bypass: yes		109 (85.8%)
Postoperative variables		
Maximum grade of PGD (0-72 h), median (range)		1 (0-3)
Acute rejection, yes		44 (34.7%)
Antibody-mediated rejection, yes		10 (7.9%)
Postoperative GERD, yes		1 (0.8%)
CLAD, yes		37 (29.1%)
Time since transplant to follow-up (day), median (range)		1196 (1-4810)

CMV, cytomegalovirus; ECMO, extracorporeal membrane oxygenation; GERD, gastro esophageal reflux disease; HLA, human leukocyte antigen; PGD, primary graft dysfunction; CLAD, chronic lung allograft dysfunction.

Table 2

Univariate analyses of the associations between preoperative parameters and survival after lung transplantation

Variables		HR (95% CI)	*P* value
Age, years	≤28	2.170 (1.05-4.486)	0.021
Sex	Female	0.650 (0.318-1.329)	0.21
Body mass index	≥24.2	2.826 (0.842-9.484)	0.0098
Diagnoses	Interstitial lung disease	1.851 (0.874-3.919)	0.11
	Non- Interstitial lung disease		
History of hematopoietic stem cell transplantation, yes		1.312 (0.498-3.459)	0.54
Preoperative diabetes mellitus, yes		1.543 (0.370-6.427)	0.47
Preoperative ECMO support, yes		0.352 (0.046-2.667)	0.31
Preoperative use of glucocorticoids, yes		1.684 (0.748-3.795)	0.15
Preoperative tracheostomy, yes		0.361 (0.013-9.816)	0.55
Preoperative mechanical ventilation, yes		1.637 (0.458-5.857)	0.35
Preoperative serum creatinine level, mg/dl	≥0.61	1.793 (0.894-3.597)	0.09
Preoperative oxygen concentration, %	≥32	1.265 (0.624-2.566)	0.5
Lung allocation score	≥58.04	3.619 (1.124-11.66)	0.00038
CMV mismatch (recipient negative/ donor positive), yes		1.102 (0.412-2.952)	0.84
Total number of HLA-A, HLA-B and HLA-DR mismatches	≥6	1.671 (0.777-3.591)	0.17
Prognostic nutrition index	≤46.35	2.441 (1.233-4.832)	0.018

CI, confidence interval; CMV, cytomegalovirus; ECMO, extracorporeal membrane oxygenation; HLA, human leukocyte antigen; HR, hazard ratio

Table 3

Multivariate analysis of the associations between preoperative parameters and survival after lung transplantation

Variables		HR (95% CI)	*P* value
Age, years	≤28	3.979 (1.757-9.009)	0.00093
Body mass index	≥24.2	5.126 (1.958-13.420)	0.00087
Prognostic nutrition index	≤46.35	3.595 (1.482-8.718)	0.0046

CI, confidence interval; HR, hazard ratio

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Table 4

Perioperative variables of lung transplant recipients, according to the preoperative prognostic nutritional index score

		High PNI (N = 60)	Low PNI (N = 67)	*P* value
Preoperative variables				
Age, years, median (range)		27 (2-61)	40 (6-64)	0.0058
Sex	Male	29 (48.3%)	27 (40.3%)	0.38
	Female	31 (51.7%)	40 (59.7%)	
Body mass index, median (range)		17.82 (10.81-31.17)	17.85 (10.50-32.19)	0.32
Diagnoses	Interstitial lung disease	13 (21.7%)	30 (44.8%)	0.0083
	Pulmonary hypertension	13 (21.7%)	13 (19.4%)	0.83
	Pulmonary graft-versus-host disease	11 (18.3%)	12 (17.9%)	0.99
	Lymphangioleiomyomatosis	7 (11.7%)	3 (4.5%)	0.19
	Bronchiectasis	4 (6.7%)	4 (6.0%)	0.99
	Emphysema	6 (10.0%)	1 (1.5%)	0.052
	Other diseases	6 (10.0%)	4 (6.0%)	0.52
History of hematopoietic stem cell transplantation, yes		12 (20.0%)	13 (19.4%)	0.99
Preoperative diabetes mellitus, yes		3 (5.0%)	7 (10.4%)	0.33
Preoperative ECMO support, yes		0 (0%)	3 (4.5%)	0.25
Preoperative use of glucocorticoids, yes		9 (15.0%)	20 (29.9%)	0.058
Preoperative tracheostomy, yes		0 (0%)	3 (4.5%)	0.25
Preoperative mechanical ventilation, yes		2 (3.3%)	9 (13.4%)	0.058
Preoperative serum creatinine level, median (range)		0.51 (0.12-1.72)	0.61 (0.1-1.48)	0.13
Preoperative oxygen concentration, median (range)		28 (21-65)	28 (21-70)	0.19
Lung allocation score, median (range)		35.43 (30.31-89.26)	42.10 (33.11-89.50)	0.0028
CMV mismatch (recipient negative/ donor positive), yes		10 (16.7%)	12 (17.9%)	0.99
Lung donor				0.28
	Deceased donor	37 (61.7%)	34 (50.7%)	
	Living donor	23 (38.3%)	33 (49.2%)	
Total number of HLA-A, HLA-B and HLA-DR mismatches, median (range)		5 (3-9)	5 (1-10)	0.11
Time from preoperative blood examination to transplant (days), median (range)		1 (0-68)	1 (0-40)	0.38
Intraoperative variables				
Lung transplant procedure				0.67
	Bilateral	46 (76.7%)	54 (80.6%)	
	Single	14 (23.3%)	13 (19.4%)	
Operative time (min), median (range)		465 (223-690)	495 (247-845)	0.13
Ischemic time (min), median (range)		375 (74-701)	285.5 (84-787)	0.6
Cardiopulmonary bypass use, yes		48 (80.0%)	61 (91.0%)	0.13
Postoperative variables				
Maximum grade of PGD (0-72 h), median (range)		2 (0-3)	1 (0-3)	0.13
Acute rejection, yes		22 (36.7%)	22 (32.8%)	0.71
Antibody-mediated rejection, yes		5 (8.3%)	5 (7.5%)	0.99
Postoperative GERD, yes		0 (0%)	1 (1.5%)	0.99
CLAD, yes		13 (21.7%)	24 (35.8%)	0.12
Cause of death				0.99
	CLAD	2 (3.3%)	9 (13.4%)	
	Infection	1 (1.7%)	5 (7.5%)	
	Malignancy	1 (1.7%)	4 (6.0%)	
	Acute rejection	3 (5%)	0 (0%)	
	Other diseases	2 (3.3%)	6 (9.0%)	
Time since transplant to follow-up (day), median (range)		1279.5 (1-4810)	1044 (2-4740)	0.76

CLAD, chronic lung allograft dysfunction; CMV, cytomegalovirus; ECMO, extracorporeal membrane oxygenation; GERD, gastro esophageal reflux disease; HLA, human leukocyte antigen; PGD, primary graft dysfunction.

Figure legends

Fig. 1. Correlation between the prognostic nutrition index (PNI) and the lung allocation score (LAS). The PNI was correlated significantly and negatively with the LAS (r = -0.40, *P* = 0.0000037).

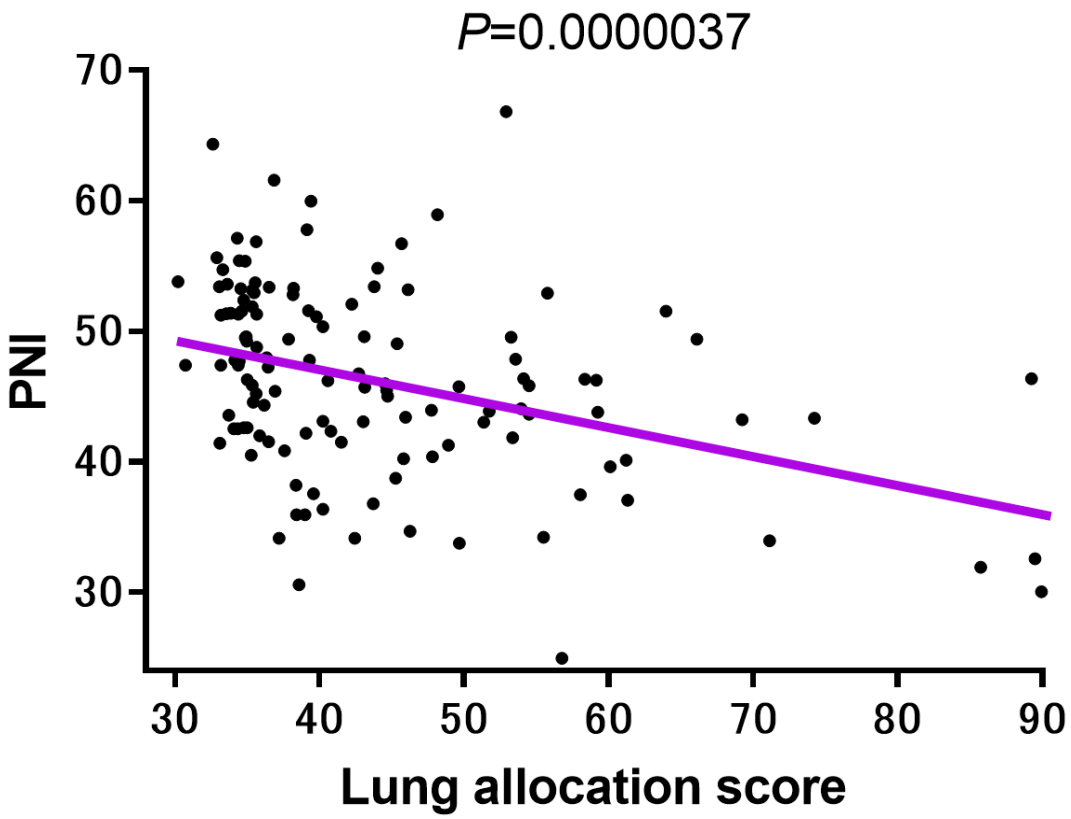

Fig. 2. Overall survival after lung transplantation (LT) according to the prognostic nutrition index (PNI). The overall survival after LT of the low PNI group was significantly worse than that of the high PNI group (cut-off value = 46.35, *P* = 0.018).

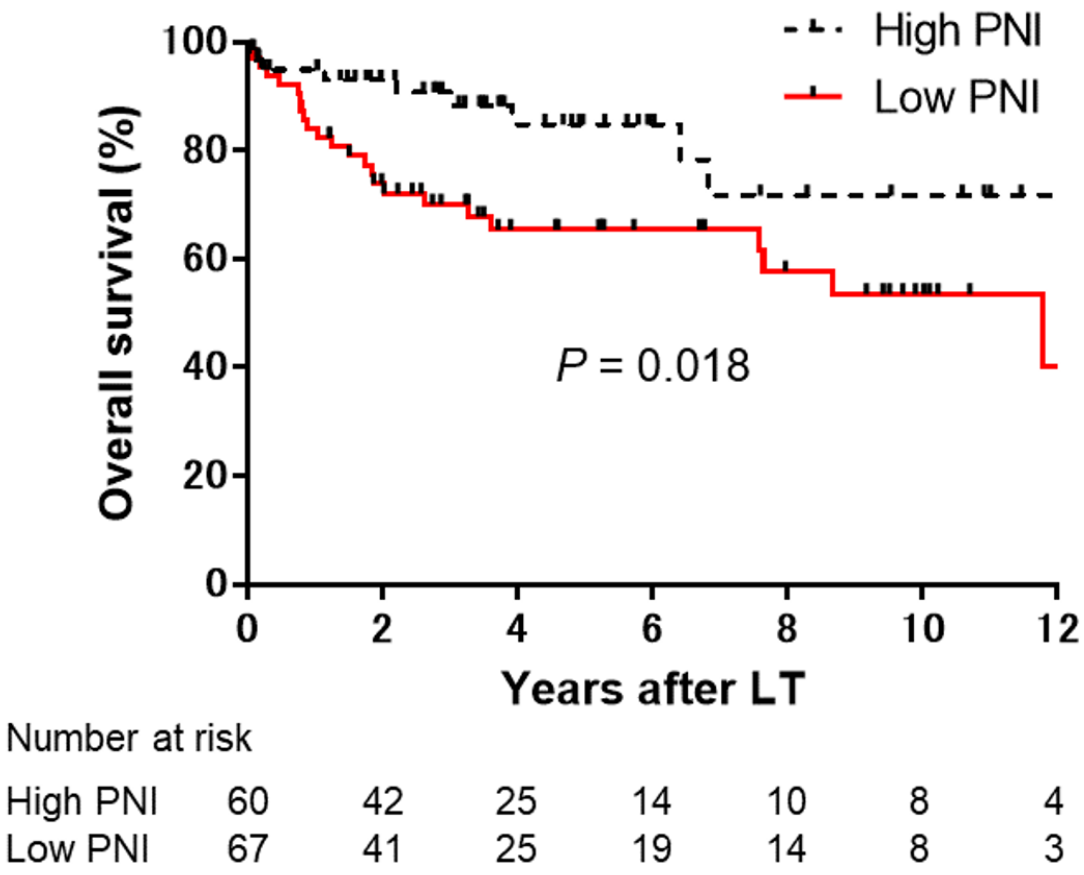

Fig. 3. Overall survival after cadaveric lung transplantation (CLT) (a) and living-donor lobar lung transplantation (LDLLT) (b) according to the prognostic nutrition index (PNI). The overall survival was significantly worse in the low PNI group than in the high PNI group after CLT (cut-off value = 49.50, c-index = 0.67, *P* = 0.015) (**a**) as well as after LDLLT (cut-off value = 40.50, c-index = 0.59, *P* = 0.041) (**b**).