The effect of nutritional status on clinical outcome in lung transplantation

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Running title: Nutritional status and lung transplantation prognosis

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ABSTRACT

Background and Objectives: Nutritional status greatly impacts the clinical outcome of the patients receiving lung transplantation. The objective of this study was to evaluate the effect of nutritional status on the clinical outcome in lung transplant recipients. **Methods and Study Design:** A single-center retrospective study was conducted including 73 patients received lung transplantation from December 2015 to April 2022 in Henan, Zhengzhou, China. Data were collected from the hospital information system. The records of BMI, malnutrition defined by the Global Leadership Initiative on Malnutrition (GLIM) diagnostic criteria, hemoglobin and plasma albumin before operation were accessed. The primary outcome assessed was survival or mortality represented by Kaplan-Meier survival curves; the log-rank test and multivariate Cox proportional hazards regression were used to evaluate the influence of each factor on survival. **Results:** Kaplan-Meier survival analysis showed that malnutrition, hemoglobin and plasma albumin were predictors of survival in lung transplantation (Log Rank $p<0.05$). Multivariate Cox regression showed that pre-operative hemoglobin <130 g/L (HR 2.532, $p=0.036$) and plasma albumin <35 g/L (HR 2.723, $p=0.016$) were associated with the decreased survival rate. **Conclusions:** Preoperative anemia and hypoalbuminemia increase the mortality risk of the lung transplantation patients. Pre-operative nutrition support, therefore, is likely to be critical for improving clinical outcome in patients undergoing lung transplantation.

Key Words: lung transplantation, clinical outcome, malnutrition, hypoalbunemia, preoperative anemia

INTRODUCTION

Lung transplant is an effective method for the treatment of end-stage pulmonary diseases.[1] The increase in lung transplants is the largest among the major types of organ transplant surgery (e.g., kidney, liver, and heart). However, the early-stage prognosis of lung transplant recipients is poorer than that of patients receiving other organ transplants.[2] Improving the prognosis for lung transplant recipients depends not only on research but also on recipient selection and management among lung transplant surgeons during the perioperative period.[3,4] The major causes of patient death during the perioperative period include primary transplant lung dysfunction, primary graft dysfunction, and postoperative infection.[5] However, global nutritional status and whole-body function are also closely associated with clinical outcomes.[6] The effect of nutritional status on patient prognosis during the perioperative period requires investigation. Such research may inform clinical decision making in the context of lung transplants.

Precise nutritional therapy is based on global nutritional assessment and accurate nutritional diagnosis. Previously, subjective global assessment and patient-generated subjective global assessment were the most commonly used tools for the nutritional assessment of preoperative patients. In September 2018, the Global Leadership Initiative on Malnutrition (GLIM) diagnostic criteria were published online.[7] The GLIM diagnostic criteria became the new standard in the diagnosis of various degrees of malnutrition; they are applied to clinical presentation, etiology, and the diagnosis of malnutrition in hospitalized patients.[8] This study explored the association of malnutrition diagnosed on the basis of the GLIM criteria and patient prognosis after lung transplantation and the nutritional factors influencing patient prognosis after lung transplantation.

MATERIALS AND METHODS

Ethical considerations

All lung transplant recipients signed an informed consent form before surgery, and the source of the donor lung was uniformly allocated by the National Organ Transplant Center. These protocols satisfy the requirements of medical ethics.

Participants and procedure

This retrospective cohort study was conducted in the Lung Transplant Center of the Affiliated Henan Provincial People's Hospital of Zhengzhou University. The participants were in-patients with end-stage lung diseases, including pneumoconiosis, pulmonary fibrosis, and chronic obstructive pulmonary disease, who had undergone lung transplantation between December 2015 and April 2022. Participants were excluded from the study if they: 1) were aged younger than 18 years, 2) survived less than 72 hours after lung transplantation because of primary lung graft dysfunction or other reasons, or 3) lacked medical information.

Data from the medical records of the participants were collected from the hospital information system. The following data were collected: age, sex, medical history, smoking history, diagnostic information, body mass index (BMI), laboratory tests, surgical method, extracorporeal membrane oxygenation, and hemorrhage during operation. After discharge, regular follow-up was conducted by specialized medical staff every half year to guide daily care. Causes of death were recorded. At the end of the study, data from patients who were still alive were treated as censored data. The median follow-up time was 20.6 months.

Statistical analysis

Statistical analysis of the data was performed using SPSS 25.0 (IBM, Armonk, NY, USA). Continuous variables are represented as means ± standard deviations. Categorical variables are presented as frequencies and percentages. A Kaplan–Meier curve was used to depict survival, and the log-rank test was used to compare the influence of each nutritional factor on survival rate. Variables of interest were analyzed through univariate Cox proportional hazards regression analysis ($p<0.1$), and covariates considered clinically influential were analyzed through a multivariate Cox proportional hazards regression model to evaluate the influence of each factor on the survival rates of the patients. R 4.0.2 was used to generate the accumulated death trend. A p value of <0.05 was considered statistically significant.

RESULTS

Patient characteristics

The study diagram is presented in Figure 1. A total of 73 patients diagnosed with end-stage lung diseases who underwent lung transplantation were included in this study; 66 (90.4%) were men, and 7 (9.6%) were women. Characteristics of the participants are presented in Table 1. The median age of the participants was 50.5±11.5 years. Among the participants, 23.3% were aged over 60 years, and 28.8% were aged younger than 45 years. Most patients reported regular oral consumption of meals (84.9%), some patients consumed oral nutritional supplements (12.3%), and a small minority of patients received combined enteral or parenteral nutritional support because of the low quantity of food they consumed (2.7%). Approximately 46.6% of the participants had a smoking history. The major diagnoses were pneumoconiosis (45.2%), pulmonary fibrosis (35.6%), and chronic obstructive pulmonary disease (15.1%). On the basis of the GLIM diagnostic criteria, half of the participants (50.7%) exhibited malnutrition. The median BMI of the participants was 19.8±3.3 kg/m^2. The rates of anemia and hypoalbuminemia were 46.6% and 37.0%, respectively, and the median serum albumin concentration was 37.1±3.4 g/L in preoperative patients. Details are presented in Table 1.

Survival determinants (hierarchical GLIM, hemoglobin, and serum albumin)

Independent predictors were identified using univariable and multivariable Cox regression analyses. The univariate analysis indicated that the following variables significantly influenced the prognosis of the patients: GLIM-determined malnutrition ($p=0.027$, hazard ratio [HR]=2.546; 95% confidence intervals [CI]: 1.111–5.836), preoperative anemia (*p*=0.006, HR=3.212; 95% CI: 1.402–7.357), hypoalbuminemia (*p*=0.001, HR=3.617; 95% CI: 1.653–7.914). Detailed results of the univariate and multivariate analyses are presented in Table 2. In the adjusted proportional hazards model, preoperative anemia (<130 g/L) and hemoglobin, expressed as a continuous variable, were both associated with increased risk of death (preoperative anemia, HR=2.532, 95% CI: 1.063–6.033; continuous increase of 1 g/L in hemoglobin, HR=0.972, 95% CI: 0.952–0.992). Hypoalbuminemia (<35 g/L) and serum albumin, expressed as a continuous variable, were both associated with increased death risk (hypoalbuminemia, HR=2.723, 95% CI: 1.204–6.161, continuous increase of 1 g/L in serum albumin, HR=0.888, 95% CI: 0.800–0.986). Both preoperative anemia and hypoalbuminemia were included in the model for interaction analysis; the *p* value for interaction was 0.142. No additive or synergistic association of anemia and hypoalbuminemia with patient mortality was observed.

On the basis of the Kaplan–Meier survival analysis, probability of mortality graphs were generated using R software. These demonstrated that the patients with malnutrition, hypoalbuminemia, or preoperative anemia had a higher probability of death (*p* values were 0.017, <0.05, and 0.003, respectively). Details are presented in Figure 2A–C. The Kaplan–Meier survival analysis indicated that the overall survival rates for 1 year and 3 years after lung transplantation were 68.86% and 56.54%, respectively (Figure 2D).

DISCUSSION

The major disease types encountered and considered for lung transplant are COPD, idiopathic pulmonary interstitial fibrosis, pneumoconiosis in China. With repeated infection, tissue damage, and long-term wasting, these end-stage pulmonary disease patients present with high energy depletion, disorder of homeostasis, and lean mass loss due, which in turn, result in malnutrition.[9] In current study, the prevalence of pre-operative malnutrition was 50.7% by GLIM diagnostic criteria, concordant with Emsley's report,[10] while the prevalence of underweight was 39.7% based on the BMI standard. The about 10% difference might underestimate of malnutrition as judged by BMI standards. To avoid this underestimation, it is better to apply the GLIM diagnostic criteria in evaluating nutritional status for pre-operation patients prepared for organ transplant. Although the incidence of malnutrition was high, this study still did not find malnutrition to be an independent risk factor for the lung transplant recipient survival. Perhaps this reflected the relatively small sample size. Further study is needed with larger sample size. Global assessment of nutritional status and a nutritional management plan would appear to be mandatory in pre-operative and perioperative lung transplant care, for successful operative outcome and long-term survival.[9] Management team inclusion of a dietician can facilitate these practices.[11]

The present study demonstrated that pre-operative anemia is an independent risk factor for mortality in patients who underwent lung transplant and increased the death risk for 2.5-fold. Patients with end-stage pulmonary disease suffer from respiratory failure. The capacity for gas exchange is seriously low, with tissue hypoxia.[12] A low Hb and/or red blood cell count, further reduces tissue oxygen delivery with fatigue and wider compromised organ function. Although blood transfusion during Intra-operative blood transfusion can ameliorate these phenomena, although the risk of infection is increased with frequent blood transfusion.[13,14] The increased mortality and morbidity with pre-operative anemia has been confirmed by In Fowler’s meta-analysis of 949,445 non-transplant surgical patients[15] anemia was associated with a 2.9 fold increase in the mortality. However, it could not be ascertained whether anemia was an independent risk factor for poor prognosis or an indicator of co-existent chronic disease. Hernandez-Morgan found anemia to be an independent risk factor for re-operation (due to post-operation bleeding with exploratory thoracotomy),[16] the low Hb prolongs hospital stay, and pre-operative anemia increases post-operative acute renal damage. In the present study, the prevalence of pre-operative anemia was 46.6%, a management challenge to the responsible clinicians where nutrition input can be valuable. [17-19]

Pre-operative hypoalbuminemia increased the post-operative mortality risk 2.7 fold, similar to that reported by Baldwin and Halpern.[20] Halpern indicated that sarcopenia and 6-min walk distance together could not predict the mortality and short-term outcome of post lung transplantation, while the serum albumin was negatively associated with survival and complications of the patients.[21] Therefore, the pre-operative serum albumin might be an important predictor of mortality and short-term outcome of the patients underwent lung transplant.

The application of immunosuppressive agent, such as Tacrolimus, to prevent organ rejection after transplant, might down regulate the immunity of the patients, which makes them under high chance and risk of infection from bacteria, fungi, and virus. The patients face double challenges of organ rejection and infection. The entire immune response relies on normal serum albumin level, at mean time, the biological activity of lipids is affected by albumin oxidation and degradation, while lipid media plays important roles in defense of anti-bacteria and tissue repairing. Therefore, pre-operative hypoalbuminemia intensifies the risk of infection and immune disorder of the patients underwent lung transplant. There are cause and effect relationships between hypoalbuminemia and increased risk of both primary and secondary infection. Except for a component of malnutrition diagnosis, hypoalbuminemia is also an indicator for the severity of pulmonary diseases or other diseases.

Human serum albumin is the primary transport and reservoir protein in the human circulatory system, interacting with numerous endogenous and exogenous ligands with varying structural characteristics. It has been found that the therapeutic failure rate is higher in hypoalbuminemia than in controls during treatment of ulcerative colitis with the immunosuppressive Tacrolimus.[22] As a therapy transporter, albumin is crucial for therapeutic effectiveness and safety of immunosuppressive agents like Tacrolimus, used in lung transplantation.[23]

With respect to the importance of hemoglobin and albumin, which are two indicators of health and nutrition, to the prognostic capacity in lung transplant patients, nutritional assessment and intervention may be critical for pre-operative patients. As for the clinical practice, the dietitian or nutritionist comprehensively assess nutritional status through dietary intake, body composition analysis, coupled by relevant laboratory investigation, and develop a malnutrition management plan collaboratively with the clinicians.

Conclusion

Preoperative anemia and hypoalbuminemia are the risk factors of higher mortality in lung transplantation. Pre-operative nutrition support is potentially critical for improved clinical outcomes and survival in lung transplantation.

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CONFLICT OF INTEREST AND FUNDING DISCLOSURE

The authors declare no conflict of interest.

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Table 1. Characteristics of the patients

Variables	n (%)	$\bar{X}+S$
Number of patients	73 (100)	
Age (years), median		50.5±11.5
Age ≤45	21 (28.8)	36.1±1.4
45< Age <60	35 (47.9)	52.2±0.6
Age ≥60	17 (23.3)	64.9±1.0
Gender		
Male	66 (90.4)	
Female	7 (9.6)	
Background diet		
RMO	62 (84.9)	
ONS	9 (12.3)	
EN or PN	2 (2.7)	
Smoke	34 (46.6)	
Diabetes	8 (11.0)	
Disease type		
Pneumoconiosis	33 (45.2)	
Pulmonary fibrosis	26 (35.6)	
COPD	11 (15.1)	
Others	3 (4.1)	
GLIM diagnosis		
Malnutrition	37 (50.7)	
Non-malnutrition	36 (49.3)	
BMI (kg/m^{2})		19.8±3.3
≥18.5	44 (60.3)	21.8±0.4
< 18.5	29 (39.7)	16.8±0.3
Hemoglobin (g/L)		132.9±15.4
≥130	39 (53.4)	144.3±1.7
<130	34 (46.6)	115.0±2.4
Serum albumin (g/L)		37.1±3.4
≥35	46 (73.0)	38.8±0.4
< 35	27 (37.0)	32.5±0.4
ECMO assisted	27 (37.0)	

RMO: regular meal orally; ONS: oral nutrition supplements; EN: enteral nutrition; PN: parenteral nutrition.

Table 2. Univariate and multivariate predictor analysis of all-cause death

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Age	1.031 (0.997-1.066)	0.074		
Age>45	2.537 (0.948-6.789)	0.064		
Sex	1.355 (0.474-3.869)	0.571		
BMI	0.958 (0.855-1.074)	0.461		
GLIM	2.546 (1.111-5.836)	0.027		
Hemoglobin	0.963 (0.944-0.982)	0.000	0.972 (0.952-0.992)	0.008
Serum albumin	0.841 (0.761-0.928)	0.001	0.888 (0.800-0.986)	0.026
Pre-albumin	0.998 (0.993-1.003)	0.426		
Preoperative anemia	3.212 (1.402-7.357)	0.006	2.532 (1.063-6.033)	0.036
Hypoalbuminemia	3.617 (1.653-7.914)	0.001	2.723 (1.204-6.161)	0.016
Type of disease	1.191 (0.746-1.901)	0.465		
Surgical method	1.441 (0.709-2.926)	0.312		
Diabetes	2.046 (0.774-5.412)	0.149		
Smoke	1.163 (0.541-2.497)	0.699		
ECMO	2.060 (0.964-4.403)	0.062		
Hemorrhage	0.780 (0.580-1.040)	0.093		

HR: Hazard ratio; CI: confidence interval.

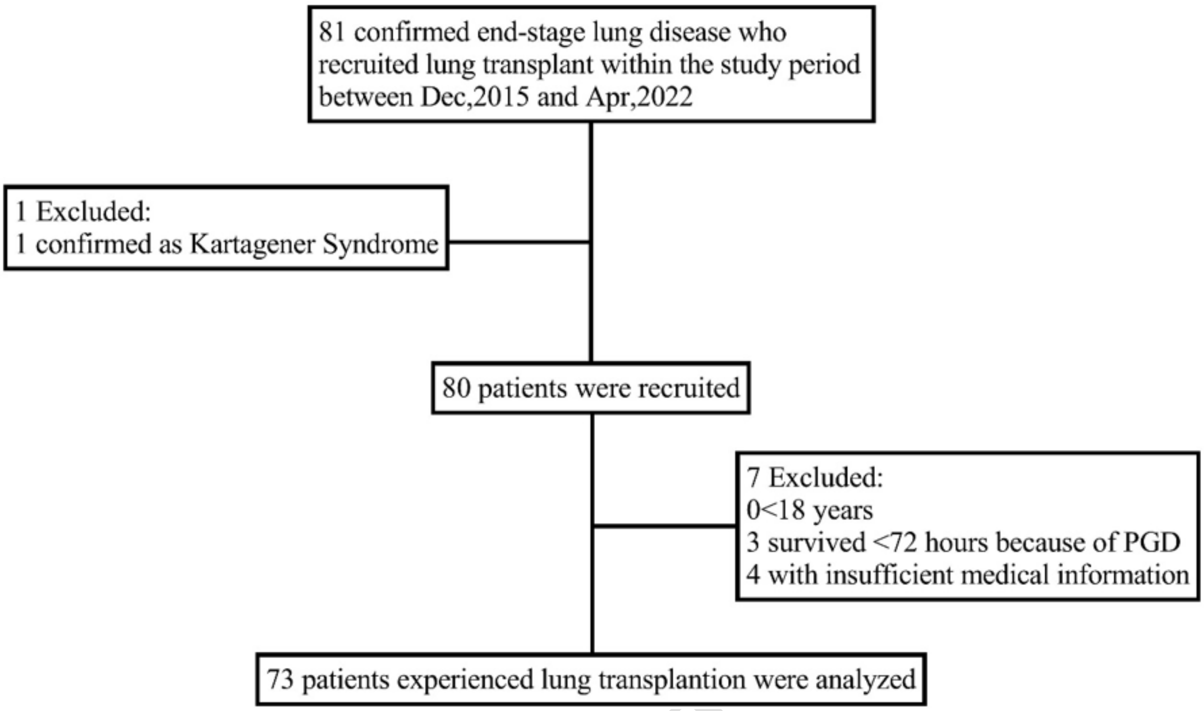

Figure 1. Diagram of the study.

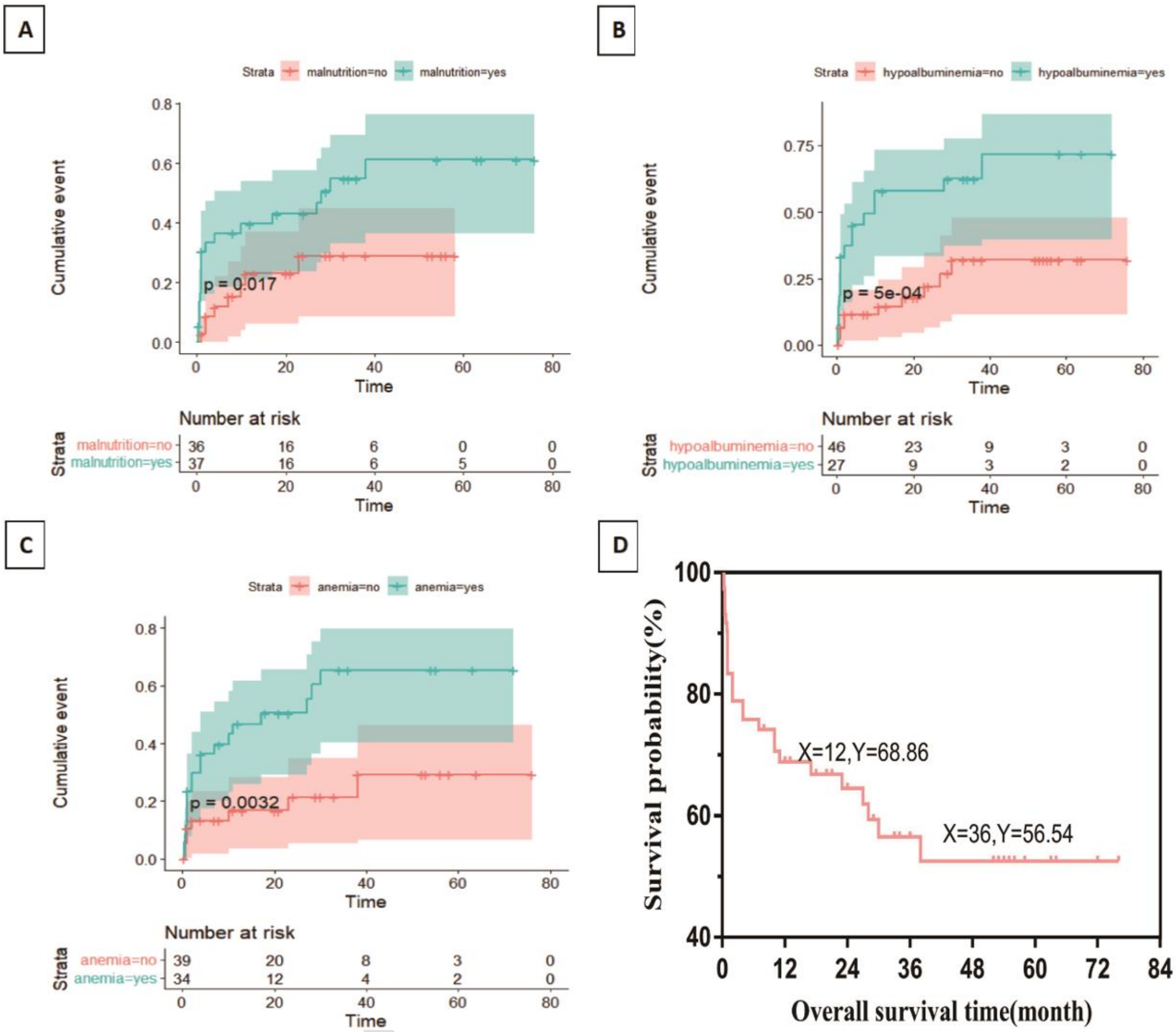

Figure 2. Survival Curves of the subjects underwent lung transplant. (A) Unadjusted Kaplan-Meier curves for patients with and without malnutrition; (B) Unadjusted Kaplan-Meier curves for patients with and without hypoalbuminemia; (C) Unadjusted Kaplan-Meier curves for patients with and without abnormal hemoglobin; (D) Overall Survival Curve.