Analysis of nosocomial infection and risk factors in lung transplant patients: a case-control study

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Background: Infection is the leading cause of short-term mortality after lung transplantation. This study aimed to investigate the epidemiology and risk factors of infection in Chinese lung transplant recipients.

Methods: A total of 107 lung transplant patients from 2016 to 2020 were included in this study. The basic data of patients were collected, combined with clinically relevant physiological and biochemical indicators and laboratory test results. Transplant patients with new infections 48 hours after surgery were included in the infected group, and the rest were in the Uninfected group. The risk factors of postoperative infection were analyzed between the two groups.

Results: A total of 107 patients were included in the study, including 89 males and 18 females. All patients underwent lung transplantation. A total of 80 patients (74.8%) experienced a postoperative infection. Pathogenic microorganisms were found in 136 samples, predominantly in the sputum (n=120 samples; 88.2%). We detected 107 strains of Gram-negative bacteria (78.7%), including 30 strains of *Acinetobacter baumannii* (22.1%) and 27 strains of *Klebsiella pneumoniae* (19.9%); 18 strains of Gram-positive bacteria (13.2%), including 11 strains of *Staphylococcus haemolyticus* (8.1%) and 2 strains of *Enterococcus faecium* (1.5%); and 11 strains (8.1%) were infected by fungi. There were 87 strains of multidrug-resistant bacteria. The main multidrug-resistant bacteria included 28 strains of *Acinetobacter baumannii* (32.2%) and 25 strains of *Klebsiella pneumoniae* (28.7%). Multivariate analysis showed that ventilator use over 3 days was an independent risk factor for postoperative infection [odds ratio (OR): 4.94, 95% confidence interval (CI): 1.31 to 18.66, P=0.019].

Conclusions: The infection rate after lung transplantation in our hospital is similar to that of other lung transplantation studies, but higher than that following transplantation of other organs. The pathogens of postoperative infection were similar to those identified in other lung transplantation studies. Using a ventilator for more than 3 days is a risk factor for postoperative infection, suggesting that preventive measures for postoperative infection should be taken in such patients, and early postoperative discontinuation of the ventilator may reduce postoperative infection.

Keywords: Lung transplantation; postoperative infection; risk factors

Submitted May 30, 2022. Accepted for publication Jul 18, 2022.

doi: 10.21037/atm-22-3023

View this article at: https://dx.doi.org/10.21037/atm-22-3023

Introduction

Lung transplant is the most effective method to rescue end-stage lung diseases, which include chronic obstructive pulmonary disease (COPD), pneumoconiosis, idiopathic pulmonary fibrosis (IPF), and so on (1).The number of lung transplant operations in China is increasing with 489 cases in 2019 and over 500 cases in 2020 (2). With the continuous development of lung transplantation technology, countless lives have been saved, while post-transplant complications including infection, acute pulmonary edema, and rejection reactions also continue to emerge (3-5). Patient quality of life and long-term survival rates have improved due to advancements in lung transplantation-related surgical techniques, perioperative management, and immunosuppressive programs. However, an infectious complication is still the one of most important causes of adverse outcomes of lung transplantation (6,7). Infection is the second leading cause of death within 30 days after lung transplantation, and also the main cause of death within 30 days to 1 year (8). The respiratory tract is the most common area of infection after lung transplant, and bacterial pneumonia is the most common infectious complication. Compared with other surgical patients, lung transplant patients are more prone to infections for reasons of interruption of the bronchial circulation, anastomotic site complications, use of immunosuppressive agents, and so on (9,10). In China, in contrast with liver and kidney transplantation patients, who receive greater attention with post-transplant infection-related research due to the larger surgery volumes, the postoperative infections in patients after lung transplantation are currently less researched (11). Compared with other transplants, the transmission of infection between the donor and the recipient is the most common disease after lung transplantation, because lung transplants cannot guarantee complete sterility of the donor (12). This study aimed to investigate the epidemiology and risk factors of infection in Chinese lung transplant recipients. We present the following article in accordance with the STROBE reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-3023/rc).

Methods

Study design

We retrospectively collected the general clinical data and postoperative infection data of lung transplant patients between 2016 and 2020. Patients were divided into two groups according to whether they had experienced infection or not: the infected group and the uninfected group. Risk factors for postoperative infection were sought by comparing the clinical data of the two groups of patients. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of Shanghai Pulmonary Hospital (No. k22-259). Written informed consent was taken from patients or their families.

Setting

A total of 107 lung transplant patients admitted to Shanghai Pulmonary Hospital from January 2016 to December 2020 were included in the study. All patients were suitable for lung transplant and underwent surgery. All donors donated their organs after cardiocirculatory or brain death. Since January 2015, China has implemented a citizen-based voluntary donation program for deceased organs. Therefore, the distribution and donation of each organ of all study participants are carried out within the judicial system.

Variables

This study adopted a retrospective analysis method to collect clinical data of 107 patients in the order of admission. The specific indicators were as follows: age, gender, ventilator, urinary catheter, and central venous catheter usage, relevant physiological and biochemical indicators, and so on. The normal range of relevant biochemical indicators was defined as follows: carbon dioxide partial pressure, 35–45 mmHg; oxygen partial pressure, 80–100 mmHg; hemoglobin (Hb), 110–150 g/L; white blood cell (WBC) count, 4.0–10.0×10^9/L; neutrophil count, 1.8–6.3×10^9/L; and platelet count, 100–300×10^9/L.

Postoperative infection was defined as follows: the patient neither had symptoms of infection before surgery nor developed an infection during the operation. Infection occurred more than 48 hours after surgery. Patients who develop fever and other infection-related symptoms after surgery were sampled, including sputum, bronchoscopic alveolar lavage fluid (BALF), blood, and urine, and sent for examination. Doctors made a diagnosis based on clinical symptoms and imaging findings, and recorded the findings as follows: site of infection, pathogen of infection, and drug susceptibility results. The isolated strains are identified by the Mérieux-VITEK MS mass spectrometer (bioMérieux, Marcy-l'Étoile, France). The "Expert Recommendations on the International Standardization of Drug-resistant Bacteria MDR, XDR, and PDR in Medical Institutions (Draft)" were used to identify multidrug-resistant bacteria.

Statistics

The data was analyzed by SPSS 20.0 software (IBM Corp., Armonk, NY, USA). Measurement data which conformed to the normal distribution were expressed as the mean ± standard deviation, otherwise, they were expressed as median (quartiles). For analysis, the patients were divided into infected and uninfected groups based on whether they had been diagnosed with a postoperative infection. Comparison between groups was conducted using Student's *t*-test for continuous variables, and chi-square test or Fisher's exact test for categorical variables. Univariate and multivariate logistic regression analysis were used for risk factor analysis, age, male gender, hypertension, heart disease, diabetes, $PaCO_2$ >45 mmHg, PaO_2 <80 mmHg, Hb <110 g/L WBC count >10×10^9/L, neutrophil ratio >70%, platelet (PLT) <3.0×10^9/L, elevated C-reactive protein (CRP), elevated interleukins, unilateral lung transplantation, ventilator use for over 3 days, urinary catheter for over 3 days, and venous catheter for over 3 days were put into the above two models, and P<0.05 indicated that the difference was statistically different. The calculation method of postoperative infection rate is as follows:

$$\textit{Postoperative}\text{ infection rate} = \frac{\textit{Number}\text{ of postoperative infection}}{\textit{Total}\text{ number of patients}}\times 100\% \quad [1]$$

Results

Basic information

All 107 patients voluntarily participated in the study, including 89 male patients (83.2%) and 18 female patients (16.8%), with a median age of 59.79±11.6 years. The results of the study showed that the number of lung transplants was increasing annually, with 9 cases in 2016, 15 in 2017, 21 in 2018, 30 in 2019, and 32 in 2020. Most patients had been diagnosed with IPF and COPD before surgery, with 55 cases (51.4%) and 37 cases (34.6%), respectively. There were 18 patients (13.8%) with hypertension, 16 patients (15.0%) with heart disease, and 11 patients (10.3%) with diabetes. The preoperative biochemical indicators of all participants were as follows: 54 cases (50.5%) of $PaCO_2$ >45 mmHg, 29 cases (27.1%) of PaO_2 <80 mmHg, 39 cases (36.4%) of Hb <110 g/L, 53 cases (48.6%) of WBC count >10×10^9/L, 69 cases (64.5%) of neutrophil ratio >70%, 6 cases (5.6%) of PLT <3.0×10^9/L, 16 cases (15.0%) of elevated CRP, and 39 cases (36.4%) of elevated interleukins. Among the 107 patients, there were 83 patients (77.6%) who used ventilators for over 3 days, 76 patients (71.03%) used urinary catheters for more than 3 days, and 32 patients (29.9%) were treated with venous catheters for over 3 days. The average length of hospital stay was 58.20±41.05 days. A total of 86 patients (80.4%) were discharged, of whom 16 patients (15.0%) died postoperatively, 4 patients (3.7%) gave up treatment due to serious illness, and 1 patient (0.9%) had not been discharged. The baseline demographic and clinical characteristics of the study participants are summarized in *Table 1*.

Among the 107 study participants, 80 patients (74.8%) were diagnosed with a postoperative infection. There were no significant differences between the infected and uninfected groups in age, gender, primary disease, hypertension, heart disease, diabetes, PaO_2, $PaCO_2$, Hb, red blood cell (RBC), WBC, and PLT count, elevated CRP, bilateral lung transplantation, intravenous catheter use for over 3 days, and hospital stay. However, more patients in the infected group used catheters for over 3 days than those in the uninfected group (76.3% *vs.* 55.6%, P=0.040). Furthermore, the number of patients who used ventilators for over 3 days in the infected group was greater than that in the uninfected group.

Postoperative infection

Excluding patients whose survival time was less than 48 hours, 80 cases (74.8%) experienced postoperative infection. There were 136 postoperative infection-related samples, as follows: 120 sputum (88.2%), 7 pleural fluid (5.2%), 5 urine (3.7%), and 2 BALF (1.5%). Researchers collected sputum, pleural fluid, and lavage fluid from the lower respiratory tract, and collected remaining samples from other parts.

A total of 136 strains of pathogenic bacteria were cultivated and identified, and Gram-negative bacteria (107 strains, 78.7%) were the main infectious bacteria, including *Acinetobacter baumannii* (30 strains, 22.1%), *Klebsiella pneumoniae* (27 strains, 19.9%), *Stenotrophomonas maltophilia* (12 strains, 8.8%), and *Acinetobacter joneii* (7 strains, 5.2%). The others were Gram-positive bacteria (18 strains, 13.2%), the majority of which were *Staphylococcus*

Table 1 Clinical information of lung transplant patients in infected and uninfected groups

Variables	Total (n=107)	Uninfected group (n=27)	Infected group (n=80)	P value
Age, years (mean, SD)	59.79±11.6	59.74±10.97	59.8±11.87	0.982
Male, n (%)	89 (83.2)	23 (85.2)	66 (82.5)	1.000#
Year of transplantation, n (%)				
2016	9 (8.4)	4 (14.8)	5 (6.3)	
2017	15 (14.0)	7 (25.9)	8 (10.0)	
2018	21 (19.6)	3 (11.1)	18 (22.5)	
2019	30 (28.0)	6 (22.2)	24 (30.0)	
2020	32 (29.9)	7 (25.9)	25 (31.3)	
Diagnosis, n (%)				
COPD	37 (34.6)	7 (25.9)	30 (37.5)	
IFP	55 (51.4)	15 (55.6)	40 (50.0)	
Others	15 (14.0)	5 (18.5)	10 (12.5)	
Concomitant disease, n (%)				
Hypertension	18 (16.8)	7 (25.9)	11 (13.8)	0.150#
Heart disease	16 (15.0)	2 (7.4)	14 (17.5)	0.348#
Diabetes	11 (10.3)	2 (7.4)	9 (11.3)	0.726#
Biochemical indicators				
$PaCO_2$ >45 mmHg, n (%)	54 (50.5)	38(70.4)	16(29.6)	0.304
PaO_2 <80 mmHg, n (%)	29 (27.1)	21(72.4)	8(27.59)	0.761
Hb <110 g/L, n (%)	39 (36.4)	11 (40.7)	28 (35.0)	0.592
WBC count >10×10^9/L, n (%)	53 (48.6)	37(69.8)	16 (30.2)	0.272
Neutrophil ratio >70%, n (%)	69 (64.5)	29 (76.3)	9 (23.7)	0.821
PLT <3.0×10^9/L, n (%)	6 (5.6)	1 (20.0)	4 (80.0)	0.013
Elevated CRP, n (%)	16 (15.0)	4 (14.8)	12 (15.0)	1.000#
Elevated interleukins, n (%)	39 (36.4)	33 (41.3)	6 (22.2)	0.076
Intraoperative and postoperative information				
Bilateral lung transplantation, n (%)	20 (18.7)	6 (22.2)	14 (17.5)	0.586
Catheter use over 3 days, n (%)	76 (71.0)	15 (55.6)	71 (76.3)	0.040
Intravenous catheter use over 3 days, n (%)	32 (29.9)	5 (18.5)	27 (33.8)	0.135
Ventilator over 3 days, n (%)	39 (36.4)	5 (18.5)	34 (42.5)	0.025
Hospital stay, days (mean, SD)	58.20±41.05	58.44±51.91	58.11±37.08	0.971
Final ending, n (%)				
Benign ending (discharged)	86 (80.4)	22 (81.5)	64 (80.0)	0.867
Unfavorable outcome	21 (19.6)	5 (18.5)	16 (20.0)	
Death	16 (15.0)	3 (11.1)	13 (16.3)	
Abandon treatment	4 (3.7)	2 (7.4)	2 (2.5)	
Not discharged	1 (0.9)	0 (0)	1 (1.3)	

#, Fisher's test. COPD, chronic obstructive pulmonary disease; IPF, idiopathic pulmonary fibrosis; WBC, white blood cell; Hb, hemoglobin; PLT, platelet; CRP, C-reactive protein.

haemolyticus (11 strains, 8.1%) and *Enterococcus faecium* (2 strains, 1.5%). The rest were fungal infections (11 strains, 8.1%), which contained *Candida albicans* (5 strains, 3.7%) and *Candida glabrata* (2 strains, 1.5%).

The results of drug resistance analysis displayed that multidrug-resistant bacteria were mainly Gram-negative bacteria (79 strains, 90.8%), of which were *Acinetobacter baumannii* (28 strains, 32.2%) and *Klebsiella pneumoniae* (25 strains, 28.7%). The rest were Gram-negative bacteria (8, 44.4%), mainly *Staphylococcus hemolyticus* (4, 4.6%). The specific microbial culture situation is shown in *Table 2*.

Factors associated with postoperative infection

As shown in *Figure 1*, in the univariate analysis, using urinary catheters for over 3 days [odds ratio (OR): 2.57, 95% confidence interval (CI): 1.03 to 6.43, P=0.044] and using ventilators over 3 days (OR: 3.25, 95% CI: 1.12 to 9.46, P=0.030) were associated with higher odds of postoperative infection. In contrast, PLT $<3.0\times10^9$/L (OR: 0.28, 95% CI: 0.08 to 0.97, P=0.045) was associated with lower odds of postoperative infection. The multivariate analysis revealed that using ventilators over 3 days (OR: 4.94, 95% CI: 1.31 to 18.66, P=0.019) and PaO_2 <80 mmHg (OR: 5.49, 95% CI: 1.07 to 28.15, P=0.041) were independently associated with higher odds of postoperative infection.

Discussion

Lung transplantation is an effective means to treat end-stage lung diseases. Correspondingly, problems like infection and acute pulmonary edema have gradually emerged with continuous development. Compared with other operations, lung transplantation needs to be focused on postoperative infection due to bronchial circulation, anastomotic site complications, and the use of immunosuppressive agents. This article clarifies the risk factors related to infection after lung transplantation by studying 107 lung transplant patients from 2016 to 2020.

There were certain limitations to this study. The small number of study patients, the larger time span, and the partial missing of basic patient information will all have affected the accuracy of the final results. At the same time, this hospital has few microbiological laboratory test items, and has not yet started monitoring the viral infection of surgical patients. It will be carried out in the follow-up daily work to better control the postoperative infection of lung transplant patients.

A total of 80 patients (74.8%) experienced postoperative infections after lung transplantation, similar to the 73.3% reported in the Henan province and 63.8–75% in Europe during the same timeframe, which suggests that infection after lung transplantation was at a high level globally (13,14). In 2017, the detection rate of lung microbes in lung transplant donors from the China-Japan Friendship Hospital, Beijing was 63.8%, suggesting that a high donor-carrying rate may be the important cause of postoperative infection (15). An analysis of postoperative infections for all organ transplants in Guangdong in 2018 showed that the infection rate of organ transplant patients was 8.29%, which was lower than the level of lung transplant patients in this study (16). Compared with a rate of about 18.75% of postoperative infections in kidney transplants, 24.24% in heart transplants, and 25–50% in liver transplantation, lung transplantation has a higher probability of postoperative infection, which indicates that increased attention should be given to these patients after surgery (17,18).

Gram-negative bacteria (107 strains, 78.7%) were the main infectious bacteria in this study, including *Acinetobacter baumannii* (30 strains, 22.1%), *Klebsiella pneumoniae* (27 strains, 19.9%), and *Stenotrophomonas maltophilia* (12 strains, 8.8%). The analysis of drug resistance showed that the main multidrug-resistant bacteria were *Acinetobacter baumannii* (28 strains, 32.18%) and *Klebsiella pneumoniae* (25 strains, 28.74%). *Acinetobacter baumannii* was the major strain in this study, Oh *et al.* found that multidrug-resistant *Acinetobacter baumannii* infection was the independent risk factor for 90-day mortality after lung transplantation (19). Furthermore, a study found that the presence of *Klebsiella pneumoniae* in lung-transplant recipients significantly increased the risk of bronchial dehiscence, which was unfavorable for organ healing (20).

Combining the univariate and multivariate analysis, using a ventilator for more than 3 days after surgery (OR: 4.94, 95% CI: 1.31 to 18.66, P=0.019) was the independent risk factor for postoperative infection. It indicated that patients who use ventilators for a prolonged duration were more likely to experience postoperative infections, which required more attention from postoperative infection staff. Our findings agreed with those of Tanaka *et al.*, who found prolonged mechanical ventilation significantly increased the risk of pneumonia after lung transplantation (21). Previous studies have found that the incidence of infection complications after lung transplantation was higher than that of other solid organ recipients, and lung infection was

Table 2 Basic situations of infection after lung transplantation

Classification	Bacteria	Count, n (%)	Multidrug-resistance, n (%)
Sampling type	Sputum	120 (88.2)	
	Pleural fluid	7 (5.2)	
	Urine	5 (3.7)	
	Bronchoalveolar lavage fluid	2 (1.5)	
	Venous catheter	1 (0.7)	
	Blood	1 (0.7)	
	Total	136	
Infected strains			
Gram-negative bacteria	*Acinetobacter baumannii*	30 (22.1)	28/30 (93.3)
	Klebsiella pneumoniae	27 (19.9)	25/27 (92.6)
	Stenotrophomonas maltophilia	12 (8.8)	9/12 (75.0)
	Acinetobacter junii	7 (5.2)	4/7 (57.1)
	Enterobacter cloacae	5 (3.7)	3/5 (60.0)
	Escherichia Coli	4 (2.9)	0/4 (0)
	Klebsiella oxytoca	3 (2.2)	2/3 (66.7)
	Citrobacter freundii	3 (2.2)	2/3 (66.7)
	Burkholderia cepacia	3 (2.2)	0/3 (0)
	Proteus mirabilis	3 (2.2)	0/3 (0)
	Meningeal septicemia	3 (2.2)	3/3 (100)
	Xanthomonas maltophilia	1 (0.7)	0/1 (0)
	Raulia ornithinolytica	1 (0.7)	0/1 (0)
	Achromobacter xylosoxidans	1 (0.7)	1/1 (100)
	Acinetobacter	1 (0.7)	0/1 (0)
	Pseudomonas aeruginosa	1 (0.7)	1/1 (100)
	Enterobacter aerogenes	1 (0.7)	1/1 (100)
	Citrobacter brucei	1 (0.7)	0/1 (0)
Gram-positive bacteria	*Staphylococcus haemolyticus*	11 (8.1)	4/11 (36.4)
	Enterococcus faecium	2 (1.5)	2/2 (100)
	Staphylococcus epidermidis	1 (0.7)	0/1 (0)
	Enterococcus faecalis	1 (0.7)	1/1 (100)
	Staphylococcus aureus	1 (0.7)	0/1 (0)
	Rare coprophilous	1 (0.7)	0/1 (0)
	Corynebacterium jergeri	1 (0.7)	1/1 (100)
Fungus	*Candida albicans*	5 (3.7)	
	Candida glabrata	2 (1.5)	
	Candida guilliermondii	1 (0.7)	
	Candida parapsilosis	1 (0.7)	
	Trichosporon asahii	1 (0.7)	
Total		136	87/136 (64.0)

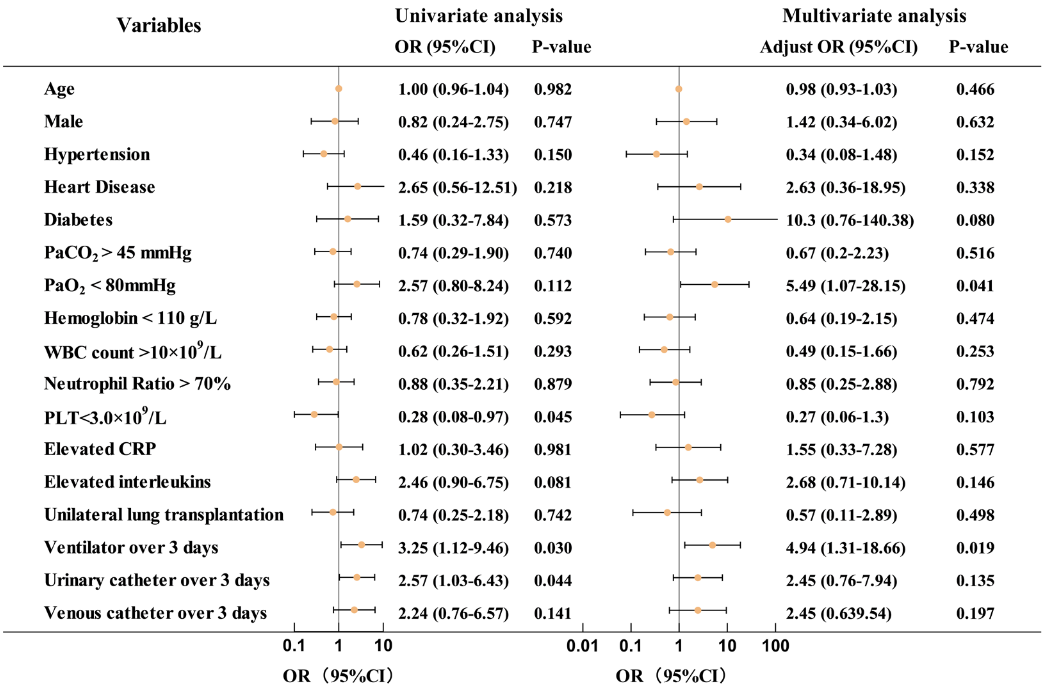

Figure 1 Logistic regression analysis of factors associated with in lung transplant patients. WBC, white blood cell; PLT, platelet, CRP, C-reactive protein.

the important cause of early death after lung transplantation (22,23). Similar to this study, bacterial pneumonia occurred most frequently in the early post-operative phase, and long-term use of ventilator after operation was a high-risk factor for lung infection (24). Therefore, for patients who require long-term use of ventilators after lung transplantation, increased attention should be paid to the potential of nosocomial infection.

Acknowledgments

Funding: None.

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-3023/rc

Data Sharing Statement: Available at https://atm.amegroups.com/article/view/10.21037/atm-22-3023/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-3023/coif). 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 study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of Shanghai Pulmonary Hospital (No. k22-259). Written informed consent was taken from patients or their families.

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Cite this article as: Meng D, Chang R, Zhu R. Analysis of nosocomial infection and risk factors in lung transplant patients: a case-control study. Ann Transl Med 2022;10(14):804. doi: 10.21037/atm-22-3023

