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TANAFFOS

Bronchiolitis Obliterans Syndrome and Death in Iranian Lung Transplant Recipients: A Bayesian Competing Risks Analysis

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Background: Bronchiolitis obliterans syndrome (BOS) is delayed allograft deterioration after lung transplant (LTX) that is clinically characterized by ≥ 20% decline from the baseline value of forced expiratory volume during the first second (FEV1). BOS is still a major obstacle limiting long-term survival post-LTX. The main aim of this study was to determine the predictors of BOS and death in Iranian LTX recipients.

Materials and Methods: This retrospective cohort study included 44 LTX recipients who survived ≥ 3 months post-LTX at the Masih Daneshvari Hospital, Tehran, Iran from 2000 to 2014. The outcome was time from lung transplantation to BOS and/or death (due to all causes except BOS). We used competing risks analysis to assess the effect of other factors on the cumulative incidence function of BOS and death. We applied a Fine and Gray model with Bayesian approach.

Results: The recipients' age (Mean ± SD) was 36.7 ± 14.5 yr. 11 (25%) recipients developed BOS as the first event within the first five years post-LTX and 13 (30%) died due to all causes except for BOS. Our results showed that CMV infection was associated with a significant increase in risk of developing BOS [hazard ratio (HR) 1.22 (95% credible set: (1.01, 3.2)] controlling for other variables. Bilateral transplantation [HR (95% credible set): 2.4(1.51, 4.05)] and CMV infection [HR (95% credible set): 2.02 (1.67, 2.55)] were predictors of the mortality risk.

Conclusion: CMV infection was a predictor of BOS risk in the studied patients. Moreover, bilateral transplantation and CMV infection were significant predictors of mortality in the present sample. Multi-center studies with larger sample sizes are required to better study the other risk factors, and the pathophysiologic mechanisms of BOS.

Key words: Lung transplant; Bronchiolitis obliterans syndrome; Competing risks analysis; Cumulative Incidence Function; Fine and Gray model; Bayesian analysis

INTRODUCTION

Lung transplantation (LTX) is an accepted treatment for patients with advanced lung disease. Bronchiolitis obliterans syndrome is defined as delayed allograft deterioration, which presents as the onset and persistence of airflow obstruction. From the clinical standpoint, BOS is characterized by ≥ 20% decline in FEV1 from the baseline (1). It has been reported that BOS is a major cause of mortality and its cumulative incidence ranges from 43% to 80% within the first five years post-LTX (2, 3). Between

1994 and 2010, 49% and 75% of the recipients (including 13,000 recipients who survived at least 14 days post-LTX) developed BOS by 5 and 10 years after LTX, respectively (4). Recent investigations have shown that immunosuppressive drugs, surgical techniques, lung preservation, and the management of infectious processes have improved substantially. However, BOS remains as a major obstacle in the long-term survival post-LTX. Previous studies have found infections (viral, bacterial, and fungal), acute rejection (AR), humoral rejection and anti-HLA antibodies, primary graft dysfunction, and gastroesophageal reflux to be associated with increased risk of BOS (5), with AR being the primary risk factor for developing BOS (3, 6-8). Similarly, cytomegalovirus (CMV) infection post-LTX is associated with an increased risk of developing BOS (8, 9). In addition, AR, CMV, underlying disease, and the type of transplant were risk factors for mortality post-LTX (4, 10, 11).

BOS was the primary event of interest, and death due to all causes except BOS was considered as the other event. The main purpose of this study was to find the prevalence of BOS and identify the predictors of BOS in the LTX recipients at the Masih Daneshvari Hospital. Furthermore, we studied the risk factors for mortality post-LTX.

MATERIALS AND METHODS

This retrospective cohort study included 44 patients who underwent LTX and survived at least 3 months post-LTX at the Masih Daneshvari Hospital, the National Research Institute for Tuberculosis and Lung Diseases, Shahid Beheshti University of Medical Sciences, Tehran, Iran from 2000 to 2014. All the donors in the studied center were CMV infected. Therefore all the recipients received ganciclovir or valganciclovir up to three months post-LTX (12).

The primary outcome of interest was time from LTX to diagnosis of BOS and/or death, whichever came sooner. However, not all recipients in whom a decline in FEV1 and/or airflow obstruction develops have BOS, and obliterative bronchiolitis (OB) may be present in allografts that do not display a significant pattern of airflow obstruction that meets previously defined criteria for the diagnosis of BOS.

The type of transplant (single vs. bilateral) and the underlying disease that necessitated LTX were included in the analysis. All recipients were categorized into three main groups based on their underlying disease that required LTX: Bronchiectasis, chronic obstructive pulmonary disease (COPD), and pulmonary fibrosis (as the reference group). Based on the intensity of the infiltrates, the International Society for Heart and Lung Transplantation (ISHLT) considers AR classification as follows: AR0 (none), AR1 (minimal), AR2 (mild), AR3 (moderate), AR4 (severe) (13). In this study, patients with AR1 or higher grades based on pathological findings were included as a binary variable; the occurrence of at least one episode of AR versus none. The CMV antigen (Ag) was checked monthly and recipients with CMV Ag higher than 2.5/50,000 copy/ml were considered CMV infected (CMV+) or CMV Ag+. CMV infection was included as a binary variable (i.e. at least one episode of CMV infection versus none).

Statistical analysis

In survival analysis, a competing risks setting occurs when a patient can experience more than one type of event and the occurrence of one event hinders the occurrence of the other event(s) (14). Naturally, in this study, the recipients who expired early post-operatively did not survive long enough to develop BOS. Therefore, BOS was considered as the primary event of interest and mortality (due to all causes except BOS) was considered as the competing event. Recipients who did not experience any of the aforementioned events before the study ended were censors.

Results are expressed as mean ± standard deviation (SD) for numeric variables and frequency (%) for categorical variables. Cumulative incidence function (CIF) is the probability of occurrence of a particular event. CIF was calculated for BOS as well as for death. The Fine and Gray model was used to assess the effect of the factors on the cumulative incidence of either BOS or death through two separate models. In the former, BOS was the primary

event of interest and in the latter, death was the primary event of interest. Bayesian analysis was used to overcome the limitation of small sample size through OpenBUGS 3.2.3. Hazard ratio (HR) is the measure of the effect of each variable adjusted for the other variables in a model (15). An approximation of the lower and upper endpoint of the 95% credible set were calculated for HR. Monte Carlo error (MC-error), the computational accuracy of the mean, was monitored. MC-error values lower than 0.01 reveal that the estimation is accurate. Independent normal priors were assumed for the coefficients and independent gamma priors for piecewise baseline hazard function. Statistical significance was set at *P* 0.05.

RESULTS

The mean (SD) age of 44 LTX recipients was 36.7 (14.5). There were 25 (55%) bilateral LTX recipients. Table 1 shows the recipients' characteristics. 11 (25%) recipients developed BOS as the first event (during the first five years) and 13 (30%) died (due to all causes except BOS) post-LTX. CMV infection was observed in 13.5% of the patients with BOS and 16% of deceased cases (data not shown).

Table 1. The recipients' characteristics

Characteristics	Mean ± SD or No (%)
Age at LTX (yr)	36.7 ± 14.5
Type of transplant	
Single	19 (45)
Bilateral	25 (55)
AR*	
None	36 (80)
At least one episode	8 (20)
Underlying lung disease	
COPD**	10 (22)
Bronchiectasis	18 (41)
Pulmonary fibrosis	16 (36)
CMV†	
At least one episode	21 (47)
None	23 (53)
Competing risks	
BOS††	11 (25)
Death (due to all causes except BOS)	13 (30)
Censor	20 (45)

*Acute rejection, **Chronic obstructive pulmonary disease, †Cytomegalovirus, ††Bronchiolitis obliterans syndrome

Figure 1 illustrates that CIF of death was higher than that of BOS over time. The cumulative incidence of BOS increased up to 30% and stabilized afterwards, whereas that of death increased to 60%.

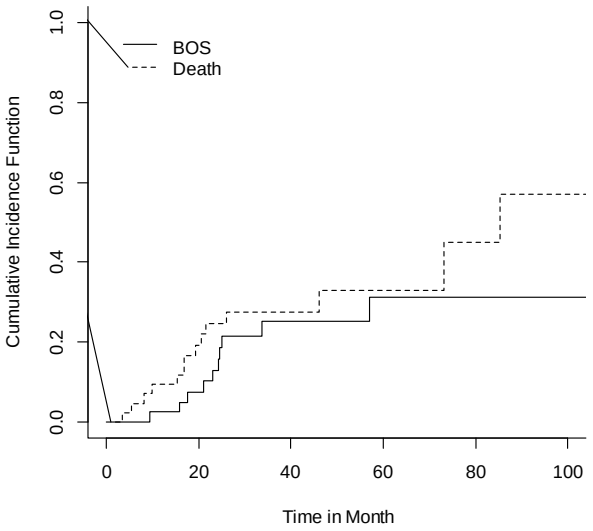

Figure 1. The cumulative incidence estimation of BOS (solid line) and death (dash line) over time

Figure 2 shows the cumulative incidence estimation of BOS and death based on the CMV status of the recipients.. CMV+ recipients had a higher cumulative incidence of BOS and the incidence of death was higher in CMV+ recipients.

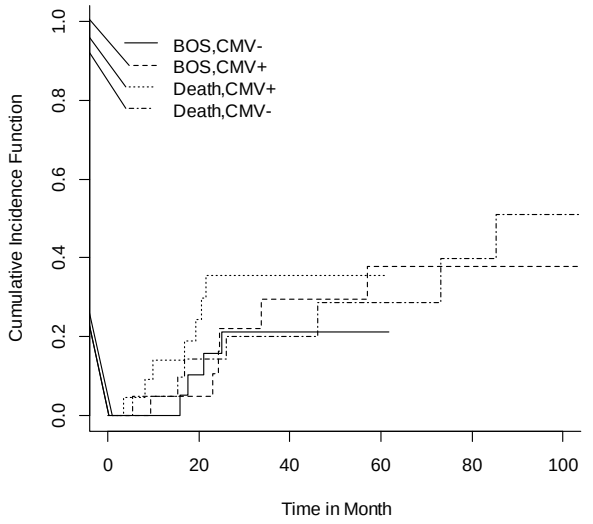

Figure 2. The cumulative incidence estimation of BOS and death in terms of the CMV- and CMV+

Table 2. Hazard ratio ± SD and 95% credible set on the cumulative incidence function of BOS

Variable	HR† ± SD††	95% Credible set†††	MC-error◊
Type of transplant (Bilateral vs single)	0.99 ± 0.44	(0.39, 2.29)	0.001
AR* (At least one episode vs none)	1.92 ±1.61	(0.09, 9.3)	0.007
CMV** (At least one episode vs none)	1.22 ± 0.51	(1.01, 3.2)	0.009
Underlying lung disease			
Pulmonary fibrosis	Reference group	-	-
Bronchiectasis	0.82 ± 1.57	(0.02, 13.4)	0.009
COPD***	0.07 ± 1.63	(0.002, 1.82)	0.007

*Acute rejection, **Cytomegalovirus, ***Chronic obstructive pulmonary disease, †Hazard ratio, ††Standard deviation, †††95% Credible set including 1 means a non-significant effect of the variable, ◊Mont Carlo error <0.01 shows convergence

Table 3. Hazard ratio ± SD and 95% credible set on the cumulative incidence function of mortality

Variable	HR† ± SD††	95% Credible set†††	MC-error◊
Type of transplant (Bilateral vs single)	2.4 ±0.24	(1.51, 4.05)	0.003
AR* (At least one vs none)	1.28 ±0.15	(0.93, 1.74)	0.001
CMV (At least one vs none)	2.02 ±0.21	(1.67, 2.55)	0.001
Underlying lung disease			
Pulmonary fibrosis	Reference group	-	-
Bronchiectasis	0.47 ±0.38	(0.22, 1.00)	0.004
COPD**	0.78 ±0.24	(0.48, 1.24)	0.002

*Acute rejection, **Chronic obstructive pulmonary disease, †Hazard ratio, ††Standard deviation, †††Monte Carlo error (MC-error) <0.01 shows convergence, ◊95% Credible set including 1 means a non-significant effect of the variable

Table 2 presents the effects of the covariates on the CIF of BOS. The risk of developing BOS in the CMV infected recipients was 22% higher than that of CMV - recipients [HR (95% credible set): 1.22(1.01, 3.2).] In addition, AR, the type of transplant, and the underlying disease requiring LTX were not significant risk factors for developing BOS.

The analysis of the BOS risk factors cannot be fully interpreted without assessing the effects of other covariates on death. The results in Table 3 demonstrate that the risk of death in the bilateral LTX recipients was 2.4 (1.51, 4.05) times that of the single LTX recipients.

Moreover, the mortality risk was significantly higher in the CMV+ recipients compared with the CMV- recipients [HR (95% credible set): 2.02 (1.67, 2.55)]. AR and underlying disease were not predictors of mortality. MC-errors in Tables 2 and 3 values showed that the effects are accurately estimated.

DISCUSSION

Lung transplantation is the only effective therapy that improves survival in patients with end-stage lung diseases. However, BOS is still a main limitation for long-term survival post-LTX (16). In 2009, the first report of the survival rates in Iranian LTX was published (17). Five years later, another study revealed an improvement in survival rates post-LTX in the Iranian recipients (18). The present study showed that 25% of the recipients developed BOS, and identified BOS as the major risk factor that limits long-term survival. As outlined in the introduction, the present study used a competing risks model to evaluate the predictors of BOS development in Iranian LTX recipients.

This study found that CMV Ag+ status after the third month post-LTX increased the risk of BOS significantly, controlling for AR and other factors.

Furthermore, CMV infection and the type of transplant were predictors of mortality in the studied sample,

showing the hazardous effect of a bilateral LTX versus a single lung transplant.

Two previous studies that used univariate analysis reported a significant association between CMV status and development of BOS. Similarly, a separate study found a significant association between CMV pneumonitis and BOS and/or OB in 543 recipients (6). However, multivariate analyses controlling for AR did not show an association between CMV status and increased risk of developing BOS (19, 20). Similarly, other studies have not found any association between CMV and BOS (7, 9). Finally, the ISHT reported donor-recipient CMV matching was significantly associated with 1- and 5-year mortality (4) while a study including diabetic recipients found no significant effect of CMV matching on mortality (10).

It has been shown that AR is a significant risk factor for the development of BOS (7, 19). A systematic review including 320 cases of BOS and OB identified AR as a significant risk factor (6). In 2011, ISHLT reported that AR increases the risk of death (4). In Iran, a study including 38 LTX recipients using joint modeling showed that recipients who developed AR had a considerably higher mortality rate, controlling for other covariates (21). In the current study AR was not associated with development of BOS or mortality. In a retrospective review of 221 LTX recipients with COPD, BOS was significantly more likely in bilateral LTX recipients than in single LTX recipients at 3, and 5 years post-LTX (22). Our findings revealed that the type of transplant was not a significant predictor of BOS development, whereas it was a significant predictor of mortality. It is worth noting that the type of transplant was not a significant factor affecting mortality in a previous study in 71 Iranian LTX recipients (18). However, our results suggest that the type of LTX significantly affects mortality. The current data showed that the underlying disease at the time of LTX was not a predictor of BOS or mortality.

CONCLUSION

It can be concluded that BOS risk was higher in the recipients who were CMV+. Furthermore, bilateral lung transplantation and CMV infection were predictors of mortality (after 3 months) in this sample. Since the purpose of LTX is to improve patients' survival and their quality of life, it is important to determine the significant predictors of BOS development to prevent or delay the onset of this disorder by managing the recipients' health more effectively in Iran. The main limitation of this study is that the recipients were only from one center. Therefore it is suggested to conduct multi-center studies in the future, with larger sample sizes in order to better understand the other risk factors and the pathophysiologic mechanisms in BOS. Though the low sample size limits the generalizability of the results, we used Bayesian analysis to overcome this limitation. Another strength of this study is using a new statistical technique, competing risks analysis, to achieve results that are more precise.

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