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# Minimal acute rejection in pediatric lung transplantation does it matter?

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## Abstract

In adult lung transplantation, a single minimal acute rejection (AR) episode is a significant predictor of bronchiolitis obliterans syndrome (BOS) independent of other factors. However, the significance of single minimal AR episodes in children is unknown.

A retrospective, multi-center analysis was performed to determine if isolated single AR episodes are associated with an increased BOS risk in children. Risk factors for BOS, death or re-transplantation, and a combined outcome of BOS, death or re-transplantation were assessed.

Original data included 577 patients (<21 yr of age). 383 subjects were eligible for the study. 15% of patients developed BOS, 13% either died or underwent re-transplant within one year post-transplant. In the multivariable survival model for time to BOS, there was no significant risk to developing BOS after a single minimal AR (A1) episode (HR 1.7, 95% CI 0.64–4.8; p=0.28). Even after a second minimal AR episode, no significant risk for BOS was appreciated. However, a single episode of mild AR (A2) was associated with twice the risk of BOS within one year post-transplant.

In this select cohort, a single minimal AR episode was not associated with an increased risk for BOS within one year following lung transplantation, in contrast to previous reports in adults.

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**COMPETING INTEREST STATEMENT**

The authors do not have any competing interests to declare.

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**Keywords**

Lung transplantation; acute allograft rejection; bronchiolitis obliterans syndrome; children; pediatrics

## INTRODUCTION

Lung transplantation is an accepted therapy for children and adolescents with end-stage lung disease [1]. More than 1,500 pediatric lung and heart-lung transplant procedures have been performed between 1984 and June 2007 according to the 2008 Pediatric Registry Report of the International Society for Heart and Lung Transplantation (ISHLT) [2]. Outcome following lung transplantation in children is reported to be similar to adults, with a median survival of just less than five years [2,3]. Results following lung transplantation in children are improving, although figures indicate, that better survival is solely due to improved early outcomes with key improvements in areas such as organ preservation, surgical technique and pediatric intensive care management [2]. However, long-term outcome after pediatric lung transplantation remains inferior compared to other pediatric solid organ transplants. Late allograft failure continues to limit the long-term success of lung transplantation for both children and adults alike [4]. Bronchiolitis obliterans (BO) is the major cause of morbidity and mortality following lung transplantation, and accounts for more than 40% of deaths in pediatric recipients by five years after transplantation. Moreover, the prevalence of bronchiolitis obliterans syndrome (BOS) is more than 50% in surviving children and adolescents by five years post-transplant [2]. The underlying mechanisms of the chronic graft deterioration are not completely understood [5]. It has been shown that multiple and higher-grade episodes of acute graft rejection are associated with BOS in adults and children after lung transplant. In addition, a recent study suggested that a single episode of minimal acute rejection without recurrence or subsequent progression to a higher-grade is a significant predictor of BOS in adults independent of other risk factors [6]. However, the significance of a single episode of minimal acute rejection in pediatric lung transplant recipients is unknown. This study aims to determine if isolated single episodes of acute rejection and/or multiple episodes of acute rejection are associated with an increased risk for the development of BOS in pediatric lung (and heart-lung) transplant recipients. In addition, we aim to evaluate the risk of early BOS, re-transplantation or death in relation to acute rejection episodes based on their number, severity and sequence of acute rejection.

## METHODS

A retrospective, multi-center analysis was performed in 14 pediatric lung transplant centers in Europe and North America, all of which are members of the International Pediatric Lung Transplant Collaborative (IPLTC). The principal investigator (L.A. DI) carried out a chart review of all medical records of patients undergoing primary single lung, double lung, or heart-lung transplantation in the participating centers between January 1988 and the time of data collection (August 2004-January 2007). Patient data were recorded for the first year following lung transplantation.

No unified immunosuppressant regimen existed in the participating centers; however, most recipients received a maintenance triple immunosuppressant therapy consisting of a calcineurin inhibitor (cyclosporine A or tacrolimus), an anti-proliferative agent (azathioprine or mycophenolate mofetil) and prednisolone plus induction therapy in the majority of participating centers (lympholytic agent or interleukin-2 receptor antagonist). Post-transplant anti-infective prophylaxis was not standardized across centers. All recipients underwent serial laboratory lung function tests according to local laboratory protocols, and regular

outpatient clinic visits. BOS was diagnosed according to published diagnostic criteria [4]. Briefly, BOS stage 1 defined as 66–80% of the mean of the two best measurements of forced expiratory volume in one second ($FEV_1$) after transplantation taken at least 3 weeks apart, BOS stage 2 $FEV_1$ 51–65%, and BOS stage 3 $FEV_1$ <50. The histopathological diagnosis of acute rejection was based on the working formulation for the classification of pulmonary allograft rejection from the ISHLT Lung Rejection Study Group, as described elsewhere [7]. In brief, acute graft rejection is based on perivascular and interstitial mononuclear cell infiltrates, grade A0 (none), grade A1 (minimal), grade A2 (mild), grade A3 (moderate) and grade A4 (severe), respectively. Episodes of acute rejection diagnosed and treated on clinical suspicion were excluded from the analysis.

Approval was obtained from institutional review boards in the North American centers and local ethics committees in European centers. All patient data were anonymized at the time of data extraction from medical records.

### Statistical analysis

Risk factors for BOS, death or re-transplantation, and a combined outcome of BOS, death, or re-transplantation were assessed using univariable and multivariable Cox proportional hazards regression models with follow-up censored at death, re-transplantation, or one year post-transplant. Episodes of rejection were modeled as time-dependent covariates: first minimal (A1) rejection, second A1 rejection, first mild (A2) rejection, second A2 rejection, and mixed multiple rejection, defined as a second rejection following a first rejection at a different grade. Additional episodes of rejection beyond the first two were not modeled. Post-transplant morbidities including episodes of pulmonary fungal infection, post-transplant lympho-proliferative disease (PTLD), respiratory viral infection, and CMV infection were also modeled as time-dependent covariates. Data analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC, USA) software. All tests were two-tailed and performed at a significance level of 0.05. Samples sizes for individual variables reflect missing data. All analyses were performed on a complete-case basis.

## RESULTS

The original data included 577 patients (<21 yr of age). We consolidated 68 acute rejection episodes that were within two weeks of previous episodes, classifying the episodes as having the higher of the two grades where they differed.

At the 14 centers, 383 subjects were eligible for this study. Patient demographic data are displayed in Table 1. Of the overall cohort, 58 (15%) of patients developed BOS, and 48 (13%) either died or underwent re-transplantation within the first year after transplant. The outcome for subjects based on the acute rejection group including BOS, re-transplant and death is presented Table 2.

In the univariable analysis, risk of BOS was not associated with underlying etiology for transplant, age at transplant, type of transplant surgery, induction treatment, CMV status, post-transplant respiratory viral and fungal infections, but was significantly higher for the earliest transplant era and for those on cyclosporine maintenance therapy (Table 3).

A multivariable survival model was constructed to evaluate associations between BOS and acute rejection episodes (Table 4). As the number of patients with BOS constrained the number of variables in the model to five, only the time-dependent variables for acute rejection events were considered in the multivariable modelling. In the multivariable survival model for time to BOS, there was no significant risk to developing BOS after a single A1 rejection episode (hazard ratio (HR) 1.7, 95% CI 0.64–4.8; P=0.28). Furthermore,

even following a second minimal A1 rejection episode, no significant risk for BOS was appreciated (HR 1.1; 95% CI 0.25–5.2; P=0.86). However, a single episode of A2 rejection doubled the risk of developing BOS within the first year after transplantation (HR 2.4, 95% CI 1.1–5.1; P=0.022), and the risk of BOS was increased four-fold after a second episode of A2 rejection (HR 4.1, 95% CI 1.9–9.0; P<0.001). Moreover, the risk for BOS following any second, mixed type rejection episode was significantly increased (HR 4.2, 95% CI 2.2–9.10; P<0.001). Multiple mixed grades of acute rejection were also associated with increased risk of re-transplantation or death within the first post-transplant year (HR 2.0, 95% CI 1.00–4.1; P=0.048). For patients with multiple episodes of acute rejection, the median time interval between episodes was 42 days (range 15–322). The risk of developing a composite outcome including BOS, death or re-transplantation was significantly increased after multiple episodes of mixed grades of acute rejection (HR 2.7, 95% CI 1.6–4.6; P<0.001) and after a second episode of A2 rejection (HR 1.8; 95% CI 1.01–3.2; P=0.046).

## DISCUSSION

Our study demonstrates that a single episode of minimal acute allograft rejection was not associated with an increased risk of developing BOS within one year after lung transplantation in this selected pediatric cohort, but the risk for developing BOS was increased in pediatric recipients following one or more A2 rejection episode. In addition, we found an increased risk of BOS, re-transplantation or death following a second A2 or mixed-type rejection episode.

Pediatric lung transplantation is an accepted therapy for end-stage lung disease of different etiologies, which not only aims to prolongation of life but also provide for an improved quality of life [8]. Individual transplant centers have reported favorable outcomes particularly for children and adolescents with CF, the major indication for lung transplantation in patients <18 yr of age [9,10]. Moreover, more than 80% of the children who survive to five years post-transplant retain full functional status and no activity limitation, according to the most recent ISHLT Registry Report [2]. However, long-term survival following pediatric lung transplantation is less favorable compared to other pediatric solid organ transplants. Chronic graft failure remains the major obstacle to better long-term outcome and improved quality of life after lung transplantation in children [2].

BO has been defined pathologically as the airway response to chronic allograft rejection, which manifests physiologically as BOS. The mechanisms underlying the development of chronic graft deterioration are not entirely known, though multiple factors seem to play a role [11–14]. Several authors have reported an association between an increased frequency and severity of acute allograft rejection and the subsequent development of BOS, while non-alloimmunological factors, such as bacterial, viral, and fungal infection may also play a role [4]. Also, multiple and higher-grade acute rejection episodes are associated with the development of BOS after lung transplantation. Even a single episode of minimal acute graft rejection has been shown to be a significant predictor of BOS in adult lung transplant recipients independent of other risk factors [6,15]. The recipients in both adult studies were followed up for three years compared to a 1-yr follow-up of our patient cohort.

To our knowledge, there are no published pediatric studies investigating the impact of an isolated single episode of minimal acute rejection in the development of BOS in lung (and heart-lung) transplant recipients. However, studies in adults have shown an association between minimal rejection and BOS. Khalifah et al demonstrated that the occurrence of isolated minimal acute rejection is a risk factor for all stages of BOS in adult lung transplant recipients. Furthermore, the authors showed that minimal acute rejection is associated with a higher risk of BOS distinct from the risk attributable to other factors and BOS progression

after A1 rejection was comparable to that of patients diagnosed with mild A2 acute rejection [16]. However, there is an ongoing debate regarding whether treatment of minimal rejection lowers the risk of developing BOS. Khalifah and colleagues investigated the impact of treatment of minimal acute graft rejection and the development of BOS in a retrospective study on a cohort of adults [16]. Symptomatic recipients with mild A1 acute rejection episodes were treated with intravenous methylprednisolone (10–15 mg/kg) for three days; grade A1 episodes in asymptomatic patients were not treated. The study revealed that treatment of a minimal acute rejection episode reduced the risk for the subsequent development of BOS stage 1. In our study cohort, a single minimal acute rejection episode was not associated with an increased risk for the development of BOS within one year post lung transplant. Therefore, the impact of treatment of minimal acute rejection episodes to abrogate development of BOS seems unlikely to reveal any association in this select patient cohort. However, our analysis was not designed to evaluate whether and when to treat minimal acute rejection. In general, symptomatic minimal acute rejection episodes were treated with augmented immunosuppression. A1 rejection episodes without clinical symptoms were usually not treated. Episodes of ≥A2 rejection prompted a therapeutic intervention. However, no unified treatment protocol was followed among centers during the more than 15-yr study period.

Our study has some limitations that are inherent in retrospective, multi-center study designs; however, this is the largest pediatric cohort ever to investigate if an isolated single episodes of acute rejection and/or multiple episodes of acute rejection are associated with an increased risk for the development of BOS in pediatric lung transplantation. Our study period was limited to one year. Patient pre-transplant assessment, listing criteria and transplant surgery were not standardized across centers. Additionally, immunosuppressant therapies and anti-infective prophylaxis varied across centers, and in more recent years, changes have been implemented in many centers' therapeutic regimens, which likely have influenced post-transplant survival within the first year. In the majority of centers, surveillance bronchoscopy protocols were followed; a few centers undertook clinically indicated bronchoscopies instead. However, in centers without surveillance, a low threshold existed to perform clinically indicated bronchoscopies, thus, the diagnosis of minimal acute rejection is probably not underestimated in the whole cohort as recently shown by Valentine et al [17]. Finally, while pathological assessments were assigned based on published standardized criteria formulated by the ISHLT Lung Rejection Study Group, the final diagnoses were not confirmed by a reference panel of pathologists. Nonetheless, our analysis evaluated the outcome of 'A' grade acute rejection episodes only, which tends to elicit more uniformity in diagnosis among pathologists, according to a recent study of more >200 lung transplant recipients which revealed that 'A' grades (perivascular inflammation) demonstrate a very good reliability when biopsy samples were reviewed and re-classified by a single, blinded pathologist [18].

In conclusion, a single minimal acute rejection episode was not associated with an increased risk for the development of BOS within one year after lung transplantation in this large select pediatric cohort, in contrast to previous reports in adult lung transplant recipients. Nonetheless, the authors believe that any minimal acute rejection episode in children after lung transplantation requires close surveillance. If there is evidence of clinical deterioration, a repeat transbronchial biopsy is warranted to assess the need for a targeted therapeutic intervention. However, the impact of such therapeutic interventions on the long-term patient outcome after pediatric lung transplantation is yet to be determined.

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## Abbreviations

| | |
|---|---|
| **BO** | bronchiolitis obliterans |
| **BOS** | bronchiolitis obliterans syndrome |
| **CMV** | cytomegalovirus |
| **$FEV_1$** | forced expiratory volume in 1 sec |
| **IPLTC** | International Pediatric Lung Transplant Collaborative |
| **ISHLT** | International Society for Heart and Lung Transplantation |

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**Table 1**

Patient demographics by acute rejection (AR) group (Note: A0 episodes and 'B' grades are ignored)

| | No acute rejection | | One A1 | | One A2 | | Multiple A1 | | Multiple A2 | | Multiple AR of mixed types | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **N** | | **N** | | **N** | | **N** | | **N** | | **N** | |
| **Median age at transplant** (P25, P75) [yr] | 108 | 10.3 (1.4, 15.1) | 50 | 13.7 (7.4, 16.6) | 44 | 12.0 (5.1, 15.4) | 34 | 12.4 (7.6, 15.7) | 73 | 14.2 (12.0, 16.1) | 73 | 13.2 (10.2, 16.2) |
| **Gender** | | | | | | | | | | | | |
| Male | 69 | 64% | 21 | 42% | 24 | 59% | 20 | 59% | 43 | 59% | 49 | 66% |
| Female | 39 | 36% | 29 | 58% | 20 | 41% | 14 | 41% | 30 | 41% | 25 | 34% |
| **Cystic fibrosis** | 38 | 35% | 27 | 54% | 21 | 48% | 18 | 53% | 50 | 69% | 54 | 73% |
| **Type of transplant** | | | | | | | | | | | | |
| Single lung | 1 | 1% | 0 | 0% | 0 | 0% | 1 | 3% | 3 | 4% | 1 | 1% |
| Double lung | 74 | 79% | 37 | 74% | 33 | 75% | 28 | 82% | 61 | 84% | 62 | 84% |
| Heart/lung | 25 | 23% | 10 | 20% | 7 | 16% | 5 | 15% | 3 | 4% | 7 | 10% |
| Living donor | 7 | 7% | 3 | 6% | 4 | 9% | 0 | 0% | 6 | 8% | 4 | 5% |
| **Induction therapy** | | | | | | | | | | | | |
| No | 60 | 59% | 25 | 57% | 23 | 58% | 16 | 52% | 42 | 61% | 37 | 56% |
| Yes | 41 | 41% | 19 | 43% | 17 | 42% | 15 | 48% | 27 | 39% | 29 | 44% |
| **Maintenance** | | | | | | | | | | | | |
| Cyclosporine | 77 | 71% | 32 | 64% | 32 | 73% | 20 | 59% | 63 | 86% | 52 | 71% |
| Tacrolimus | 31 | 29% | 18 | 36% | 12 | 27% | 14 | 41% | 10 | 14% | 21 | 29% |

## Table 2

Outcome at one year by acute rejection (AR) group

| AR Group | Outcome at 1 year | | | |
|---|---|---|---|---|
| N | No BOS, Death or Re-tx | BOS | Re-tx or Death | Total |
| No AR (%) | 81 (75) | 4 (4) | 23 (21) | 108 (100) |
| One A1 AR (%) | 40 (80) | 4 (8) | 6 (12) | 50 (100) |
| One A≥2 AR (%) | 31 (71) | 8 (18) | 5 (11) | 44 (100) |
| Two A1 AR (%) | 29 (85) | 2 (6) | 3 (9) | 34 (100) |
| Two A≥2 AR (%) | 51 (70) | 19 (26) | 3 (4) | 73 (100) |
| Multiple AR of mixed types (%) | 45 (61) | 21 (28) | 8 (11) | 74 (100) |
| Total | 277 | 58 | 48 | 383 |

**BOS**, bronchiolitis obliterans syndrome; **Re-tx**, re-transplantation

## Table 3

| Table 3.1: Univariable models for time to BOS, time to BOS/death/re-tx, and time to death/re-tx. Post-transplant events were modelled as time-dependent risk factors. | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | Univariable risk factors for BOS | | Univariable risk factors for Death/Re-tx | | Univariable risk factors for BOS/Death/Re-tx | |
| **Risk factor** | **Level** | **N** | **Hazard ratio (95% CI)** | **P-value** | **Hazard ratio (95% CI)** | **P-value** | **Hazard ratio (95% CI)** | **P-value** |
| Donor (D) and recipient (R) CMV status | | 370 | | 0.44 | | 0.44 | | 0.44 |
| | D+R+ vs. D−R− | | 1.1 (0.51, 2.5) | | 1.1 (0.51, 2.5) | | 1.1 .5) | |
| | D+R− vs. D−R− | | 1.7 (0.87, 3.2) | | 1.7 (0.87, 3.2) | | 1.7 (0.87, 3.2) | |
| | D−R+ vs. D−R− | | 1.4 (0.62, 3.4) | | 1.4 (0.62, 3.4) | | 1.4 (0.62, 3.4) | |
| Transplant type | | 382 | | 0.28 | | 0.11 | | 0.39 |
| | Single vs. living donor | | 8.9 (0.81, 98.5) | | 1.04 (0.22, 5.0) | | 1.6 (0.43, 6.1) | |
| | Double vs. living donor | | 3.3 .46, 24.2) | | 0.42 (0.19, 0.93) | | 0.69 (0.34, 1.4) | |
| | Heart/lung vs. living donor | | 2.6 (0.31, 20.8) | | 0.42 (0.15, 1.1) | | 0.69 (0.29, 1.6) | |
| Age at transplant | | 382 | | 0.11 | | 0.13 | | 0.81 |
| | 0–5.4 vs. 16.6 –20.6 | | 0.43 (0.13, 1.4) | | 0.88 (0.44, 1.8) | | 0.70 (0.38, 1.3) | |
| | 5.511.3 vs. 16.6 –20.6 | | 1.7 (0.74, 3.8) | | 0.55 (0.25, 1.2) | | 0.80 (0.45, 1.4) | |
| | 11.4–14.1 vs. 16.6 –20.6 | | 1.3 (0.54, 3.0) | | 0.68 (0.32, 1.4) | | 0.81 (0.45, 1.4) | |
| | 14.2–16.5 vs. 16.6 –20.6 | | 1.7 (0.74, 3.7) | | 0.32 (0.13, 0.81) | | 0.75 (0.42, 1.3) | |
| Era of transplant | | 383 | | 0.011 | | 0.11 | | <0.001 |
| | 1985–1994 vs. 2003–2005 | | 4.1 (1.5, 11.1) | 0.005 | 2.0 (0.88, 4.3) | 0.098 | 3.2 (1.6, 6.3) | <0.001 |
| | 1995–1997 vs. 2003–2005 | | 1.6 (0.57, 4.7) | 0.35 | 0.88 (0.37, 2.1) | 0.78 | 1.4 (0.69, 3.0) | 0.34 |
| | 1998–1999 vs. 2003–2005 | | 1.4 (0.44, 4.4) | 0.57 | 0.87 0.34, 2.3) | 0.78 | 1.3 (0.58, 2.8) | 0.55 |
| | 2000–2002 vs. 2003–2005 | | 2.1 (0.77, 5.7) | 0.15 | 0.91 0.39, 2.1) | 0.83 | 1.5 (0.76, 3.1) | 0.24 |

| Table 3.2: Univariable models for time to BOS, time to BOS/death/re-tx, and time to death/re-tx. Post-transplant events were modelled as time-dependent risk factors. | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | Univariable risk factors for BOS | | Univariable risk factors for Death/Re-tx | | Univariable risk factors for BOS/Death/Re-tx | |
| **Risk factor** | **Level** | **N** | **Hazard ratio (95% CI)** | **P-value** | **Hazard ratio (95% CI)** | **P-value** | **Hazard ratio** | **P-value (95% CI)** |
| Female gender | | 383 | 0.83 (0.49, 1.4) | 0.47 | 0.84 (0.50, 1.4) | 0.49 | 0.82 (0.56, 1.2) | 0.30 |
| Cystic fibrosis etiology | | 383 | 1.2 (0.70, 2.0) | 0.55 | 1.03 (0.62, 1.7) | 0.91 | 1.1 (0.76, 1.6) | 0.56 |
| Any induction treatment | | 351 | 1.08 0.63, 1.9) | 0.77 | 0.82 (0.48, 1.4) | 0.45 | 0.91 (0.61, 1.4) | 0.66 |

| Table 3.2: Univariable models for time to BOS, time to BOS/death/re-tx, and time to death/re-tx. Post-transplant events were modelled as time-dependent risk factors. | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | Univariable risk factors for BOS | | Univariable risk factors for Death/Re-tx | | Univariable risk factors for BOS/Death/Re-tx | |
| **Risk factor** | **Level** | **N** | **Hazard ratio (95% CI)** | **P-value** | **Hazard ratio (95% CI)** | **P-value** | **Hazard ratio** | **P-value (95% CI)** |
| Cyclosporine | | 383 | 2.6 (1.2, 5.6) | 0.011 | 1.09 (0.61, 1.9) | 0.78 | 1.6 (0.99, 2.5) | 0.056 |
| Caucasian | | 382 | NA | 0.98 | 1.2 (0.49, 3.1) | 0.66 | 2.4 (0.99, 6.0) | 0.052 |
| PFI prior to event | | 383 | 1.3 (0.67, 2.6) | 0.42 | 2.4 (1.3, 4.3) | 0.005 | 1.7 (1.02, 2.7) | 0.041 |
| PTLD prior to event | | 383 | 1.5 (0.58, 3.7) | 0.42 | 1.7 (0.61, 4.9) | 0.31 | 1.4 (0.65, 3.1) | 0.38 |
| BOS prior to event | | 383 | NA | | 6.2 (3.0, 12.8) | <0.001 | NA | |
| RVI prior to event | | 383 | 1.2 (0.56, 2.7) | 0.60 | 3.0 (1.6, 5.6) | <0.001 | 2.1 (1.3, 3.5) | 0.005 |
| CMV syndrome/disease prior to event | | 383 | 1.3 (0.70, 2.5) | 0.38 | 2.5 (1.3, 4.8) | 0.004 | 1.7 (1.05, 2.8) | 0.030 |

**BOS**, bronchiolitis obliterans syndrome; **CMV**, cytomegalovirus, **PFI**, pulmonary fungal infection; **PTLD**, post-transplant lympho-proliferative disease; **RVI**, respiratory viral infection; **Re-tx**, re-transplantation

**Table 4**

Multivariable survival models for time to BOS and time to death with acute rejection episodes as time-dependent risk factors

| | BOS: 383 subjects, 58 events | | Death/Re-tx: 383 subjects, 51 events | | BOS/Death/Re-tx: 383 subjects, 106 events | |
|---|---|---|---|---|---|---|
| **Risk factor vs. no rejection** | **Hazard ratio (95% CI)** | **P-value** | **Hazard ratio (95% CI)** | **P-value** | **Hazard ratio (95% CI)** | **P-value** |
| Risk following first A1 | 1.7 (0.64, 4.8) | 0.28 | 0.82 (0.36, 1.9) | 0.65 | 1.10 (0.57, 2.1) | 0.78 |
| Risk following first A2 | 2.4 (1.1, 5.1) | 0.022 | 0.49 (0.21, 1.2) | 0.11 | 1.09 (0.62, 1.9) | 0.76 |
| Risk following second A1 | 1.1 (0.25, 5.2) | 0.86 | 1.10 (0.32, 3.7) | 0.88 | 1.1 (0.43, 2.9) | 0.80 |
| Risk following second A2 | 4.1 (1.9, 9.0) | <0.001 | 0.74 (0.30, 1.9) | 0.52 | 1.8 (1.01, 3.2) | 0.046 |
| Risk following second rejection, mixed rejection types | 4.4 (2.2, 9.1) | <0.001 | 2.0 (1.00, 4.1) | 0.048 | 2.7 (1.6, 4.6) | <0.001 |

**BOS**, bronchiolitis obliterans syndrome; **Re-tx**, re-transplantation