

**Survival after Bronchiolitis Obliterans Syndrome among Bilateral Lung Transplant  
Recipients**

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**Online Supplement**

### *Supplemental Materials*

*Detailed Description of Cox Models:* Cox proportional hazards models permit analysis of time-independent and time-dependent predictors in subjects with variable follow-up assigned either a failure time or censor date if the event of interest has not occurred by the last known follow-up. Time-independent covariates are fixed at the start of follow-up (e.g. demographic characteristics). In contrast, time-dependent covariates status changes over follow-up (e.g. development of post transplant CMV infection). Time-dependent variables require special treatment in an extended Cox model. Time-dependent variables are created within the “PROC PHREG” SAS programming code such the variable’s status is recalculated at every follow-up interval and permitted to change over time as an event occurs (1).

*Effect of timing of BOS on survival after BOS:* To further understand the relationship between timing of BOS onset and survival after BOS, we considered time to the onset of BOS, as a continuous predictor in years, rather than a dichotomous variable. In this analysis, each year of earlier onset BOS was associated with a significantly increased hazard for death after the onset of BOS (p= 0.0014, HR 1.43, 95 % CI 1.15-1.66), consistent with the results obtained when time to BOS onset was dichotomized at two years after transplant.

*Relationship of Early Onset, High Grade Onset BOS, and Post BOS Treatments:* Distribution of treatments between the early and late onset groups or the high grade onset BOS and grade 1 onset BOS groups was similar (Table E2). Further, the effects of early onset BOS or high grade onset BOS persisted when adjusted for post-BOS treatments in multivariable models (Table E3).

Table E1

Early and Late or High Grade and Grade 1 BOS onset groups underwent a similar number of pulmonary function tests after lung transplantation.

<b>Pulmonary Function Tests/Year</b>	<b>Early Onset</b>	<b>Late Onset</b>	<b>P-value<sup>†</sup></b>	<b>High Grade</b>	<b>Grade 1</b>	<b>P-value<sup>†</sup></b>
Post-Transplant Year 1 <sup>*</sup>	12 (10-16)	12 (11-14)	0.83	12 (10-15)	12(11-14)	0.76
Post-Transplant Years 2 and 3 <sup>*</sup>	9 (7-12)	9 (8-12)	0.47	9 (8-12)	9 (7-12)	0.53
Post-Transplant Years 4 and 5 <sup>*</sup>	7 (4-9)	8 (6-11)	0.14	7 (3-10)	8 (6-11)	0.19

\* Median number of PFTS (IQR)

† Wilcoxon Rank Sum Test

Table E2

Comparable Incidence of Post BOS Treatments among Early versus Late Onset BOS or High Grade Onset versus Grade 1 Onset BOS

<b>RISK GROUP</b>	<b>TREATMENTS AFTER BOS</b>							
	Nissen <sup>*</sup>	P <sup>†</sup>	Alemtuzumab	P <sup>†</sup>	Anti-Thymocyte Globulin	P <sup>‡</sup>	Azithroymcin	P <sup>‡</sup>
Early Onset BOS	16% (5)	0.30	9% (3)	0.75	28% (9)	0.21	60% (28)	0.50
Late Onset BOS	8% (5)		14% (9)		41% (26)		53% (27)	
High Grade Onset BOS	8% (2)	1.00	14% (10)	0.51	36% (9)	0.92	48% (12)	0.24
Grade 1 Onset BOS	11% (8)		8% (2)		37% (27)		61% (43)	

\* % (N)

† Fisher's Exact Test

‡ Chi-Square

Table E3

Impact of Early Onset BOS or High Grade Onset BOS on Mortality after BOS Adjusted for Post BOS Treatments

RISK GROUP	TREATMENTS AFTER BOS											
	NISSEN			ALEMTUZUMAB			ANTI-THYMOCYTE GLOBULIN			AZITHROMYCIN		
	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P
Early Onset BOS	1.80	1.00-3.23	0.05	2.04	1.11-3.74	0.02	2.03	1.12-3.70	0.02	1.98	1.10-3.57	0.02
High Grade Onset BOS	2.40	1.33-4.31	0.004	2.58	1.41-4.73	0.002	2.38	1.32-4.28	0.004	2.30	1.27-0.17	0.006

Table E4

Acute rejection incidence and adjusted cumulative acute rejection score, measured prior to BOS, does not differ between the Early and Late or High Grade and Grade 1 BOS onset groups.

Acute Rejection Prior to BOS	Early Onset	Late Onset	P	High Grade	Grade 1	P
Any Acute Rejection	63% (20/32)	78% (49/63)	0.11*	68% (17/25)	74% (52/70)	0.55*
Acute Rejection Score <sup>†</sup>	0.27 (0-0.78)	0.31 (0.08-0.50)	0.96 <sup>‡</sup>	0.27 (0-0.80)	0.31 (0-0.50)	0.53 <sup>‡</sup>

\* Chi-Square

<sup>†</sup> Adjusted for the number of transbronchial biopsies (acute rejection score/# biopsies) , Median (IQR)<sup>‡</sup> Wilcoxon Rank Sum Test

References:

- E1. Allison P, 1995. *Survival Analysis Using SAS: A Practical Guide*: Cary, SAS Institute Inc.