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FEATURED ARTICLES

Time-dependent changes in the risk of death in pure bronchiolitis obliterans syndrome (BOS)

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KEYWORDS:
chronic lung allograft dysfunction;
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survival

BACKGROUND: The timing of disease onset may affect the prognosis in chronic lung allograft dysfunction (CLAD). The relationship between the timing of disease onset and the prognosis of CLAD and its sub-types, bronchiolitis obliterans syndrome (BOS) and restrictive allograft syndrome (RAS), was examined.

METHODS: Clinical records and pulmonary function data of 597 patients who underwent bilateral lung transplantation from 1996 to 2010 and survived for >3 months were examined.

RESULTS: Among 155 patients with a final diagnosis of BOS, patient survival *after disease onset* was significantly different according to disease-onset timing (BOS onset/post-BOS median survival: overall/1,438 days; <1 year/511 days; 1–2 years/1,199 days; 2–3 years/1,403 days; >3 years/did not reach median survival; $p < 0.0001$). The prognosis of RAS was generally poorer than that of BOS (overall post-RAS median survival, 377 days). Treating non-CLAD, CLAD, BOS, and RAS as time-dependent covariates, recipient sex-adjusted and age-adjusted Cox regression analysis demonstrated an overall mortality risk of BOS (reference: no CLAD) of 6.7 (95% confidence interval, 4.6–9.9). However, when patients survived 3 years without CLAD, the mortality risk of subsequent BOS was only 1.9 (95% confidence interval, 0.8–4.4) compared with no CLAD. The number of RAS patients was too small to obtain sufficient power to estimate time-dependent mortality risk.

CONCLUSION: Late-onset BOS showed a better prognosis than early-onset BOS. Studies that do not distinguish BOS from RAS may overestimate the mortality risk of BOS. Multicenter studies will be required to further elucidate risk factors toward the development of better management strategies for CLAD.

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Bronchiolitis obliterans syndrome (BOS) is the conventional form of chronic lung allograft dysfunction (CLAD) characterized by obstructive physiologic changes.[1] BOS is considered to be a major obstacle to long-term success of lung transplantation. It reportedly affects almost 50% lung transplant recipients within 5 years after transplant, causing significant morbidity and mortality.[2] In particular, BOS that manifests early after transplantation reportedly shows a poorer prognosis than late-onset BOS.[3–6]

Increasing evidence, however, suggests that CLAD is a heterogeneous condition and that BOS is not the only form of CLAD.[7–9] We recently identified patients with CLAD who showed restrictive physiology and peripheral lung

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fibrosis and named the condition "restrictive allograft syndrome" (RAS).[10] RAS is the pathophysiologic presentation of as many as 30% of CLAD cases.[10,11] Moreover, the prognosis of RAS is much poorer than that of BOS.[10,11] Because of this significant prevalence of RAS and its markedly negative effect on survival, results of previously reported studies on BOS may have been significantly biased with the inclusion of unidentified RAS cases.[10]

The purpose of the present study was to analyze the relationship between timing of disease onset and prognosis using the newly defined CLAD, BOS, and RAS definitions. Using a Cox regression model that considers CLAD, BOS, and RAS as time-dependent covariates, we demonstrate that the effect of late-onset BOS ($\geq$3 years) on prognosis is significantly better than that of early-onset BOS.

Materials and methods

This study was approved by the University Health Network Research Ethics Board.

Patients

Of 724 patients who underwent bilateral lung or heart-lung transplantation from January 1996 to March 2010 in the Toronto Lung Transplant Program, 127 died within 3 months after transplant or had insufficient pulmonary function test (PFT) results with which to diagnose CLAD. Clinical records of the remaining 597 patients were systematically reviewed.

Pulmonary function tests

In our protocol, monthly spirometry was recommended for post-transplant patients for at least the first 2 years, with testing every 1 to 3 months thereafter. Total lung capacity (TLC) was measured using plethysmography at least every 3 months during the first year, every 6 months during the second year, and annually thereafter. Most recent patients after 2004 have been receiving TLC assessments in the same schedule as forced expiratory volume in 1 second (FEV_1). The baseline FEV_1 was calculated as the average of the 2 best FEV_1 values at least 3 weeks apart. Baseline TLC and FEV_1/forced vital capacity (FVC) values were defined as the average of the 2 measurements obtained at the same time as the 2 best FEV_1 measurements. If TLC was not measured at the same time as the baseline FEV_1 measurement, we accepted the value of TLC measured when FEV_1 was stable within the same range as the baseline FEV_1 (difference from the baseline FEV_1 was $<$0.2 liters). We monitored the patients until their last visit before March 31, 2011.

Definition of CLAD, BOS, RAS, and CLAD-unclassified

CLAD was defined as an irreversible decline in FEV_1 to $<$80% of baseline. *RAS* was defined as CLAD with an irreversible decline in TLC to $<$90% of baseline, as previously described.[10] *BOS* was defined as CLAD without restrictive changes of RAS. *CLAD-unclassified* was defined as CLAD without a diagnosis of BOS or RAS because of a lack of sufficient TLC measurements with which to distinguish these two conditions. The first date on which a decline in PFTs that met the criterion of each condition occurred was recorded as the onset date. Allograft survival was defined as patient death or retransplantation.

Statistical analyses

Baseline characteristics were summarized using proportions and mean $\pm$ standard deviation, as appropriate. To estimate the post–disease-onset survival difference by disease-onset timing of CLAD, BOS, and RAS, we first used a log-rank test based on the final diagnosis. We then conducted a multivariate Cox regression analysis in which the number of person-years at risk was counted for each patient from the date of diagnosis of CLAD, BOS, or RAS until the date of death or censoring. Patients with CLAD, BOS, or RAS diagnosed within 1 year after transplantation were defined as references. The *p*-values for the linear trend test were calculated by setting the disease-onset timing category as an ordinal variable.

Because the diagnosis of non-CLAD, CLAD, BOS, RAS, and CLAD-unclassified may change over time in a single patient, we also treated these conditions as time-dependent covariates and examined crude incidence rates and causes of death for different observation periods. The association among non-CLAD, CLAD, BOS, and RAS and mortality was also assessed using time-dependent Cox regression analysis.[12,13] The number of person-years of follow-up for each patient was counted from 3 months after transplantation until the date of diagnosis of CLAD for patients without CLAD, the date of death or retransplantation, or the time at which FEV_1 measurement became impossible because of lung resection or the end of follow-up, whichever occurred first. We used separate models to estimate the relative risk (RR) for CLAD and the RRs for BOS and RAS. To estimate the RRs for BOS and RAS, patients who were diagnosed as CLAD-unclassified and who did not undergo further FEV_1 measurements were censored at the time of diagnosis of CLAD-unclassified. We repeated the analyses after excluding all patients who were diagnosed with CLAD, BOS, or RAS or who died within the first year, within the first 2 years, or within the first 3 years after transplantation.

Multivariate models were adjusted for the following variables: donor and recipient age at transplantation, recipient primary disease (cystic fibrosis, chronic obstructive pulmonary disease, idiopathic pulmonary fibrosis, α_1-antitrypsin deficiency, pulmonary artery hypertension, bronchiectasis, and others), transplant type (heart-lung transplant, bilateral lung transplant), transplant year (1996–2000, 2001–2005, and 2006–2010), sex-matching, and cytomegalovirus-matching. In the analysis of BOS grades and timing of BOS onset, we statistically evaluated effect modification with the use of a cross-product term. All reported *p*-values were two-tailed, and differences at $p<0.05$ were considered statistically significant. Statistical analyses were performed using SAS 9.2 software (SAS Institute Inc, Cary, NC).

Results

Effect of disease-onset timing on patient survival after onset of CLAD, BOS, and RAS

Among 597 lung transplant recipients, 256 patients developed CLAD by the end of the observation period. Among the patients who developed CLAD, 155 were diagnosed with BOS and 48 were diagnosed with RAS. The remaining 53 patients were not classified into BOS or RAS (CLAD-unclassified) because of a lack of baseline TLC data ($n = 36$) or a lack of sufficient PFT data toward the end of