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Title
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Permalink
https://escholarship.org/uc/item/98h8k69f

Journal
Transplantation, 100(11)

ISSN
0041-1337

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Publication Date
2016-11-01

DOI
10.1097/tp.0000000000001346

Peer reviewed

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Author manuscript

Transplantation. Author manuscript; available in PMC 2017 November 01.

Published in final edited form as:

Transplantation. 2016 November ; 100(11): 2424–2431. doi:10.1097/TP.0000000000001346.

GRAFT LOSS AND CLAD ONSET IS HASTENED BY VIRAL PNEUMONIA AFTER LUNG TRANSPLANTATION

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Abstract

Background—Community acquired respiratory virus (CARV) infections occur frequently after lung transplantation and may adversely impact outcomes. We hypothesized that while asymptomatic carriage would not increase the risk of chronic lung allograft dysfunction (CLAD) and graft loss, severe infection would.

Methods—All lung transplant cases between January 2000 and July 2013 performed at our center were reviewed for respiratory viral samples. Each isolation of virus was classified according to clinical level of severity: asymptomatic, symptomatic without pneumonia, and viral pneumonia. Multivariate Cox modeling was employed to assess the impact of CARV isolation on progression to CLAD and graft loss.

Results—4408 specimens were collected from 563 total patients with 139 patients producing 324 virus positive specimens in 245 episodes of CARV infection. Overall, the risk of CLAD was elevated by viral infection (HR 1.64, $p < 0.01$). This risk, however, was due to viral pneumonia alone (HR 3.94, $p < 0.01$), without significant impact from symptomatic viral infection (HR 0.97, $p = 0.94$) nor from asymptomatic viral infection (HR 0.99, $p = 0.98$). The risk of graft loss was not

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Disclosures:

The authors declare no conflicts of interest.

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increased by asymptomatic CARV infection (HR 0.74, p = 0.37) nor symptomatic CARV infection (HR 1.39, p = 0.41). Viral pneumonia did, however, significantly increase the risk of graft loss (HR 2.78, p < 0.01).

Conclusions—With respect to CARV, only viral pneumonia increased the risk of both CLAD and graft loss after lung transplantation. In the absence of pneumonia, respiratory viruses had no impact on measured outcomes.

Introduction

Chronic lung allograft dysfunction (CLAD), most commonly bronchiolitis obliterans syndrome (BOS), remains the leading cause of morbidity and mortality after lung transplantation.[1,2] A diverse group of both infectious and noninfectious posttransplant events are associated with an increased risk of subsequent CLAD.[3–10] Bacterial and viral infections, however, make up the bulk of identifiable posttransplant insults.[5,11–13]

The introduction of respiratory virus multiplex polymerase chain reaction (PCR) has increased the detection and awareness of the community acquired respiratory viruses (CARV). Yet, the impact of CARV infection on lung allograft function and survival after lung transplantation is not well defined. Prior studies of CARV infections after lung transplantation have come to varying conclusions with respect to CARV impact on CLAD and graft survival.[14–17] Viral infections may indirectly influence the development of CLAD via the induction of acute allograft rejection, but recent evidence argues against such a mechanism.[18–21] Not all patients with CARV infections progress to CLAD, and clinical predictors of progression are lacking.

Since CARV infections range from asymptomatic viral carriage to fulminant respiratory failure, we hypothesized that allograft outcomes are influenced by infection severity. Specifically, we hypothesized that CARV pneumonia would have a greater impact on the development of CLAD and graft loss than would asymptomatic CARV carriage. The widespread adoption of high-sensitivity PCR testing increasingly identifies the presence of virus in asymptomatic individuals.

A more precise understanding of the impact of individual viruses and virus severity on allograft outcomes will help inform clinical decisions to improve outcomes, reduce cost, and avoid unnecessary treatment.

Materials and Methods

Objectives

The primary objective of the study was to assess the impact of CARV infections on the outcomes graft loss and CLAD onset. Graft loss was defined as patient death or retransplantation. CLAD was defined according to ISHLT guidelines.[2,22,23] A secondary objective was to evaluate the impact of individual viruses on the same 2 outcomes of graft loss and CLAD. With approval from the UCLA Institutional Review Board, all patients who underwent lung transplantation at the University of California, Los Angeles (UCLA) between January 2000 and July 2013 were included in the study.

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Samples and Posttransplant Care

Patients were prospectively enrolled in an observational cohort to study outcomes after lung transplant. Recipients underwent routine bronchoscopy with bronchoalveolar lavage (BAL) at 1 day, 1 week, 1, 3, 6, and 12 months posttransplant. Additional BAL, sputum or nasopharyngeal samples were obtained at the provider's discretion. Swabs of the donor bronchus were sent for bacterial and viral organisms at the time of transplant, but were excluded from analysis. Standard care of lung transplant patients including prophylaxis, immunosuppression, lung function measurement, and acute cellular rejection (ACR) treatment are described elsewhere. ACR was diagnosed according to standard ISHLT criteria.[23]

Identification of CLAD

CLAD was identified through the following process. First, any patient with less than 6 pulmonary function tests (PFTs) was excluded, as were retransplants (for any patient with 2 transplant dates, data collected after the second transplant was excluded). Infection, pleural effusion and other causes of an FEV_1 decline were excluded by review of the medical record as per ISHLT criteria[1]. For each included patient, the following was required: 1) Baseline FEV_1 measurements (2 best values) and the dates of these measures; 2) FVC measurements at the time of the baseline FEV1 measures; and 3) CLAD yes or no. CLAD was defined as a sustained/irreversible decline in FEV_1 to <80% of the baseline, using the average of the 2 baseline measures. A sustained decline was present on at least 2 consecutive PFTs and never improved to >80% of baseline during follow-up. Next, if CLAD was present, the FEV_1 and FVC measurements at the time of CLAD onset were found. The CLAD phenotype at onset was then determined using the following formula:

$$\frac{FVC\ at\ CLAD - FVC\ baseline}{FVC\ baseline} / \frac{FEV_1\ at\ CLAD - FEV_1\ baseline}{FEV_1\ baseline}$$

If the value was <0.5, then the phenotype was BOS. If >0.5, then the phenotype was RAS. The CLAD phenotype at the time of the last PFT measurement was also determined using the above formula.

Identification of Virus

All specimens positive for virus in postlung transplant patients were identified via the UCLA Clinical Microbiology Laboratory database. Viral infection was defined as a positive viral test from BAL, expectorated sputum, tracheal suction, or nasopharyngeal wash. Isolations were considered distinct "episodes" when the same virus was isolated within 30 days and there was no change in the associated clinical severity grade (see below). Episodes of Pseudomonas and Aspergillus were similarly defined, but without regard to clinical severity. Viral detection was performed at the UCLA Clinical Microbiology Laboratory. From January 2000 until October 2009, viral identification was culture based and identified respiratory syncytial viruses A and B, influenza, parainfluenza types 1–4, enterovirus, rhinovirus, and adenovirus. Samples were set-up in the shell vial R-Mix Too system and cultured in AGMK (kidney), A549 (aveolar epithelial), and MRC-5 (fibroblast) cells.

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Cultures were held for 2 weeks. In October 2009, a respiratory virus multiplex PCR panel (Resplex II RUO, Qiagen) was introduced that was capable of detecting 18 different viruses (respiratory syncytial viruses A and B, influenza viruses A and B, parainfluenza viruses types 1–4, human metapneumovirus, Coxsackie, echovirus, rhinovirus, adenovirus serogroups B and E, bocavirus, and coronaviruses NL63, HKU1, 229E and OC43). The PCR multiplex panel could not reliably distinguish between rhinovirus and the enteroviruses, thus both culture and PCR results for these viruses were combined in the analysis under "Rhinovirus/Enterovirus". An exception was made for the category called Coxsackie/Echovirus, which was a result unique to the Resplex II RUO (ie, it contained no culture derived results). While our microbiology laboratory quality control data (not shown) found that a majority of the viruses in this Coxsackie/Echovirus group were rhinovirus, our outcome analysis found that this group behaved differently than the rhinovirus/enterovirus group, and thus it was maintained as a separate viral category for outcomes analysis. Cytomegalovirus and herpes simplex virus infections were excluded from our analyses because of our focus on community acquired respiratory viruses.

Clinical Severity Stratification

CARV infections were stratified based on 3 levels of clinical severity: asymptomatic viral infection, symptomatic viral infection, and viral pneumonia. Qualifying symptoms for symptomatic infection included new or worsening shortness of breath or hypoxemia, new or worsening cough, and or fever. Viral pneumonia was defined clinically as symptomatic viral infection plus a radiographic infiltrate without a clear alternative explanation. Therefore, the difference between symptomatic viral infection and viral pneumonia was a radiographic infiltrate. Asymptomatic episodes did not meet criteria for either symptomatic viral infection or viral pneumonia. Severity levels were determined by consensus of the study team (PRA, PI, and ALG) based on a comprehensive chart review of each viral episode. Discrepancies (11 isolations) and difficult cases (72 isolations), together totaling 84 isolations, were independently reviewed by ALG.

Statistical Approaches

Patients' demographic and clinical characteristics were described as frequency (%) for categorical variables and mean and standard deviation (SD) for continuous variables, with the addition of median and interquartile range (IQR) for time observed. Incidence of infections was computed by isolate and severity level, as well as by month of year. Multivariate Cox proportional hazard models were developed with the covariates being: age at transplantation, type of transplant (single or double), pr-transplant diagnosis, transplant era (2-year time intervals starting in 2000), time-dependent *Pseudomonas aeruginosa* respiratory isolation (including both colonizations and infections), time-dependent Aspergillus species respiratory isolations (including both small and large conidia), time-dependent cumulative acute rejection score, and time-dependent CLAD for the graft loss outcome. Aspergillus and Pseudomonas are common isolates previously identified as significant risk factors in subsets of this cohort, and were therefore included in the model to minimize confounding.[8,9] For time-dependent Aspergillus, Pseudomonas, and CLAD, each patient is considered to be unexposed to the infection or condition at the time of transplant and is then, upon first infection or diagnosis of CLAD, considered to be exposed for the

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remainder of the observation period. Variables significant at the $p < 0.10$ level in univariate analyses were included in multivariate analyses (CMV did not reach criteria for inclusion). The associations between viral infection and the outcomes CLAD and graft loss were assessed using 2 time-dependent approaches to measuring infection: 1) Patients are considered unexposed to viral infection at transplant and then considered to have viral exposure after experiencing any viral infection, and 2) patients are considered unexposed to viral infection at transplant and then categorized as having exposure to asymptomatic viral infection, symptomatic viral infection, or viral pneumonia as they experience episodes of viral infection ranging in severity level. In the time-dependent construction of viral infection severity, a patient retained the highest severity level experienced to date. Univariate Cox proportional hazard models were used to assess the association between time-dependent exposure to the virus's adenovirus, coronavirus, coxsackie/echovirus, influenza A or B, metapneumovirus, parainfluenza, rhinovirus/enterovirus, and RSV and the outcomes CLAD and graft loss. A repeated measure, mixed effects model incorporating all tacrolimus values was used to account for intra-subject correlation among observations. Hazard ratios (HR) are reported with their corresponding confidence intervals (CI) in brackets. Tests for significance were 2-tailed with a statistically significant p-value threshold of <0.05 and analyses were conducted using SAS (SAS Institute Inc., Cary, NC, USA, v9.3).

Results

Cohort Characteristics and Isolate Epidemiology

No statistically significant differences in baseline characteristics were found between those with and without viral infection (Table 1). CLAD developed in 37.4% (210) of all patients after a mean of 2.7 (SD 2.0) years and 46% (249) of patients experienced graft loss at a mean of 3.8 (SD 2.9) years. Of the total cohort, 97 patients (17.2%) could not be assessed for CLAD, primarily because of an insufficient number of pulmonary function tests required to make the diagnosis, and were excluded from outcome analysis for CLAD. Overall transplant outcomes, contrasted between those with and without viral infections, are shown in Table 2.

A total of 4262 specimens were collected from 563 patients, 139 patients of whom had viral infections during our study period. There were 282 specimens positive for virus and 254 separate episodes of viral infection at a mean of 1.7 (SD 2.0) years after transplant. There were 74 (29.1%) asymptomatic infections, 107 (42.1%) symptomatic infections, and 73 (28.7%) episodes of clinical pneumonia. Of the 282 positive specimens, 136 were BAL samples, 75 sputum, 65 nasal washing, and 6 tracheal aspirations. Only 26 specimens were positive for more than 1 virus simultaneously. Forty-one patients had more than 1 viral episode.

Of these 254 viral infection episodes, Coxsackie/echovirus group (which included some rhinoviruses) accounted for the greatest number with 55, followed by 49 rhinovirus/enterovirus, 42 parainfluenza, 36 coronavirus, 24 RSV, 20 human metapneumovirus, 13 influenza A, 9 adenovirus, 3 influenza B, and 3 bocavirus. Distribution of infections by virus and clinical severity level is shown in Figure 1. Viral infection occurred more often in

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January (9.9%), February (15.3%), and March (17.0%), while July (5.0%), August (2.8%) and September (5.0%) had the fewest infections (Figure 2).

In our cohort, there were only fourteen pulmonary bacterial isolations identified within the thirty days following a viral infection, precluding further analysis of this condition as a unique covariate. There were 342 episodes of pulmonary *Pseudomonas aeruginosa* in 185 patients and 368 episodes of respiratory Aspergillus in 194 patients.

Effect on CLAD and Graft Loss

The risk of CLAD was elevated by CARV infection when all clinical severities were analyzed as a group (HR 1.64 [1.17, 2.28], $p < 0.01$). However, when stratified by infection severity, clinical pneumonia (HR 3.94 [1.97, 7.90], $p < 0.01$) drove this relationship, without contribution from symptomatic (HR 0.97 [0.46, 2.08], $p=0.94$) nor from asymptomatic viral infection (HR 0.99 [0.54, 1.80], $p = 0.98$) (Figure 3). As has been previously shown, both Pseudomonas (HR 1.53 [1.13, 2.07], $p=0.01$) and cumulative AR score (HR 1.17 [1.10, 1.25], $p<0.01$) were associated with an elevated risk of subsequent CLAD. We did not find that any particular CLAD phenotype was more commonly associated with viral pneumonia.

CARV did not impact graft loss (HR 1.34 [0.98, 1.83], $p = 0.07$) when analyzed without regard for clinical severity. However, when consideration of clinical severity was included in the analysis, viral pneumonia alone was associated with increased risk (HR 2.78 [1.55, 5.00], $p < 0.01$) (Figure 4). Asymptomatic viral infection (HR 0.74 [0.39, 1.43], $p = 0.37$) and symptomatic viral infection (HR 1.39 [0.63, 3.04], $p = 0.41$) did not reach statistical significance for graft loss. Aspergillus (HR 1.37 [1.04, 1.79], $p=0.03$), Pseudomonas (HR 1.90 [1.44, 2.51], $p<0.01$), and CLAD (HR 5.06 [3.72, 6.88], $p<0.01$) also increased the risk of graft loss (Figure 4).

We also considered whether some individual viruses were more likely than others to increase the risk of CLAD or graft loss. Indeed, adenovirus (HR 13.42 [2.81, 64.59], $p < 0.01$), parainfluenza (HR 2.18 [1.34, 3.56], $p < 0.01$) and Coxsackie/echovirus (HR 2.60 [1.29, 5.29], $p = 0.01$) increased the risk of CLAD. Adenovirus alone increased the risk of graft loss (HR 17.16 [6.42, 45.60], $p < 0.01$).

The respiratory virus PCR panel was introduced in October 2009 and greatly increased testing sensitivity for picornaviruses. Coronavirus and metapneumovirus were not identifiable by culture methods. Interestingly, this new testing modality did not influence the outcomes of CLAD or graft loss. There also was no effect on either CLAD or graft loss from the era of transplantation.

The level of immunosuppression at the time of CARV was assessed using tacrolimus trough blood levels as a proxy. We found that the median tacrolimus level of the overall cohort was lower (7.9 mcg/L) than it was at the time of viral infection. Median levels at the time of asymptomatic (10.4 mcg/L), symptomatic (8.6 mcg/L), and pneumonia (8.2 mcg/L) tended to decrease with increasing clinical severity, but this was not statistically significant ($p=0.13$).

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Discussion

Our data show that the severity of viral infection after lung transplantation is the critical factor in determining whether or not viral isolation has a significant effect upon the lung allograft. Lung transplant recipients with viral pneumonia (symptoms plus a positive radiograph) were more likely to progress to CLAD and graft loss, while symptomatic and asymptomatic viral infection had no demonstrable effect. We also found that adenovirus, parainfluenza and Coxsackie/echoviruses were independently associated with the subsequent development of CLAD, and in the case of adenovirus, graft loss as well. We did not find a tendency towards any particular CLAD phenotype.

Our findings are supported by a 2004 retrospective study by Khalifah, which showed an increased risk of BOS, death, and death after BOS following CARV infections.[14] Lower respiratory tract CARV infections, defined similarly to our symptomatic cohort, correlated with the greatest risk of BOS and death. The study was limited, however, by the 259 patients with only 21 total CARV infections, of whom only 15 had lower tract infections, 8 with positive radiographs (53%), and four of whom had developed BOS prior to CARV infection. Furthermore, the use of immunofluorescence and viral culture for detection of virus reduced the sensitivity and limited detection to RSV, parainfluenza, influenza, and adenovirus. This lower sensitivity may have biased the sample towards patients with a higher viral burden and more severe infection, a group we have shown herein to be at elevated risk of poor outcome.

In a prospective study of CARV, identified by multiplexed PCR of the BAL, 48 of 93 lung transplant recipients were found to have CARV infection.[24] FEV1 decline at 3 months was more frequent in those with CARV infection versus those without; the study did not assess for BOS as a primary outcome. There were no significant differences between symptomatic (14 persons) and asymptomatic patients (34 persons), but this is likely due to their very restrictive definition of a symptomatic patient (2 or more of cough, coryza, myalgias, sore throat, and fever on the day of BAL), which may have led to misclassification of patients, with the study missing most symptomatic patients using our definition herein. A more recent single-center study of 250 lung transplant recipients, only 50 of whom developed CLAD, also found that CARV was associated with subsequent CLAD.[17] In this most recent study, CARV identification relied upon techniques similar to ours, but cases of CARV were not stratified according to clinical severity.

The importance of the present study is in quantifying the risk of developing CLAD and graft loss based on severity of clinical presentation, which may help guide treatment decisions and patient counseling. In Kumar, et al 2005, only 8% of patients initially without lower respiratory tract symptoms progressed to lower respiratory tract disease, and all those progressing had either influenza A or parainfluenza viruses.[25] Our data argues against nonpneumonia CARV infections negatively impacting CLAD onset and graft survival. This is clinically important with the contemporary use of high-sensitivity nucleic acid amplification testing that detects viruses in lower and potentially clinically insignificant numbers. Although specific anti-viral medications are only available for a limited number of CARV, the decision to administer adjunctive therapy or inhaled ribavirin is complicated by

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issues of cost, physical isolation of patients, potential aggravation of respiratory symptoms, and concerns of teratogenicity among healthcare personnel.[26,27]

The finding that infections caused by adenovirus and parainfluenza virus were more likely to progress to CLAD is probably because these viruses were more often associated with viral pneumonia when encountered. We were not able to statistically demonstrate this for Coxsackie/echovirus group, but we suspect the association with CLAD is being driven by a subpopulation of the viruses detected with this PCR reaction, thereby diminishing our ability to see an association with viral pneumonia in this viral group. Prior studies have emphasized that at least for human rhinoviruses, lower respiratory tract disease is associated with a higher viral load.[28] It may be that the PCR-only group of viruses categorized as Coxsackie/echovirus, which contained a large number of HRV, represented HRV infections with higher viral loads and lower respiratory tract disease. RSV was not an independent risk for CLAD in our study, but has been independently associated with BOS in numerous pre-PCR era studies. We suspect this is due to an unavoidable bias in earlier studies that relied upon passive case detection, limiting CARV identification to sicker patients, and the use of less sensitive, non-PCR based methods in which the paramyxoviruses are more likely to be identified.

It appears that even mild disease from CARV can have a deleterious effect on lung function. A recent prospective study of 112 lung transplant recipients found a mean transitory loss of 106 mL of FEV1 compared with preinfection lung function testing.[21] Yet, the mechanism by which viral pneumonia increases the risk for CLAD and graft loss is not entirely understood and this study does not directly address this issue. Cases of viral pneumonia may evolve to acute lung injury and diffuse alveolar damage.[29,30] Diffuse alveolar damage does increase the subsequent risk of CLAD and death after lung transplantation, perhaps via the CXCR3 chemokine axis.[31] Weigt et al also demonstrated that increased CXCR3 ligand CXCL10 and CXCL11 concentrations in BAL during CARV infections predicted FEV1 decline at 6 months.[7] Although these studies suggest a potential mechanism for how CARV pneumonia leads to CLAD, further studies of the lung allograft inflammatory state during and after CARV are necessary to better elucidate the responsible pathways.

We further describe the largest cohort yet of Pseudomonas isolations after lung transplantation and find that any respiratory Pseudomonas isolation elevated the risk of CLAD and graft loss.[9] The importance of CLAD in determining graft loss is again noted, highlighting the need for novel, effective interventions to prevent or treat CLAD in order to improve survival after lung transplantation.

This study has the advantage of being the largest cohort published to date addressing the effect of community viral infections on CLAD onset and graft loss after lung transplantation. To our knowledge, with up to 13 years follow-up, this data is the longest observation period to monitor for adverse outcomes in the lung allograft with respect to CARV. The effects of viral isolation upon transplant outcomes are therefore not limited to events within the first year after transplant, but span the entire posttransplant follow-up period.

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Study limitations include the retrospective, single-center nature of this study with an inherent risk of bias that was minimized by using multivariate analysis. Multiplex PCR was not introduced in our laboratory until October 2009, over 9 years into our study time period, although this did not impact our assessment of outcomes. We hypothesize that the reason its introduction did not impact our model is that significant viral infections caused by influenza, parainfluenza, enterovirus, RSV, and adenovirus were already being identified adequately prior to the introduction of PCR testing. We suspect that our relatively low rates of influenza infection can be explained in part by high rates of influenza vaccination in our cohort and preemptive therapy with oseltamivir during peak season. Another limitation includes the difficulty in diagnosing viral pneumonia in immunocompromised patients who may have subtle imaging findings not easily seen on chest radiographs. Most patients in our study did not have CT scans at the time of CARV diagnosis. This may have resulted in underestimating the total number of patients with pneumonia. The irregular PFT follow-up times after CARV episodes in our cohort did not allow us to determine what is the greatest time period of risk for CLAD following CARV without introducing significant bias into our models. Furthermore, while we have positive data for each CARV episode, we have little negative data and cannot comment upon the duration of viral exposure. Bacterial coinfection during or shortly after CARV may contribute to graft loss and CLAD. However, we observed only 14 cases of this concurrent viral and bacterial infection state in our data set (defined as within 30 days of 1 another). Given this small sample size we were underpowered to detect our expected effect.

Our results lend credence to clinical assessment and argue that all positive tests are not the same. Attention and treatment should focus on those with evidence of symptomatic disease, rather than on those with incidentally positive specimens. Since outcomes depend on both infection severity and perhaps virus type, we propose that future studies evaluating the impact of CARV infections on lung allografts stratify by infection severity and virus type.

Acknowledgments

Funding:

NIH/NHLBI K23 HL102220 & Cystic Fibrosis Foundation Pilot and Feasibility Grant: Gregson

NIH/NHLBI R01 HL112990 & CTOT 11532596: Belperio

Joyce & Saul Brandman Foundation Fund: Weigt

NCATS/CTSI UL1 TR000124

We are grateful to the patients for their participation in this study and for the dedicated clinical care provided by their physicians. We are also grateful for the editorial input from Dr. Rosalinda Mendez and Xochitl Gonzalez, MFA.

Abbreviations

CARV	community acquired respiratory virus
BOS	bronchiolitis obliterans syndrome
CLAD	chronic lung allograft dysfunction

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HR	hazard ratio
AR	acute allograft rejection
PCR	polymerase chain reaction
UCLA	University of California, Los Angeles
BAL	bronchoalveolar lavage fluid
SD	standard deviation
IQR	interquartile range
FEV1	forced-expiratory volume 1 second
ISHLT	International Society for Heart and Lung Transplantation
ATG	antithymocyte globulin

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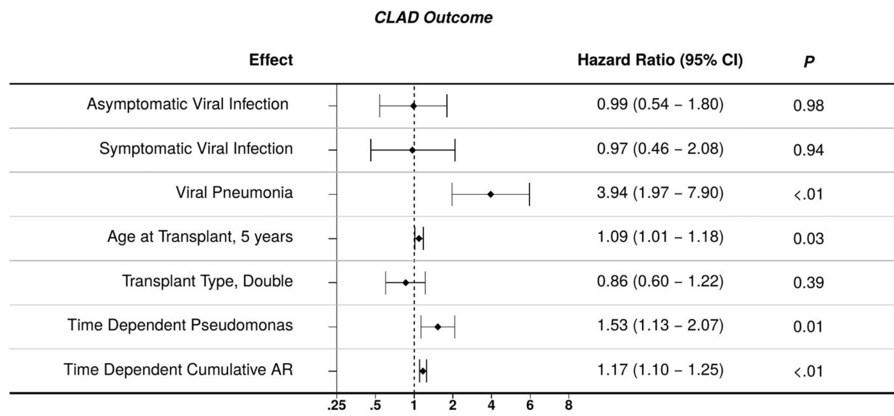

Figure 1.

Histogram showing number of CARV infections after lung transplant by virus type and severity of illness in patients transplanted between January 2000 and July 2013. Abbreviations: CARV, community acquired respiratory virus; RSV, respiratory syncytial virus.

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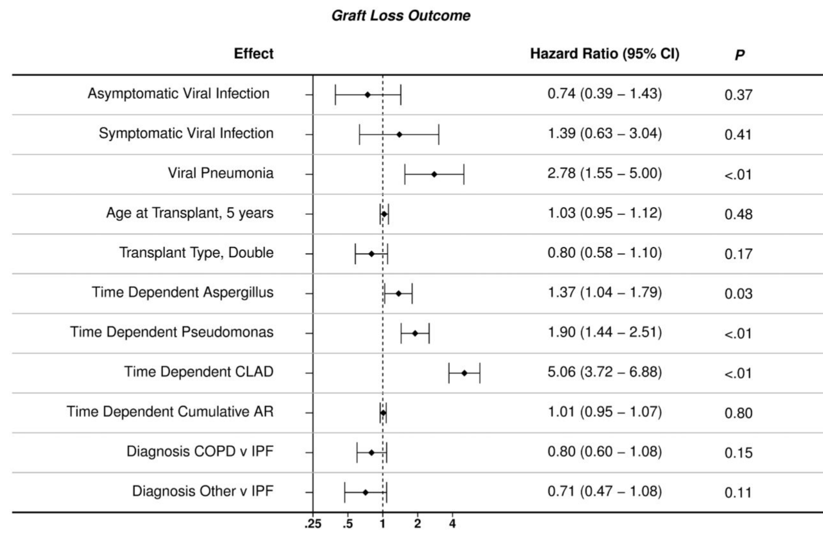

Figure 2.

Frequency of community acquired virus episodes by month and season in patients transplanted between January 2000 and July 2013. Larger dots represent greater number of episodes than smaller dots. The number of episodes is given above each dot in numbers whose size also correlates with the number of episodes.

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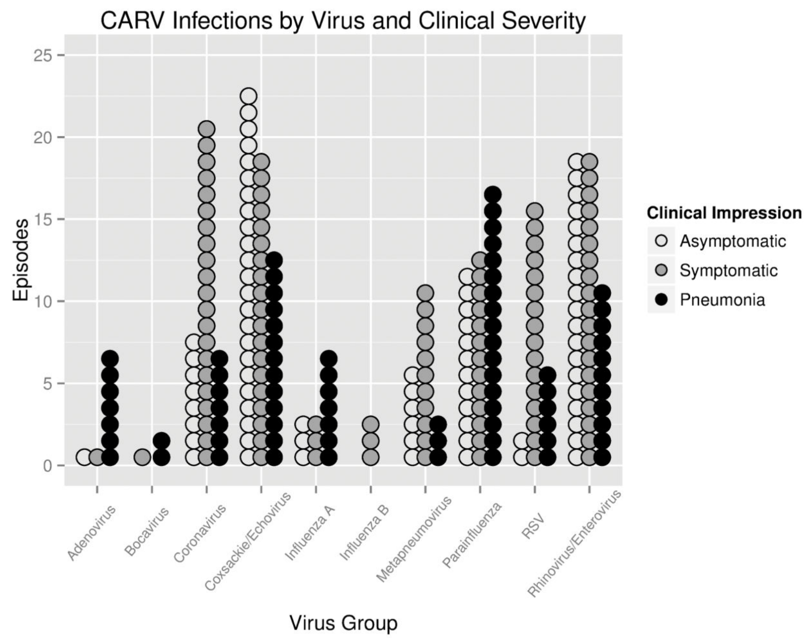

Figure 3.

Multivariate Cox proportional hazards model for CLAD onset with covariates significant at $p < 0.10$ in univariate analysis and time-dependent viral infection based on clinical severity. In this mutually exclusive model, patients retain the highest level of severity to date with the reference condition being negative for any viral infection. Abbreviations: AR, acute rejection; CI, confidence interval; CLAD, chronic lung allograft dysfunction; IPF, idiopathic pulmonary fibrosis.

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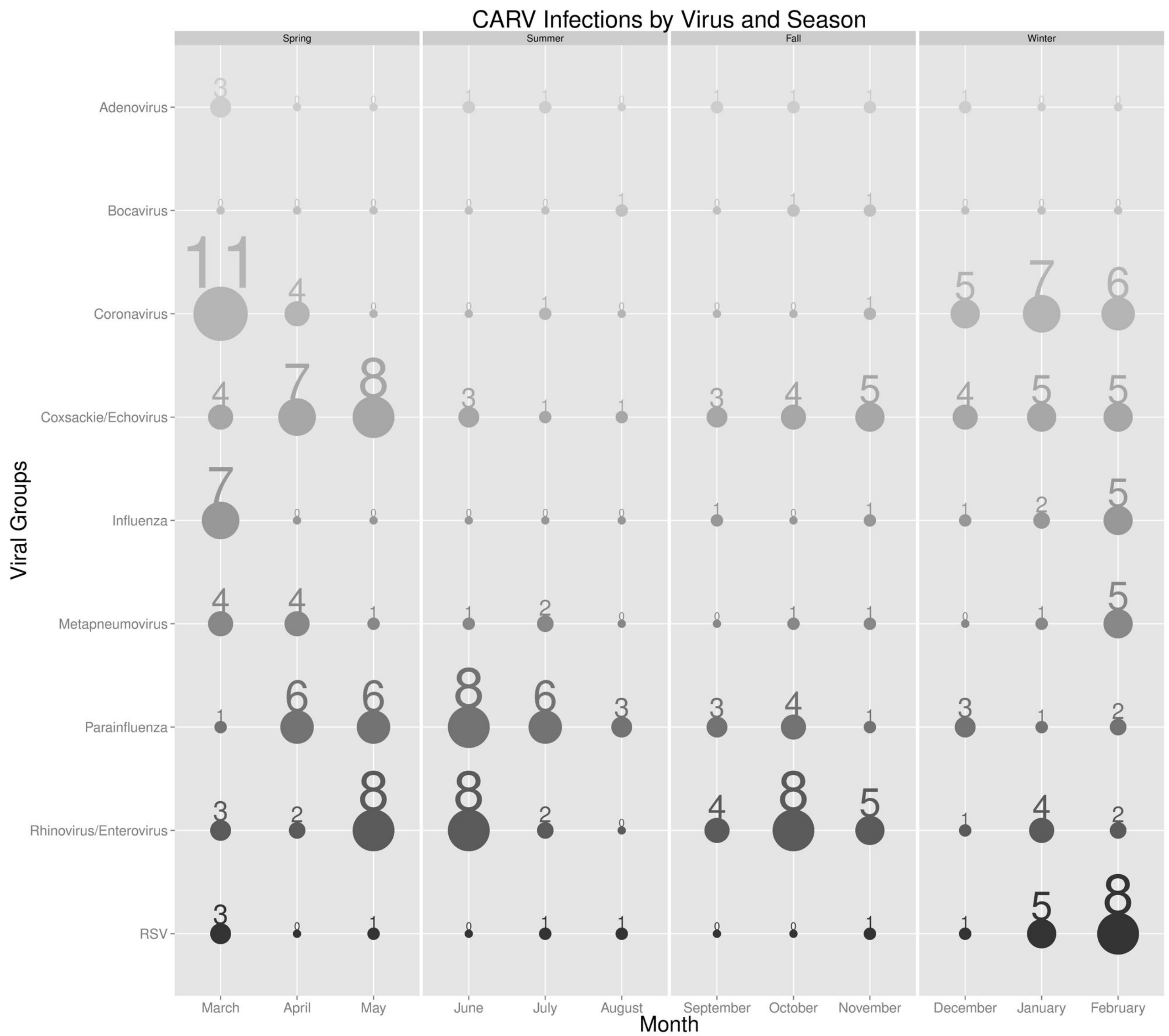

Figure 4.

Multivariate Cox proportional hazards model for graft loss with covariates significant at $p < 0.10$ in univariate analysis and time-dependent viral infection based on clinical severity. In this mutually exclusive model, patients retain the highest level of severity to date with the reference condition being negative for any viral infection. Abbreviations: AR, acute rejection; CI, confidence interval; CLAD, chronic lung allograft dysfunction; COPD, chronic obstructive pulmonary disease; IPF, idiopathic pulmonary fibrosis.

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Table 1

Baseline Characteristics

Variable	Patients without Viral Infection (n = 424)	Patients with Viral Infections (n = 139)	Severity Level 1 (n = 31)	Severity Level 2 (n = 54)	Severity Level 3 (n = 54)
Mean Age at Transplant (SD)	58.5 (10.5)	56.4 (11.7)	60 (7.5)	54.2 (12.8)	56.5 (12.1)
Sex					
Male	250 (59%)	79 (57%)	17	32	30
Female	174 (41%)	60 (43%)	14	22	24
Single Lung Transplants	203 (48%)	61 (44%)	15	26	25
Double Lung Transplants	221 (52%)	78 (56%)	16	28	29
Mean Lung Allocation Score (SD)	47.5 (14.6)	49 (16.7)	46.3 (14.9)	52.6 (18.2)	46.7 (15.8)
Mean Donor Ischemic Time (SD)	298 (78)	308 (81)	284 (81)	306 (83)	321 (77)
Transplant Diagnosis					
Pulmonary Fibrosis	231	83	19	32	32
Chronic Obstructive Pulmonary Disease	117	30	9	8	13
Other	76	26	3	14	9
Induction Type					
ATG	196	71	14	27	30
Basiliximab	222	67	16	27	24
Campath	0	1	1	0	0
None	5	0	0	0	0
Pulmonary Hypertension					
Present	11	6	0	5	1

Abbreviations: ATG, anti-thymocyte globulin; SD, standard deviation.

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Table 2

Transplant Outcomes

Variable	Patients without Viral Infection (n = 424)	Patients with Viral Infection (n = 139)	Severity Level 1 (n = 31)	Severity Level 2 (n = 54)	Severity Level 3 (n = 54)
Mean Observation Time in Years (SD)	3.8 (3.0)	3.8 (2.6)	3.7 (2.4)	4.3 (2.5)	3.3 (2.7)
Median Observation Time in Years (IQR)	3.0 (4.5)	3.2 (2.8)	2.9 (1.8)	3.6 (2.8)	2.7 (2.6)
Graft Loss	198	61	8	14	39
Mean Time to Graft Loss in Years (SD)	2.7 (2.3)	3.0 (2.4)	2.7 (2.3)	3.9 (2.5)	2.7 (2.5)
Patients with CLAD					
Yes	135	75	13	28	34
No	210	46	13	17	16
Unable to be Assessed	79	18	6	7	6
Mean Time to CLAD in Years (SD)	2.4 (2.0)	2.4 (1.6)	2.3 (1.5)	2.6 (1.6)	2.2 (1.7)
Mean Time to First CARV in Years (SD)	NA	1.7 (2.0)	0.9 (1.8)	2.0 (2.0)	1.8 (2.0)

Abbreviations: CARV, community acquired respiratory virus; CLAD, chronic lung allograft dysfunction; IQR, interquartile range; NA, not applicable; SD, standard deviation.