Characterization of Community Acquired Respiratory Virus (CARV) Infections, Treatment, and Outcomes in Lung Transplant Recipients

Mahsa Movahedan, PharmD; Robert C. Wright, PharmD; Roland G. Nador, MD; Robert. D. Levy, MD; Monica Norena, MSc; Joel Singer, PhD; Nilufar Partovi, PharmD.

Background

- CARV infections are common post-lung transplant likely as a result of anatomical, physiologic, and immunologic changes.
- CARV infections result in varying short and long-term complications:
  - Short term: asymptomatic infection ⇨ pneumonia, acute lung allograft dysfunction, acute rejection, hospitalization
  - Long term: chronic lung allograft dysfunction (CLAD), allograft failure
- CLAD is defined as a persistent decline of ≥20% in forced expiratory volume in one second (FEV_1), a persistent decline of ≥10% in total lung capacity (TLC), or both, compared with the post-transplant baseline.
- CLAD is the leading cause of mortality in patients surviving more than one year post transplant.
- Limited CARV treatment options available and no expert consensus. Local protocol includes:
  - High dose intravenous (IV) glucocorticoid (steroid pulse)
  - Oral glucocorticoid taper following steroid pulse in select patients (steroid taper)
  - IV immunoglobulin (IVIG)
  - Antivirals (e.g. oseltamivir for influenza, ribavirin for respiratory syncytial virus)

Objectives

- Describe the incidence, etiology, and treatment of community acquired respiratory virus (CARV) infections in post-lung transplant patients
- Identify adverse drug events associated with glucocorticoids in treatment of CARV infections
- Determine the relationship between initial CARV infection and chronic lung allograft dysfunction (CLAD) development at 3 years follow up

Methods

Design
- Single-center retrospective chart review

Population
- Adult lung transplant recipients transplanted at VGH

Data Source
- Paper charts, provincial transplant database, and electronic medical records

Analysis
- Descriptive analysis used to identify meaningful trends
- Kaplan-Meier curves used to determine the association of CARV infections with CLAD
- Univariate Cox modeling used to evaluate CARV as a time-dependant variable and a risk factor for CLAD development
  - A second similar modeling performed with CARV stratified according to infection severity: no CARV, mild infection, and lower respiratory tract infection.

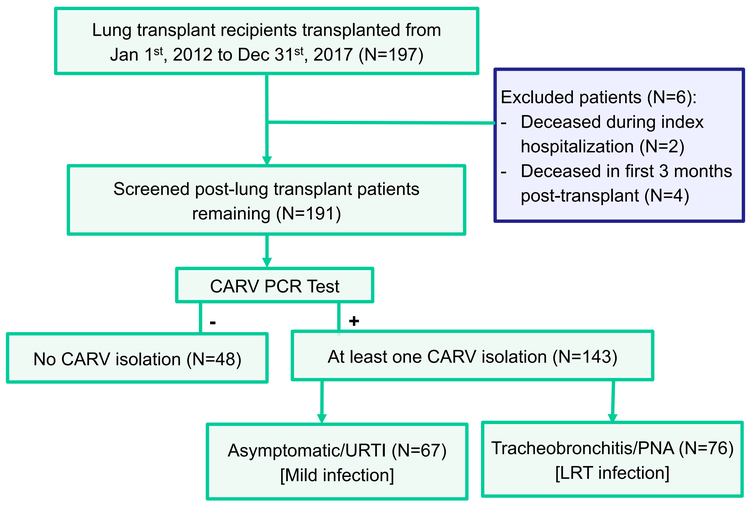


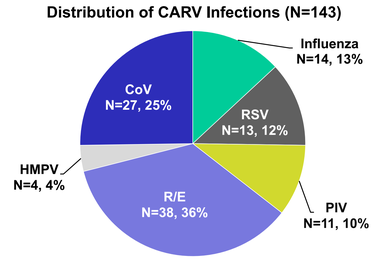
Figure 1: Overview of patient screening and selection, and a breakdown of incidence of first CARV isolation in VGH's post lung-transplant population. URTI=Upper Respiratory Tract Infection, PNA=Pneumonia, LRT=Lower Respiratory Tract

Results

Table 1: Baseline Characteristics

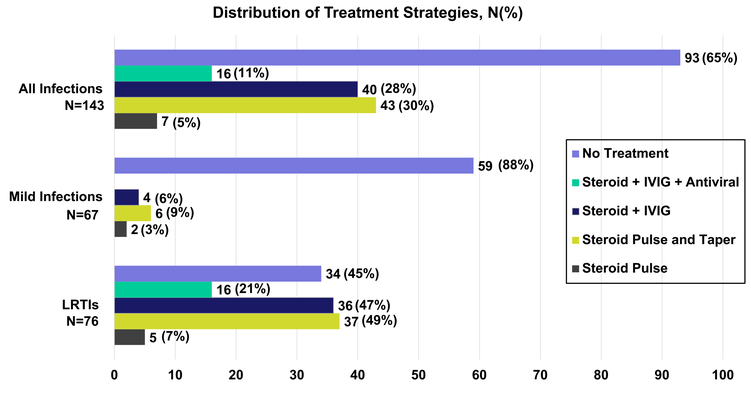
Demographics	CARV Infections (N=143) n(%)	No CARV (N=48) n(%)
Age at transplant [median, (range)]	59 (19-69)	59.5 (31-69)
Male Sex	96 (67)	32 (59)
Pre-transplant Lung Disease		
Obstructive	51 (36)	27 (56)
Restrictive	81 (57)	19 (40)
Vascular	8 (6)	1 (2)
Suppurative	17 (12)	4 (7)
Pre-transplant comorbidities		
Diabetes	23 (16)	8 (15)
Asthma	4 (3)	1 (2)
GERD	47 (33)	8 (15)
CMV serostatus		
R+	83 (58)	23 (43)
D+/R-	31 (22)	14 (26)
D-/R-	29 (20)	11 (20)
Medications		
Inhaled or intranasal corticosteroids	14 (10)	14 (26)
Type of lung transplant		
Single	16 (11)	3 (6)
Bilateral	127 (89)	45 (83)

GERD = Gastroesophageal Reflux Disease, R+ = Recipient CMV IgG positive, D+/R- = Donor CMV IgG positive, recipient CMV IgG negative (mismatch), D-/R- = Donor CMV IgG negative, recipient CMV IgG negative



CoV = Non-SARS-CoV-2 coronavirus, HMPV = Human Metapneumovirus, PIV = Parainfluenza virus, R/E = Rhinovirus/Enterovirus, RSV = Respiratory syncytial virus

Figure 2: Distribution of type of initial CARV infection.



LRTI = Lower respiratoy tract infections
Steroid Pulse = Methylprednisolone 10mg/kg once daily x 3 doses
Steroid taper = Prednisone 1mg/kg/day reduce by 5mg daily dose every 3 days until at previous baseline dose of 10-15mg/day
IVIG = Intravenous immunoglobulins 0.5g/kg x 1 dose
Antiviral = Oseltamivir 75mg BID x 10 days for influenza and Ribavirin 10mg/kg BID x 10 days for RSV/PIV/HMPV. In this initial CARV population 9 patients (6%) received ribavirin and 7 patients (5%) received oseltamivir.

Figure 3: Treatment strategies used in management of initial CARV infections.

Results

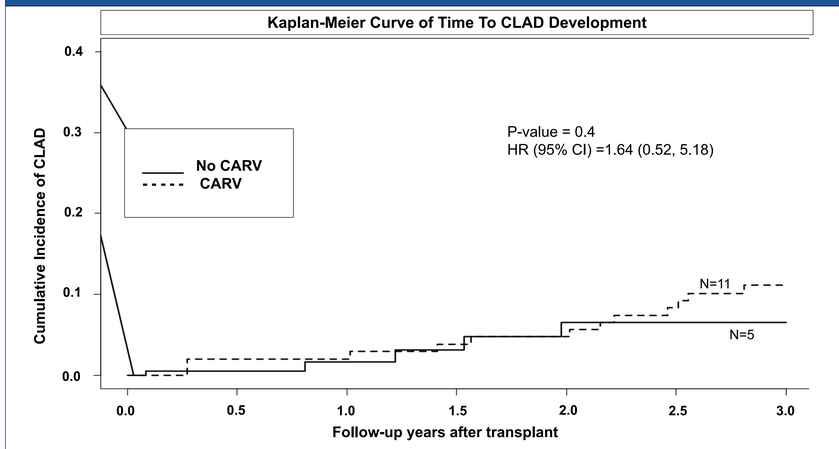


Figure 4: Time to CLAD curve is shown. CARV is a time-dependant variable and accounts for isolations before CLAD development only. Total of 16 CLADs in this figure.

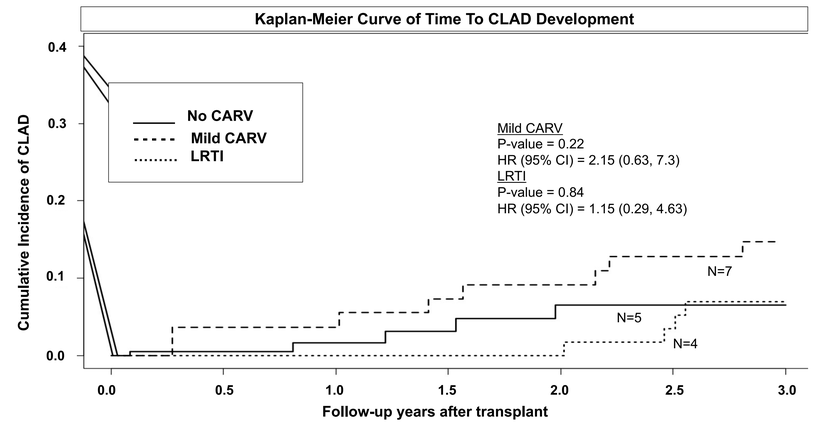


Figure 5: Time to CLAD curve for each type of CARV is shown. CARV is a time-dependant variable and accounts for isolations before CLAD development only. Total of 16 CLADs in this figure.

- Median time from transplant to first CARV infection was 5.33 months (IQR 2.18 – 12.45).
- Cytomegalovirus (CMV) reactivation was the most commonly identified adverse drug reaction associated with glucocorticoid treatment of CARV infections.

Limitations

- The limitations of this study include:
  - Retrospective design, small sample size, and low event rate

Conclusions

- Majority of patients (75%) developed at least one CARV infection during the follow up period, most commonly in the first year post-transplant.
- 40% of patients had lower respiratory tract infections (LRTIs), which were treated more aggressively with steroid pulse and taper regimen and IVIG.
- CARV was not associated with a more rapid progression to chronic lung allograft dysfunction (CLAD) in our population.
- Glucocorticoid treatment of CARV was associated with important adverse drug events, including Cytomegalovirus reactivation.
- Future studies with larger sample sizes, and assessment of later time points are needed.