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Incidence, Risk Factors and Outcomes of Delayed-Onset Cytomegalovirus Disease in a Large Retrospective Cohort of Lung Transplant Recipients

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Abstract

Background—Cytomegalovirus (CMV) replication and disease commonly occur in lung transplant recipients after stopping anti-CMV prophylaxis. The epidemiology of CMV disease is not well-studied given difficulties in assembling representative study populations with prolonged follow-up. We hypothesized that delayed-onset CMV disease (> 100 days post-transplant) occurs more commonly than early-onset CMV disease in lung transplant recipients, and is associated with an increased risk of death.

Methods—We assembled a large cohort of lung transplant recipients using 2004 to 2010 ICD-9-CM billing data from 3 Agency for Healthcare Research and Quality (AHRQ) State Inpatient Databases (SID), and identified demographics, comorbidities, CMV disease coded during hospital readmission and inpatient death. We used Cox proportional hazard multivariate analyses to assess for an independent association between delayed-onset CMV disease and death.

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Results—In the cohort of 1,528 lung transplant recipients from 12 transplant centers, delayed-onset CMV disease occurred in 13.7% (n=210) and early-onset CMV disease occurred in 3.3% (n=51). Delayed-onset CMV pneumonitis was associated with inpatient death > 100 days post-transplant (aHR 1.6, 95% CI 1.1-2.5), after adjusting for transplant failure/rejection (aHR 2.5, 95% CI 1.5-4.1), bacterial pneumonia (aHR 2.8, 95% CI 2.0-3.9), viral pneumonia (aHR 1.5, 95% CI 1.1-2.1), fungal pneumonia (aHR 1.8, 95% CI 1.3-2.3), single lung transplant (aHR 1.3, 95% CI 1.0-1.7) and idiopathic pulmonary fibrosis (aHR 1.4, 95% CI 1.0-1.8).

Conclusions—Delayed-onset CMV disease occurred more commonly than early-onset CMV disease among lung transplant recipients. These results suggest that delayed-onset CMV pneumonitis was independently associated with an increased risk of death.

Introduction

Cytomegalovirus (CMV) infection and disease commonly occur in lung transplant recipients^{1, 2}, and can be asymptomatic or manifest as CMV syndrome or tissue-invasive lung or gastrointestinal disease³⁻⁵. CMV infection has been demonstrated to be associated with an increased risk of acute allograft rejection^{1, 6} and bronchiolitis obliterans syndrome (BOS)⁷⁻¹¹. Because of its association with poor outcomes, preventive anti-CMV strategies in lung transplant recipients are utilized¹², with the majority of transplant centers using anti-CMV prophylaxis with oral valganciclovir or intravenous ganciclovir for 3 to 6 months. An international consensus committee convened in 2010 recommended at least 6 months of anti-CMV prophylaxis for CMV-seronegative lung transplant recipients that received lungs from CMV-seropositive donors (D+/R-) and 3 to 6 months of anti-CMV prophylaxis for CMV seropositive recipients (R+)¹³. A randomized controlled trial that demonstrated the superiority of 12 months over 3 months of valganciclovir prophylaxis in preventing CMV disease among D+/R- and R+ lung transplant recipients^{14, 15} supports even longer treatment.

Increasing the duration of anti-CMV prophylaxis can lead to delaying the onset of CMV disease in the absence of effective anti-CMV immunity^{16, 17}. It is unclear whether delayed-onset CMV disease is similarly linked to poor outcomes as CMV disease that occurs earlier after lung transplantation, when the immunocompromised state can be most marked.

Researchers have had difficulty studying delayed-onset CMV disease since assembling large and representative study cohorts with prolonged follow-up is challenging. To understand the epidemiology of delayed-onset CMV disease among lung transplant recipients, we used data from the Agency for Healthcare Research and Quality Healthcare Cost and Utilization Project (AHRQ-HCUP) State Inpatient Databases (SID) of California, Florida and New York. These SID consist of demographic and billing data based on inpatient *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) coding with encrypted patient-level identifiers allowing identification of admissions within and across hospitals over time in a state. Presuming the administration of anti-CMV prophylaxis to D +/R- and R+ patients for at least 3 months after lung transplantation¹², we hypothesized that delayed-onset CMV disease (> 100 days post-transplant) occurs more commonly than early-

onset CMV disease, and delayed-onset CMV disease is associated with an increased risk of death compared to no delayed-onset CMV disease.

Methods

Study design and patient population

We performed a retrospective cohort study of adult (≥ 18 years of age) lung transplant recipients (ICD-9-CM codes 33.50, 33.51, 33.52) who underwent transplantation from 2004 to 2010 in the California SID and 2006 to 2010 in the Florida and New York SID (total $n=1,982$). We chose the cohort inception years to include 1 year of prior data to identify comorbidities, and obtain at least 1 year of follow-up data. We excluded patients who lived in states other than the one where transplantation was performed ($n=300$) since the SID contain only hospitalizations that occur within a state and lung transplant recipients from out of state were likely to have missing follow-up. We also excluded patients who received another solid-organ transplant during the same hospitalization or underwent transplantation at a pediatric hospital as identified by the American Hospital Association (AHA) Annual Hospital Survey ($n=12$), or had coding for CMV disease within 1 year before lung transplantation or during the transplant hospitalization ($n=142$). The final study population consisted of 1,528 lung transplant recipients. The study protocol was reviewed by the Institutional Review Board of Washington University in St. Louis and was exempted from Human Research Protection Office oversight.

Demographic data, comorbidities and follow-up

ICD-9-CM diagnosis and procedure codes used in this study are given in Table 1. Demographic characteristics of the study population were determined at the time of transplantation, comorbidities were identified using the Elixhauser classification¹⁸, and possible reasons for lung transplant and prior solid-organ transplantation were identified using codes in Table 1. Inpatient readmissions were identified using the encrypted patient-level identifier. New-onset CMV disease coded during hospital readmission was identified and further characterized using diagnosis codes for CMV pneumonitis and hepatitis. There are no ICD-9-CM codes for CMV esophagitis, gastritis, enteritis or colitis. New-onset CMV disease was categorized as either early-onset (< 100 days post-transplant) or delayed-onset (≥ 100 days post-transplant). Other conditions identified at readmission were newly-coded transplant failure or rejection, clinical sepsis, hemodialysis, repeat solid-organ transplant during readmission, bacterial pneumonia, viral pneumonia and fungal pneumonia. There is no distinct ICD-9-CM code for BOS apart from the one used for transplant failure or rejection. Inpatient death was determined using the discharge status variable.

Statistical analysis

Descriptive statistics were used to describe the demographic and clinical characteristics of the study population. Potential risk factors for delayed-onset CMV disease and inpatient death coded during hospital readmission were analyzed using univariate and multivariate Cox proportional hazards modeling. In the analysis for risk factors for delayed-onset CMV disease, patients were censored at the time of repeat any solid-organ transplant, inpatient death or maximum follow-up (December 31, 2011). In the analysis for risk factors for

inpatient death > 100 days post-transplant, patients were censored on December 31, 2011. Only patients who survived > 100 days post-transplant and were not coded with CMV disease 100 days post-transplant were included in the analysis for risk factors for delayed-onset CMV disease and death. The proportional hazards assumption was evaluated for each variable using visual inspection of log-log survival curves and the correlation between Schoenfeld residuals for a particular covariate and the ranking of individual failure times¹⁹. Dummy variables for transplant center, state and year of transplant added to the models did not change the parameter estimates of the primary explanatory variables by more than 10%, indicating no significant effect of clustering. Statistical significance was set at a p-value of 0.05. All analyses were performed using SAS version 9.2 (Cary, North Carolina).

Results

Demographic and clinical characteristics

The study population consisted of 1,528 adult lung transplant recipients from 12 transplant centers (Table 2). The median age at the time of transplant was 58 years, and 42% were female. Seventy-seven percent were white, 95% of patients lived in metropolitan centers, progressively more patients lived in ZIP codes with increasing median incomes by quartile, and private insurance companies accounted for 50% of the patients' expected primary payers. Thirty-four percent of the study population underwent single lung transplantation. Chronic obstructive pulmonary disease was the most common indication for lung transplant. Four percent of the recipients had a prior solid-organ transplant, of which 85% were lung transplant. Thirty-eight percent of patients had hypertension and 33% had diabetes mellitus. The median duration of follow-up was 3.0 years, with an interquartile range of 1.6 to 4.7 years.

New-onset CMV disease coded during hospital readmission

New-onset CMV disease was identified in 17% of the study population, with a median time to onset of 253 days after lung transplantation (interquartile range 126 – 516 days) (Table 3). Early-onset CMV disease occurred in 3.3% and delayed-onset CMV disease occurred in 14% of recipients. Among the delayed-onset cases of CMV disease, 48% occurred > 365 days post-transplant. Twenty-five percent of delayed-onset CMV disease was coded as CMV pneumonitis, and there were no identified cases of CMV hepatitis. The remaining 75% not coded as CMV pneumonitis may have had asymptomatic viremia, CMV syndrome or tissue-invasive gastrointestinal disease, which do not have specific ICD-9-CM codes. Transplant failure or rejection was coded in 76% of hospital readmissions with new-onset CMV disease. Thirty-five percent of lung transplant recipients coded with CMV disease subsequently died during follow-up, with a median time to death of 290 days. Among patients coded with CMV pneumonitis, 51% subsequently died during follow-up, with a median time to death of 233 days.

Analysis of risk factors for delayed-onset CMV disease using univariate Cox proportional hazard (Table 4) found a 34% increased risk of delayed-onset CMV disease for recipients that had a single lung transplant, compared to double or unspecified lung transplant (p-value=0.039). Analyses did not identify other risk factors.

Other first-time conditions coded during hospital readmission

Coding for transplant failure or rejection was found in 77% of lung transplant patients, with median time to onset of 26 days post-transplant (interquartile range 10 – 141 days). There is no specific code for BOS. Bacterial pneumonia was identified in 55% of patients, with median time to onset of 74 days post-transplant (interquartile range 14 – 344 days). Viral pneumonia was identified in 7.7% of patients, with median time to onset of 388 days post-transplant (interquartile range 221 – 795 days), and fungal pneumonia was identified in 8.9% of patients, with median time to onset of 326 days post-transplant (interquartile range 128 – 877 days). Transplant failure or rejection was coded in 74%, 89% and 82% of hospitalizations coded for first-time bacterial pneumonia, viral pneumonia and fungal pneumonia respectively.

Inpatient death

Inpatient death was identified in 27% of the lung transplant cohort on follow-up, with approximately 6.3% occurring $\leq$ 100 days post-transplant and 20% occurring $>$ 100 days post-transplant (Table 3). Commonly co-occurring conditions during hospitalizations wherein death was coded included transplant failure or rejection (81%), bacterial pneumonia (56%), clinical sepsis (45%) and hemodialysis (33%). On Kaplan-Meier analysis, patients with delayed-onset CMV disease had lower survival compared to patients without CMV disease identified during a hospitalization (Figure 1A). The survival curves diverged after approximately 1 year post-transplant. Patients with bacterial pneumonia, viral pneumonia and fungal pneumonia also had lower survival compared to patients without these conditions on Kaplan-Meier analysis (Figures 1B, 1C, 1D).

Univariate and multivariate Cox proportional hazard ratios for risk factors associated with inpatient death $>$ 100 days post-transplant are shown in Table 5. On multivariate analysis, delayed-onset CMV pneumonitis was associated with a 63% increased risk of death, whereas other types of CMV disease were not associated with death. Other risk factors for death identified on multivariate analysis were transplant failure or rejection (HR_{adj} 2.5), bacterial pneumonia (HR_{adj} 2.8), viral pneumonia (HR_{adj} 1.5), fungal pneumonia (HR_{adj} 1.8), single lung transplant (HR_{adj} 1.3) and idiopathic pulmonary fibrosis (HR_{adj} 1.4). Delayed-onset CMV disease was associated with a 2-fold increased risk of death $>$ 365 days post-transplant on univariate analysis (HR 95% CI 1.5 – 2.8), and was marginally significant on multivariate analysis (HR_{adj} 1.3, 95% CI 0.99 – 1.84, p -value=0.058). Delayed-onset CMV disease was not associated with an increased risk of death 101 to 365 days post-transplant.

Discussion

We conducted a retrospective cohort study of 1,528 adult lung transplant recipients from 2004 to 2010 using inpatient administrative billing data from 12 transplant centers located in 3 large and diverse states to determine the incidence, risk factors and outcomes associated with delayed-onset CMV disease coded during hospital readmission.

We found that newly-coded CMV disease occurring > 100 days post-transplant was more common than early-onset CMV disease. This may reflect the widespread use of anti-CMV prophylaxis for at least 3 months after lung transplant^{11-14, 20, 21}, thereby leading to a delay in the onset of CMV disease. Almost a quarter of new-onset CMV disease in this study population was coded as CMV pneumonitis. CMV pneumonitis in lung transplant recipients is well-described²²⁻²⁵, and is likely due to the predilection for CMV to involve the transplanted allograft³, as well as the large reservoir of latent CMV in lungs²⁶ that can reactivate with increased immunosuppression.

Coding for transplant failure or rejection occurred in the majority of hospitalizations wherein CMV disease was identified, indicating a strong bidirectional relationship between allograft rejection and CMV replication⁶. Allograft rejection can result in increased inflammation, tumor necrosis factor (TNF) release and CMV transactivation²⁷. Moreover, it typically leads to augmented immunosuppression which increases the risk of CMV disease^{5, 28, 29}. Conversely, CMV replication can upregulate alloantigens³⁰, and increase the expression of adhesion molecules that activate inflammatory cells in the allograft⁶, thereby promoting allograft rejection.

The only risk factor for delayed-onset CMV disease identified by our analysis was single lung transplantation. However, the association was small, and not adjusted for potential risk factors for CMV disease such as donor and recipient CMV serostatus³¹, type, timing and dose of immunosuppressive therapy^{28, 29, 32}, or CMV prevention practices^{14, 15}. It is possible that native lung infections such as bacterial pneumonia and fungal infections result in increased inflammation^{33, 34}, thereby leading to transactivation of latent CMV in the transplanted lung and subsequent CMV disease^{26, 27}. The association between delayed-onset CMV disease and single lung transplantation must be confirmed using clinical data.

Delayed-onset CMV pneumonitis (but not other types of CMV disease), was associated with an increased risk of death. Interestingly, death in these patients was not immediate, and occurred at a median of 7.8 months from the time of readmission with CMV disease. These results suggest that the effect of CMV pneumonitis on mortality is indirect, and an event such as bronchiolitis obliterans syndrome (BOS) may mediate the association between CMV pneumonitis and death. CMV pneumonitis has been reported to be associated with BOS⁸⁻¹⁰, and BOS frequently causes death in lung transplant recipients^{2, 7}. It is possible that increased inflammation as a result of CMV replication and upregulation of pro-inflammatory chemokines in the lungs³⁵ contributes to the development of BOS and death. Other risk factors for BOS include acute rejection^{7, 36-41}, pneumonia or bacterial airway colonization⁴², viral lower respiratory tract infections⁴³⁻⁴⁵, *Aspergillus* colonization of the lung allograft⁴⁶ and single lung transplant⁴⁷. We adjusted for these risk factors for BOS in multivariate analysis using coding for transplant failure or rejection, bacterial pneumonia, viral pneumonia, fungal pneumonia and single lung transplantation, and found that delayed-onset CMV pneumonitis was independently associated with death. We could not assess the association between delayed-onset CMV disease and BOS directly since there is no specific ICD-9-CM code for BOS. Notably, delayed-onset CMV disease with no codes for CMV pneumonitis was not associated with death, suggesting milder illness such as asymptomatic viremia or CMV syndrome, or disease misclassification.

Our study is the first to use a more representative cohort of lung transplant recipients with prolonged follow-up to determine the epidemiology of CMV disease, and contributes to our understanding of its incidence and outcomes. Moreover, it is the first study to demonstrate an association between delayed-onset CMV pneumonitis and an increased risk of death after adjusting for transplant failure or rejection, bacterial pneumonia, viral pneumonia, fungal pneumonia and single lung transplantation on multivariate analysis. It however has some limitations. The SID contain de-identified demographic and inpatient hospital ICD-9-CM billing data and do not have information on medications, laboratory test results or donor/recipient CMV serostatus. Since the SID are de-identified, the data cannot be linked to more granular clinical data. Identification of comorbidities, risk factors and disease conditions depended on ICD-9-CM coding, which are not perfectly accurate⁴⁸. There are no published data regarding the accuracy of CMV disease or CMV pneumonitis coding. Misclassification could have occurred, though it likely would have resulted in more conservative estimates of the effect of CMV on mortality. Despite these limitations, this study contributes to our understanding of CMV disease in lung transplant recipients at the population level, and it clarifies the incidence and impact of delayed-onset CMV disease in the era of widespread use of anti-CMV prophylaxis after lung transplant.

In summary, we found using a large population of lung transplant recipients followed over a prolonged period of time that delayed-onset CMV disease coded during hospital readmission occurred more commonly than early-onset CMV disease. Moreover, we demonstrated that delayed-onset CMV pneumonitis is independently associated with an increased risk of death. Given the superiority of 12 months over 3 months of valganciclovir prophylaxis in preventing CMV disease among D+/R- and R+ lung transplant recipients^{14, 15}, consideration should be given to administering extended valganciclovir prophylaxis to lung transplant recipients at risk of CMV disease. Future studies should assess the comparative effectiveness of extended versus short-course valganciclovir prophylaxis as they are used in clinical practice, and determining whether extended prophylaxis leads to a decreased risk of allograft failure and improved long-term survival.

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Abbreviations

AHA	American Hospital Association
AHRQ-HCUP	Agency for Healthcare Research and Quality Healthcare Cost and Utilization Project
BOS	Bronchiolitis obliterans syndrome
CMV	cytomegalovirus
CI	confidence interval
aHR	adjusted hazard ratio
ICD-9-CM	International Classification of Diseases, Ninth Revision, Clinical Modification
SID	State Inpatient Databases
UNOS	United Network for Organ Sharing

Figure 1.

Time (days) to inpatient death > 100 days post-transplant in a cohort of adult lung transplant recipients, stratified according to presence or absence of delayed-onset CMV disease (**A**), bacterial pneumonia (**B**), viral pneumonia (**C**) and fungal pneumonia (**D**).

Table 1

ICD-9-CM diagnosis and procedure codes

Condition	ICD-9-CM diagnosis codes	ICD-9-CM procedure codes
Lung transplant		
Single		33.51
Double		33.52
Unspecified		33.50
Possible reasons for lung transplant		
Chronic obstructive pulmonary disease	490, 491, 491.0, 491.1, 491.2, 491.20, 491.21, 491.22, 491.8, 491.9, 492, 492.0, 492.8, 494, 494.0, 494.1, 495, 495.0, 495.1, 495.2, 495.3, 495.4, 495.5, 495.6, 495.7, 495.8, 495.9	
Idiopathic pulmonary fibrosis	516.3	
Cystic fibrosis	277, 277.0, 277.00, 277.01, 277.02, 277.03, 277.09	
Alpha-1 antitrypsin deficiency	273.4	
Sarcoidosis	135	
Prior solid-organ transplantation	V42.0, V42.7, V42.1, V42.6, V42.83, V42.84	
CMV disease <i>I</i>	078.5	55.69, 50.59, 33.50 to 33.52, 33.6, 52.80, 46.97
CMV pneumonitis	484.1	
CMV hepatitis	573.1	
Transplant failure or rejection	996.84	
Clinical sepsis	995.91, 995.92	
Hemodialysis		39.95
Repeat solid-organ transplantation		55.69, 50.59, 33.50 to 33.52, 33.6, 52.80, 46.97
Bacterial pneumonia		
<i>Chlamydia psittaci</i>	073.0	
<i>Streptococcus pneumoniae</i>	481	
<i>Klebsiella pneumoniae</i>	482.0	
<i>Pseudomonas aeruginosa</i>	482.1	
<i>Hemophilus influenzae</i>	482.2	
<i>Streptococcus</i> , unspecified	482.30	
Group A <i>Streptococcus</i>	482.31	
Group B <i>Streptococcus</i>	482.32	
Other <i>Streptococcus</i>	482.39	

Condition	ICD-9-CM diagnosis codes	ICD-9-CM procedure codes
<i>Staphylococcus</i> , unspecified	482.40	
<i>Staphylococcus aureus</i> , methicillin-susceptible	482.41	
<i>Staphylococcus aureus</i> , methicillin-resistant	482.42	
Other <i>Staphylococcus</i>	482.49	
Anaerobes	482.81	
<i>Escherichia coli</i>	482.82	
Other gram-negative bacteria	482.83	
<i>Legionella pneumophila</i>	482.84	
Other specified bacteria	482.89, 483.8	
Bacteria pneumonia, unspecified	482.9	
<i>Mycoplasma pneumoniae</i>	483.0	
<i>Chlamydia pneumoniae</i>	483.1	
Bronchopneumonia	485	
Pneumonia, organism unspecified	486	
Viral pneumonia		
Adenovirus	480.0	
Respiratory syncytial virus	480.1	
Parainfluenza virus	480.2	
SARS-associated coronavirus	480.3	
Other virus not elsewhere classified	480.8	
Unspecified virus	480.9	
Influenza	487.0	
Fungal pneumonia		
Aspergillosis	484.6	
Other systemic mycoses	484.7	

¹There are no ICD-9-CM codes for CMV esophagitis, gastritis, enteritis or colitis.

Table 2
Demographic and clinical characteristics of 1,528 lung transplant recipients at the time of organ transplantation

Variables	All recipients
Age, years	
Mean + SD	53.59 + 13.68
Median (range)	58 (18 – 77)
Female sex (%)	41.82
Race (%)	
White	76.90
Black	5.69
Hispanic	10.54
Asian or Pacific Islander	3.01
Other or missing	3.86
Patient location (urban-rural) (%) ¹	
Large metropolitan	71.07
Small metropolitan	24.02
Micropolitan	3.93
Not metropolitan or micropolitan, or missing	0.98
Median income of patient ZIP code (%)	
First quartile (poorest)	14.86
Second quartile	20.16
Third quartile	24.67
Fourth quartile (wealthiest)	30.76
Missing	9.55
Expected primary insurance payer (%)	
Medicare	40.05
Private insurance	49.74
Medicaid, self-pay, no charge, other or missing	10.21
Type of lung transplant (%)	
Single	34.03
Double or unspecified	65.97
Possible reasons for lung transplant (%)	
Chronic obstructive pulmonary disease	51.44
Idiopathic pulmonary fibrosis	21.01
Cystic fibrosis	16.30
Alpha-1 antitrypsin deficiency	3.34
Sarcoidosis	2.88
Other	25.33
Prior transplant (%)	3.99
Lung	3.40
Other comorbidities (%)	

Variables	All recipients
Pulmonary circulation disease	41.69
Hypertension	38.22
Diabetes mellitus	33.18
Gastroesophageal reflux disease	31.28
Depression	18.00
Congestive heart failure	10.86
Valvular disease	10.54
Rheumatoid arthritis or collagen vascular disease	8.57
Hypothyroidism	7.79
Obesity	7.46
Neurologic disorders	5.24
Renal failure	4.78
Psychoses	3.27
Liver disease	3.21
Drug abuse	2.68
Peripheral vascular disease	2.49
Alcohol abuse	2.16
Duration of follow-up, years	
Mean	3.2
Median (interquartile range)	3.0 (1.6 – 4.7)
Number of transplant centers	12

¹ Large metropolitan – at least 1 million residents; Small metropolitan – less than 1 million residents; Micropolitan – adjacent to large or small metropolitan area.

Table 3
Number of patients with new-onset CMV disease and inpatient death coded during hospitalization in a cohort of 1,528 lung transplant recipients, and coincident conditions

	All	Early (100 days post-transplant)	Delayed (> 100 days post-transplant)
New-onset CMV disease			
Number of patients (%)	261 (17.08)	51 (3.34)	210 (13.74)
CMV pneumonitis	*	*	53 (25.24)
Transplant failure or rejection	198 (75.86)	42 (82.35)	156 (74.29)
Died	91 (34.87)	20 (39.22)	71 (33.81)
Median time to death in days after diagnosis of CMV disease (interquartile range)	290 (95 – 715)	366 (204 – 914)	247 (82 – 636)
Inpatient death			
Number of patients (%)	407 (26.64)	96 (6.28)	311 (20.35)
CMV disease	32 (7.86)	*	*
Transplant failure or rejection	330 (81.08)	64 (66.67)	266 (85.53)
Bacterial pneumonia	228 (56.02)	36 (37.50)	192 (61.74)
Viral pneumonia	23 (5.65)	*	*
Fungal pneumonia	32 (7.86)	*	*
Clinical sepsis	183 (44.96)	41 (42.71)	142 (45.66)
Hemodialysis	133 (32.68)	48 (50.00)	85 (27.33)

* AHRQ-HCUP prohibits reporting cell sizes <11 in number.

Table 4
Univariate Cox proportional hazard model for risk factors associated with delayed-onset CMV disease

Risk factor	HR (95% CI)	p-value
Increasing age at time of transplantation per decade	1.01 (0.91-1.11)	0.907
Race		
White	1.00	
Black	0.68 (0.33-1.38)	0.281
Hispanic	1.06 (0.69-1.63)	0.778
Asian or Pacific Islander	1.01 (0.47-2.15)	0.981
Other or missing	0.63 (0.26-1.54)	0.315
Patient location non-metropolitan	0.91 (0.48-1.72)	0.781
Median income of patient ZIP code		
First quartile (poorest)	0.90 (0.59-1.39)	0.641
Second quartile	0.80 (0.54-1.19)	0.264
Third quartile	0.80 (0.56-1.16)	0.249
Fourth quartile (wealthiest)	1.00	
Missing	1.05 (0.67-1.64)	0.836
Expected primary insurance payer		
Medicare	0.98 (0.73-1.31)	0.875
Private insurance	1.00	
Medicaid, self-pay, no charge, other or missing	1.14 (0.74-1.77)	0.550
Diabetes mellitus	0.99 (0.74-1.32)	0.923
Gastroesophageal reflux disease	1.06 (0.79-1.41)	0.714
Previous transplant failure or rejection	1.00 (0.73-1.36)	1.000
Single lung transplant versus double or unspecified	1.34 (1.02-1.76)	0.039
Possible reasons for lung transplant		
Chronic obstructive pulmonary disease	1.10 (0.84-1.45)	0.474
Idiopathic pulmonary fibrosis	1.23 (0.89-1.69)	0.207
Cystic fibrosis	1.11 (0.78-1.57)	0.569
Alpha-1 antitrypsin deficiency	0.60 (0.22-1.63)	0.320
Sarcoidosis	0.71 (0.26-1.92)	0.501

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Risk factor	HR (95% CI)	p-value
Prior transplant	1.33 (0.70-2.50)	0.384
Lung	1.29 (0.64-2.62)	0.476

Table 5
Cox proportional hazard model for risk factors associated with inpatient death > 100 days post-transplant

Risk factor	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Delayed-onset CMV disease				
No CMV pneumonitis	1.38 (1.00-1.91)	0.051	0.93 (0.67-1.30)	0.669
CMV pneumonitis	2.58 (1.73-3.85)	<0.001	1.63 (1.09-2.46)	0.019
Delayed-onset CMV disease				
101 – 365 days post-transplant	0.85 (0.45-1.61)	0.627		
> 365 days post-transplant	2.05 (1.52-2.76)	<0.001		
Transplant failure or rejection	4.46 (2.77-7.19)	<0.001	2.50 (1.52-4.11)	<0.001
Bacterial pneumonia	3.90 (2.86-5.32)	<0.001	2.80 (2.02-3.88)	<0.001
Viral pneumonia	2.18 (1.58-3.00)	<0.001	1.49 (1.07-2.07)	0.018
Fungal pneumonia	2.61 (1.97-3.45)	<0.001	1.75 (1.31-2.34)	<0.001
Increasing age at time of transplantation per decade	1.06 (0.98-1.16)	0.164		
Female sex	1.04 (0.82-1.31)	0.746		
Race				
White	1.00			
Black	1.04 (0.63-1.73)	0.880		
Hispanic	1.11 (0.78-1.60)	0.558		
Asian or Pacific Islander	1.00 (0.51-1.95)	0.996		
Other or missing	0.98 (0.52-1.85)	0.951		
Patient location non-metropolitan	0.91 (0.53-1.55)	0.725		
Median income of patient ZIP code				
First quartile (poorest)	1.23 (0.87-1.73)	0.246		
Second quartile	0.63 (0.43-0.92)	0.017		
Third quartile	0.92 (0.67-1.26)	0.613		
Fourth quartile (wealthiest)	1.00			
Missing	0.96 (0.66-1.41)	0.846		
Expected primary insurance payer				
Medicare	1.25 (0.98-1.60)	0.072	1.27 (0.99-1.63)	0.064

Risk factor	Univariate analysis			Multivariate analysis		
	HR	(95% CI)	p-value	HR	(95% CI)	p-value
Private insurance		1.00			1.00	
Medicaid, self-pay, no charge, other or missing	1.22	(0.84-1.77)	0.293	1.09	(0.75-1.60)	0.648
Single lung transplant versus double or unspecified	1.37	(1.09-1.73)	0.008	1.31	(1.03-1.67)	0.028
Possible reasons for lung transplant						
Chronic obstructive pulmonary disease	1.15	(0.91-1.45)	0.230			
Idiopathic pulmonary fibrosis	1.23	(0.94-1.61)	0.129	1.36	(1.03-1.79)	0.030
Cystic fibrosis	0.96	(0.71-1.31)	0.803			
Alpha-1 antitrypsin deficiency	1.32	(0.72-2.42)	0.363			
Sarcoidosis	1.48	(0.81-2.71)	0.201			
Prior transplant	0.80	(0.40-1.63)	0.545			
Lung	0.73	(0.33-1.64)	0.448			
Other comorbidities						
Pulmonary circulation disease	0.93	(0.73-1.18)	0.537			
Hypertension	1.09	(0.86-1.38)	0.480			
Diabetes mellitus	1.08	(0.84-1.37)	0.556			
Gastroesophageal reflux disease	1.13	(0.88-1.44)	0.339			
Depression	1.25	(0.94-1.66)	0.120			
Congestive heart failure	0.71	(0.45-1.10)	0.126			
Valvular disease	0.83	(0.55-1.25)	0.366			
Neurologic disorders	1.39	(0.85-2.26)	0.191			
Renal failure	0.94	(0.53-1.67)	0.827			
Psychoses	1.65	(0.96-2.82)	0.068			