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

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Abstract

Background—Delayed-onset cytomegalovirus (CMV) disease can occur among heart transplant recipients after stopping anti-CMV prophylaxis. We evaluated a large retrospective cohort of heart transplant recipients in the United States using billing data from 3 Healthcare Cost and Utilization Project (HCUP) State Inpatient Databases (SID) to determine the epidemiology of delayed-onset CMV disease coded during hospital readmission.

Methods—We identified 2,280 adult heart transplant recipients from 2004 to 2010 using the California, Florida and New York SID. Demographics, comorbidities, heart failure etiology, CMV disease and inpatient death were identified. CMV disease was classified as early-onset (< 100 days) or delayed-onset (> 100 days post-transplant). Possible tissue-invasion by CMV was determined using codes for CMV pneumonitis, hepatitis and gastrointestinal endoscopy. Multivariate analysis was performed using Cox proportional hazards models.

Results—Delayed-onset CMV disease occurred in 7.5% (170/2,280) and early-onset CMV disease occurred in 2.0% (45/2,280) of heart transplant recipients. Risk factors for delayed-onset CMV disease included residence in a non-metropolitan locale (aHR 1.8, 95% CI 1.0–3.3) and ischemic cardiomyopathy as heart failure etiology (aHR 1.8, 95% CI 1.3–2.5). Inpatient death > 100 days post-transplant was associated with delayed-onset CMV disease with possible tissue-invasion (aHR 2.0, 95% CI 1.1–3.8), transplant failure or rejection (aHR 4.0, 95% CI 2.7–5.8) and renal failure (aHR 1.5, 95% CI 1.1–2.0).

Conclusions—Delayed-onset CMV disease is more common than early-onset CMV disease among heart transplant recipients. These results suggest that delayed-onset tissue-invasive CMV disease may be associated with an increased risk of death.

INTRODUCTION

Heart transplant recipients are at increased risk of developing cytomegalovirus (CMV) disease due to the use of immunosuppressive therapy to prevent allograft rejection (1). A number of anti-CMV preventive strategies have been studied among heart transplant patients, including providing anti-CMV prophylaxis to CMV-seronegative recipients of organs from CMV-seropositive donors (D+/R-) for 3 months after transplantation (2), and initiating pre-emptive anti-CMV treatment after detecting asymptomatic viral replication in blood (3–5). The American Society of Transplantation recommends 3 to 6 months of anti-CMV prophylaxis for D+/R- heart transplant recipients and 3 months of anti-CMV prophylaxis or pre-emptive anti-CMV therapy for R+ patients (1). Pre-emptive anti-CMV treatment poses logistic challenges (6), and may not prevent indirect deleterious effects of CMV replication on allograft and patient survival (7,8), thereby leading many transplant centers to use anti-CMV prophylaxis. In the absence of effective anti-CMV immunity (9), CMV replication can occur after stopping anti-CMV prophylaxis and result in delayed-onset CMV disease (2), leading to concerns over its emergence as an important infection after transplantation (10).

The epidemiology of delayed-onset CMV disease in heart transplant recipients is not well defined given difficulties in assembling representative study populations with prolonged follow-up. In a single-center study of 31 D+/R- heart transplant recipients given 3 months of ganciclovir or valganciclovir prophylaxis, 29% of patients developed delayed-onset CMV disease, occurring at a median of 225 days post-transplant (11). In an even smaller study of 7 D+/R- heart transplant recipients given CMV hyperimmune globulin, 2 weeks of intravenous ganciclovir and 3 months of valganciclovir prophylaxis, 6 patients developed delayed-onset CMV disease (12). No risk factors for delayed-onset CMV were identified in either study due to the small sample sizes.

To further understand the scope, risk factors and outcomes of delayed-onset CMV disease, we assembled a large cohort of heart transplant recipients using the United States Agency for Healthcare Research and Quality (AHRQ) Healthcare Cost and Utilization Project (HCUP) State Inpatient Databases (SID). The SID are composed of demographic and billing data that capture inpatient diagnoses and procedures through *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) coding. SID from California, Florida and New York were used because of the states' large size and diversity, and the availability of an encrypted identifier to link patient admissions within and across hospitals over time. Assuming widespread use of prophylactic anti-CMV therapy for D+/R- and R+ patients for at least 3 months post-transplant (1,6), we hypothesized that delayed-onset CMV disease (> 100 days post-transplant) in heart transplant recipients occurs more commonly than early-onset CMV disease, and is associated with an increased risk of death.

METHODS

Study design and patient population

We conducted a retrospective cohort study of heart transplant recipients 18 years of age (ICD-9-CM procedure code 37.51) who underwent transplantation from 2004 to 2010 in the California SID and 2006 to 2010 in the Florida and New York SID (n=2,700). These years were used to accrue 1 year of preexisting data to identify comorbidities, and at least one year of follow-up data. We excluded patients who received another solid-organ transplant during the same hospitalization (n=119), lived in states other than the state where the transplant was performed, or underwent transplantation at a pediatric hospital as identified by the American Hospital Association (AHA) Annual Hospital Survey (n=230). We also excluded patients coded for CMV disease within one year prior to or during the transplant hospitalization (n=71). This study was exempt from Human Research Protection Office oversight according to the Washington University Institutional Review Board.

Demographic data, clinical characteristics and follow-up

Demographic characteristics of our study cohort were defined at the time of transplant. Comorbidities within one year of heart transplant and during the transplant hospitalization were identified using the Elixhauser classification (13). ICD-9-CM diagnosis and procedure codes used in this study are enumerated in Table 1. Possible reasons for heart transplant, prior solid-organ transplantation and hyperlipidemia were determined using ICD-9-CM diagnosis codes during hospitalizations within one year before transplant. Hospital readmissions were identified using the encrypted patient-level identifier. New-onset CMV disease coded during readmission was identified by the ICD-9-CM diagnosis code 078.5, and was classified as possibly tissue-invasive in the presence of diagnosis codes for CMV pneumonitis or hepatitis, or procedure codes for esophagogastro-duodenoscopy (EGD), flexible sigmoidoscopy or colonoscopy, which indicate significant gastrointestinal symptoms and may have been used to diagnose luminal CMV disease. There are no ICD-9-CM codes for CMV esophagitis, gastritis, enteritis or colitis. Other conditions identified on follow-up were newly-coded transplant failure or rejection, performance of a heart biopsy, clinical sepsis, hemodialysis and repeat solid-organ transplant during readmission. Time to death (during an inpatient hospitalization) was determined using the discharge status variable. New-onset CMV disease and inpatient death were classified as either early-onset (occurring 100 days post-transplant) or delayed-onset (> 100 days post-transplant).

Statistical analysis

Descriptive statistics were used to describe the demographic and clinical characteristics of the study cohort. Potential risk factors for delayed-onset CMV disease and inpatient death coded during readmission were analyzed using univariate and multivariate Cox proportional hazards modeling. 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 times (14). Dummy variables for transplant center, state and year of

transplant added to the models did not alter the parameter estimates of the primary explanatory variables, 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, NC).

RESULTS

Demographic and clinical characteristics

Our study cohort consisted of 2,280 heart transplant recipients from 22 transplant centers in the United States (Table 2). The median age was 55, and 22% were female. Sixty percent were white, 96% lived in metropolitan centers, and the patients were evenly distributed across median income quartiles (by ZIP code). Private insurance was the single most common primary expected payer (45%). Ischemic cardiomyopathy was defined as the cause of heart failure in 44% of patients, 14% had cardiomyopathy due to other specific causes, and 42% had no identifiable etiology of heart failure by ICD-9-CM coding. Compared to other patients, those with ischemic cardiomyopathy were older at the time of transplantation (mean of 58 versus 49 years, $p < 0.001$), more often white (67% versus 55%, $p < 0.001$), and more frequently had hypertension (78% versus 58%, $p < 0.001$), hyperlipidemia (76% versus 36%, $p < 0.001$), diabetes mellitus (53% versus 33%, $p < 0.001$) and peripheral vascular disease (15% versus 6.9%, $p < 0.001$). Two percent of patients had a prior solid-organ transplant, of which 86% had a previous heart transplant. Twenty-four percent had a Charlson comorbidity index > 4 . The median duration of follow-up for patients in the cohort was 3.5 years (interquartile range (IQR) 1.9 – 5.2).

New-onset CMV disease coded during hospital readmission

Delayed-onset CMV disease coded during hospital readmission occurred in 7.5% of patients, and early-onset CMV disease occurred in 2.0% of patients (Table 3). The median time to onset of CMV disease was 8.1 months post-transplant (IQR 4.4 – 13.5 months). During the readmission wherein delayed-onset CMV disease was coded, 24% were coded for EGD, flexible sigmoidoscopy or colonoscopy; 8.2% were coded with CMV pneumonitis or hepatitis; and 31% had possible tissue-invasive CMV disease (coding for EGD, flexible sigmoidoscopy, colonoscopy, pneumonia or hepatitis). Transplant failure or rejection and performance of a heart biopsy were coded in 43% and 40% of readmissions with new-onset CMV disease respectively. Fourteen percent of patients coded with CMV disease during readmission died, with a median time to death of 229 days. The median time to death among patients with delayed-onset CMV disease was 176 days, compared to a median time to death of 818 days among patients with early-onset CMV disease. Cox proportional hazard ratios for risk factors associated with delayed-onset CMV disease are shown in Table 4. On multivariate analysis, patient residence in non-metropolitan locales was associated with an 83% increased risk of delayed-onset CMV disease, and ischemic cardiomyopathy was associated with a 77% increased risk.

Inpatient death

Early-onset inpatient death (≤ 100 days post-transplant) occurred in 5.6% of patients, and delayed-onset inpatient death (> 100 days post-transplant) occurred in 8% of patients (Table

3). Transplant failure or rejection, clinical sepsis and hemodialysis were coded in 65%, 48% and 46% of readmissions in which the discharge status was death, while CMV disease was coded in 3.9% of these readmissions. Univariate and multivariate Cox proportional hazard ratios for risk factors associated with inpatient death > 100 days post-transplant are shown in Table 5. Delayed-onset CMV disease and delayed-onset CMV disease with possible tissue-invasion were associated with a 1.7 and 2.3-fold increased risk of death in univariate analysis. In multivariate analysis, delayed-onset CMV disease with possible tissue-invasion was associated with a 2.0-fold increased risk of death, controlling for transplant failure or rejection, heart failure etiology and renal failure.

DISCUSSION

We assembled a large cohort of adult heart transplant recipients from 2004 to 2010 using billing data from 22 transplant centers in the United States and followed them over time to study the epidemiology of CMV disease coded during hospital readmission. We found that delayed-onset CMV disease occurred more frequently than early-onset CMV disease. This suggests that anti-CMV strategies deployed by heart transplant centers are effective in preventing early-onset CMV disease (2,4,5). Almost one-third of cases of delayed-onset CMV disease were possibly tissue-invasive, with the majority undergoing EGD, flexible sigmoidoscopy or colonoscopy which indicate significant gastrointestinal symptomatology and may have been performed to diagnose luminal CMV disease.

Other studies of heart transplant patients have demonstrated that the gastrointestinal tract is involved in the majority of cases of tissue-invasive CMV disease (2,11,12). This is similar to findings in kidney and liver transplant recipients (15,16). Tissue-invasive gastrointestinal CMV disease most commonly occurs as esophagitis or colitis, and is typically characterized by mucosal erosions (17). However, severe and atypical presentations of CMV disease can occur, as exemplified by case reports of esophageal necrosis in a kidney transplant recipient (18), an antral mass that required gastrectomy and hepaticojejunostomy in a liver transplant patient (19) and severe pancolitis and toxic megacolon occurring 5 years post-transplant in a heart transplant recipient (20).

Indicators of allograft dysfunction (i.e., transplant failure or rejection or performance of heart biopsy) frequently co-occurred with coding for CMV disease. CMV replication can result in the upregulation of alloantigens and promote allograft rejection (21), and decrease coronary artery vessel size (22). Acute cellular rejection usually results in administration of anti-lymphocyte antibodies or high-dose steroids resulting in increased immune compromise and subsequent CMV disease (23,24).

Patient residence in a non-metropolitan locale was identified as a risk factor for delayed-onset CMV disease. Patients who reside in non-metropolitan locales may more often transition ambulatory care away from transplant centers to healthcare providers nearer their homes, compared to patients who reside in metropolitan areas. Medical providers who practice in smaller cities or rural locales may be less up to date in the prevention, diagnosis and treatment of CMV disease among heart transplant recipients, and it is possible that patients under their care are at increased risk of delayed-onset CMV disease requiring

hospitalization. Kidney allograft loss from BK-virus associated nephropathy has been reported to occur more commonly among patients who were co-managed with non-transplant center nephrologists, compared to patients who were managed solely by transplant center nephrologists (25). Given the complexity of heart transplant management, it is possible that patients who transition care away from transplant centers due to distance would benefit from closer communication between healthcare providers in transplant centers and sites of outpatient follow-up.

Ischemic cardiomyopathy was identified as a risk factor for delayed-onset CMV disease. A larger proportion of patients with ischemic cardiomyopathy had hypertension, hyperlipidemia, diabetes mellitus and peripheral vascular disease compared to patients with non-ischemic cardiomyopathy, consistent with the epidemiology of atherosclerosis (26–28). It is possible that atherosclerotic cardiovascular disease is a milieu conducive to CMV replication and subsequent CMV disease. Atherosclerosis is an inflammatory disease (29) characterized by the recruitment of monocytes and T-cells to cholesterol-containing plaques, activation of monocytes to macrophages, upregulation of pattern recognition receptors, and release of cytokines, including tumor necrosis factor-alpha (TNF) (30). TNF can mediate CMV reactivation by binding to the TNF receptor of latently infected cells resulting in the activation of protein kinase C and NF- κ B, transcription of CMV immediate-early enhancer/promoter genes and viral replication (31–33). An inflammatory milieu that exists among patients with atherosclerosis and ischemic cardiomyopathy may therefore promote the development of CMV disease upon discontinuation of anti-CMV prophylaxis.

Delayed-onset CMV disease with possible tissue-invasion was associated with a 2-fold increased risk of death. It is possible that tissue-invasive CMV disease directly contributes to the causal pathway for death by causing severe morbidity (18–20). Delayed-onset CMV disease can present atypically and be challenging to diagnose (34), which can lead to delayed administration of effective treatment. Another possibility is that allograft failure is responsible for the association between delayed-onset CMV disease with possible tissue-invasion and death. Acute allograft rejection is treated with anti-rejection immunosuppressive therapy which markedly increases the risk of CMV disease (23,24). The effect of CMV disease may be minor compared to the impact of allograft failure, with tissue-invasion by CMV merely reflecting greater immunocompromise stemming from anti-rejection therapy.

The strengths of our study are the large size of the study cohort, the extended duration of follow-up and the generalizability of its findings. Limitations include lack of some transplant information, such as donor and recipient CMV seropositivity, type and duration of anti-CMV prophylaxis, and immunosuppressive therapy administered. Identification of diagnoses and procedures were based solely on ICD-9-CM codes and are not perfectly accurate. Classification of CMV disease as possibly tissue-invasive relied on diagnosis codes for CMV pneumonitis and hepatitis, and procedure codes for EGD, flexible sigmoidoscopy and colonoscopy. There are no ICD-9-CM codes for CMV esophagitis, gastritis, enteritis or colitis. The SID include only hospitalizations within a state, precluding identification of conditions managed in the outpatient setting and hospitalizations outside the state. Nevertheless, we were the first to use a large and more representative study population

of heart transplant recipients with prolonged follow-up to determine the epidemiology of CMV disease, thereby allowing us to identify risk factors for delayed-onset CMV disease and demonstrate an association between delayed-onset CMV disease and death.

In summary, we showed that delayed-onset CMV disease coded during hospital readmission occurred more commonly than early-onset CMV disease in a large retrospective cohort of heart transplant recipients, and that delayed-onset CMV disease with possible tissue-invasion was associated with death. We identified patient residence in non-metropolitan locales and ischemic cardiomyopathy as risk factors for delayed-onset CMV disease. Further research should focus on determining the timing and type of CMV disease using more detailed clinical data, and assessing whether transitioning care away from transplant centers results in an increased risk of CMV disease and other adverse outcomes. More studies are needed to determine whether atherosclerosis is a risk factor for CMV disease.

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Table 1

ICD-9-CM diagnosis and procedure codes.

Condition	ICD-9-CM diagnosis codes	ICD-9-CM procedure codes
Heart transplant		37.51
Possible reasons for heart transplant		
Ischemic cardiomyopathy	414.8, and no codes for cardiomyopathy due to other specified causes	
Cardiomyopathy with no specified cause	No codes for ischemic cardiomyopathy or cardiomyopathy due to other specified causes	
Other specified causes		
Alcoholic cardiomyopathy	425.5	
Hypertrophic obstructive cardiomyopathy	425.1	
Endomyocardial fibrosis	425.0	
Endocardial fibroelastosis	425.3	
Cardiac amyloidosis	277.30–277.39 + 425.7	
Cardiac sarcoidosis	135 + 425.8	
Chagas disease	086.0	
Friedrich's ataxia	334.0 + 425.8	
Myotonia atrophica	359.21 + 425.8	
Progressive muscular dystrophy	359.1 + 425.8	
Thyrototoxicosis	242.0–242.9 + 425.7	
Cardiac glycogenosis	271.0 + 425.7	
Prior solid-organ transplantation	V42.0, V42.7, V42.1, V42.6, V42.83, V42.84	55.69, 50.59, 33.50 to 33.52, 33.6, 52.80, 46.97
Hyperlipidemia	272, 272.0, 272.1, 272.2, 272.3, 272.4, 272.5, 272.9	
CMV disease	078.5	
CMV pneumonitis	484.1	
CMV hepatitis	573.1	
EGD, flexible sigmoidoscopy, colonoscopy *		45.12, 45.13, 45.14, 45.16, 45.23, 45.24, 45.25
Transplant failure or rejection	996.83	
Heart biopsy		37.25
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

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

Table 2

Demographic and clinical characteristics of 2,280 heart transplant recipients at the time of organ transplantation.

Variables	All recipients
Age, years	
Mean $\pm$ SD	52.86 $\pm$ 12.70
Median (interquartile range)	55 (46 – 62)
Female sex (%)	22.50
Race (%)	
White	60.13
Black	13.51
Hispanic	16.05
Asian or Pacific Islander	5.35
Other or missing	4.96
Patient location (urban-rural) (%) *	
Large metropolitan	75.70
Small metropolitan	20.04
Micropolitan	2.76
Not metropolitan or micropolitan, or missing	1.49
Median income of patient ZIP code (%)	
First quartile (poorest)	20.48
Second quartile	21.67
Third quartile	24.39
Fourth quartile (wealthiest)	24.34
Missing	9.12
Expected primary insurance payer (%)	
Medicare	36.10
Private insurance	45.53
Medicaid, self-pay, no charge, other or missing	18.38
Possible reasons for heart failure (%)	
Ischemic cardiomyopathy	43.51
Cardiomyopathy with no specified cause	42.06
Other specified causes	14.43
Alcoholic cardiomyopathy	2.54
Hypertrophic obstructive cardiomyopathy	1.45
Endomyocardial fibrosis or endocardial fibroelastosis	1.45
Cardiac amyloidosis	1.14
Cardiac sarcoidosis	1.01
Chagas disease	0.48
Friedrich's ataxia, myotonia atrophica, progressive muscular dystrophy, thyrotoxicosis or cardiac glycogenosis	0.48
Prior transplant (%)	1.89
Heart	1.62

Variables	All recipients
Other comorbidities (%)	
Hypertension	66.97
Valvular disease	54.61
Hyperlipidemia	53.46
Pulmonary circulation disease	50.18
Diabetes mellitus	41.54
Renal failure	39.82
Chronic pulmonary disease	26.67
Depression	20.31
Hypothyroidism	17.46
Obesity	15.57
Peripheral vascular disease	10.22
Neurologic disorders	8.51
Liver disease	7.41
Drug abuse	6.62
Alcohol abuse	6.18
Psychoses	4.39
Paralysis	3.51
Rheumatoid arthritis or collagen vascular disease	1.49
Solid tumor without metastasis	1.36
Lymphoma	1.14
Charlson comorbidity index (%)	
4	75.79
> 4	24.21
Duration of follow-up, years	
Mean	3.6
Median (interquartile range)	3.5 (1.9 – 5.2)
Number of transplant centers	22

* 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 2,280 heart transplant recipients, and coincident conditions.

	All	Early (100 days post-transplant)	Delayed (> 100 days post-transplant)
New-onset CMV disease			
Number of patients (%)	215 (9.43)	45 (1.97)	170 (7.46)
EGD, flexible sigmoidoscopy or colonoscopy	*	*	41 (24.12)
Pneumonia or hepatitis	*	*	14 (8.24)
Possible tissue-invasive disease /	*	*	53 (31.18)
Transplant failure or rejection	93 (43.26)	25 (55.56)	68 (40.00)
Heart biopsy	87 (40.47)	23 (51.11)	64 (37.65)
Died	31 (14.42)	*	*
Median time to death in days (interquartile range)	229 (83 – 826)	818 (162 – 1,925)	176 (69 – 582)
Inpatient death			
Number of patients (%)	311 (13.64)	128 (5.61)	183 (8.03)
CMV disease	12 (3.86)	*	*
Transplant failure or rejection	201 (64.63)	66 (51.56)	135 (73.77)
Clinical sepsis	149 (47.91)	65 (50.78)	84 (45.90)
Hemodialysis	144 (46.30)	55 (42.97)	89 (48.63)

* AHRQ-HCUP prohibits reporting cell sizes <11 in number.
/EGD, flexible sigmoidoscopy, colonoscopy, pneumonia or hepatitis.

Table 4

Cox proportional hazard model for risk factors associated with delayed-onset CMV disease.

Risk factor	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Increasing age at time of transplantation per decade	1.05 (0.93–1.18)	0.454		
Race				
White	1.00			
Black	0.92 (0.58–1.45)	0.718		
Hispanic	0.79 (0.52–1.23)	0.298		
Asian or Pacific Islander	0.59 (0.26–1.33)	0.202		
Other or missing	0.66 (0.29–1.51)	0.327		
Patient location non-metropolitan	1.82 (1.01–3.26)	0.046	1.83 (1.02–3.29)	0.044
Median income of patient ZIP code				
First quartile (poorest)	1.10 (0.69–1.73)	0.697		
Second quartile	1.07 (0.68–1.68)	0.780		
Third quartile	1.23 (0.80–1.89)	0.350		
Fourth quartile (wealthiest)	1.00			
Missing	0.93 (0.51–1.71)	0.825		
Medicaid, self-pay, no charge or other as primary payer	0.68 (0.44–1.06)	0.086	0.68 (0.44–1.06)	0.087
Diabetes mellitus	1.30 (0.96–1.75)	0.093		
Charlson comorbidity index > 4	1.15 (0.81–1.63)	0.426		
Previous transplant failure or rejection	0.99 (0.73–1.34)	0.947		
Possible causes for heart failure				
Ischemic cardiomyopathy	1.77 (1.26–2.48)	0.001	1.77 (1.26–2.48)	0.001
Cardiomyopathy with no specified cause	1.00		1.00	
Other specified causes	1.38 (0.86–2.24)	0.185	1.38 (0.85–2.24)	0.188
Prior transplant	0.62 (0.16–2.52)	0.509		
Heart	0.36 (0.05–2.55)	0.304		

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	1.74 (1.14–2.68)	0.011		
No tissue-invasion	1.49 (0.86–2.57)	0.155	1.10 (0.64–1.91)	0.729
Possible tissue-invasion	2.30 (1.22–4.37)	0.010	2.02 (1.06–3.84)	0.032
Transplant failure or rejection	4.14 (2.82–6.07)	<0.001	3.96 (2.69–5.81)	<0.001
Increasing age at time of transplantation per decade	0.89 (0.80–0.99)	0.038		
Female sex	1.26 (0.90–1.77)	0.173		
Black race	1.45 (0.98–2.15)	0.064		
Patient location non-metropolitan	1.57 (0.85–2.89)	0.148		
Median income of patient ZIP code				
First quartile (poorest)	1.10 (0.70–1.74)	0.665		
Second quartile	1.03 (0.65–1.62)	0.906		
Third quartile	1.09 (0.71–1.69)	0.684		
Fourth quartile (wealthiest)	1.00			
Missing	0.96 (0.56–1.64)	0.872		
Expected primary insurance payer				
Medicare	1.05 (0.75–1.47)	0.766		
Private insurance	1.00			
Medicaid, self-pay, no charge, other or missing	1.14 (0.77–1.69)	0.510		
Charlson comorbidity index > 4	1.46 (1.05–2.02)	0.024		
Possible causes for heart failure				
Ischemic cardiomyopathy	0.96 (0.69–1.33)	0.797	0.93 (0.67–1.30)	0.677
Cardiomyopathy with no specified cause	1.00		1.00	
Other specified causes	1.56 (1.04–2.34)	0.031	1.43 (0.95–2.14)	0.085
Prior transplant	1.79 (0.79–4.05)	0.160		
Heart	2.12 (0.94–4.79)	0.071		
Other comorbidities (%)				
Hypertension	1.04 (0.76–1.43)	0.782		

Risk factor	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Valvular disease	1.16 (0.86–1.57)	0.321		
Hyperlipidemia	0.89 (0.66–1.19)	0.426		
Pulmonary circulation disease	1.14 (0.85–1.53)	0.384		
Diabetes mellitus	1.04 (0.77–1.41)	0.777		
Renal failure	1.50 (1.11–2.03)	0.008	1.46 (1.08–1.97)	0.014
Chronic pulmonary disease	1.30 (0.95–1.79)	0.099		
Depression	1.38 (0.98–1.93)	0.063		
Hypothyroidism	0.83 (0.54–1.27)	0.394		
Obesity	1.13 (0.76–1.68)	0.559		
Peripheral vascular disease	1.11 (0.69–1.79)	0.665		
Neurologic disorders	1.19 (0.72–1.96)	0.500		
Liver disease	1.39 (0.83–2.32)	0.211		
Drug abuse	1.53 (0.93–2.53)	0.094		
Alcohol abuse	1.26 (0.72–2.22)	0.423		
Psychoses	1.05 (0.49–2.23)	0.903		