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 through the use of 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 2280 adult heart transplant recipients from 2004 to 2010 through the use of 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 ($\leq$100 days) or delayed-onset (>100 days after transplant). Possible tissue invasion by CMV was determined through the use of codes for CMV pneumonitis, hepatitis, and gastrointestinal endoscopy. Multivariate analysis was performed with the use of Cox proportional hazards models.

Results. Delayed-onset CMV disease occurred in 7.5% (170/2280) and early-onset CMV disease occurred in 2.0% (45/2280) of heart transplant recipients. Risk factors for delayed-onset CMV disease included residence in a non-metropolitan locale (aHR. 1.8; 95% confidence interval [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 after 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.

HEART transplant recipients are at increased risk of developing cytomegalovirus (CMV) disease as the result of 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].

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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 the 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 after 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 because of 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 through the use of the United States Agency for Healthcare Research and Quality Healthcare Cost and Utilization Project 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 after transplant [1,6], we hypothesized that delayed-onset CMV disease (>100 days after transplant) in heart transplant recipients occurs more commonly than does 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 ($n = 2700$). These years were used to accrue 1 year of preexisting data to identify comorbidities and at least 1 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 Annual Hospital Survey ($n = 230$). We also excluded patients coded for CMV disease within 1 year before 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 1 year of heart transplant and during the transplant hospitalization were identified through the use of 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 through the use of ICD-9-CM diagnosis codes during hospitalizations within 1 year before transplant. Hospital readmissions were identified through the use of the encrypted patient-level identifier. New-onset CMV disease coded during readmission was identified by use of 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 by means of the discharge status variable. New-onset CMV disease and inpatient death were classified as either early-onset (occurring ≤100 days after transplant) or delayed-onset (>100 days after 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 with the use of univariate and multivariate Cox proportional hazards modeling. Only patients who survived >100 days after transplant and were not coded with CMV disease ≤100 days after 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 by means of 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 value of $P \leq .05$. All analyses were performed with the use of SAS version 9.2 (Cary, NC, United States).

RESULTS

Demographic and Clinical Characteristics

Our study cohort consisted of 2280 heart transplant recipients from 22 transplant centers in the United States (Table 2). The median age was 55 years, 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