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Decreased post-transplant survival among heart transplant recipients with pre-transplant hepatitis C virus positivity

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Abstract

BACKGROUND—Transplant centers are reluctant to perform heart transplantation in patients with hepatitis C virus (HCV) infection because augmented immunosuppression could potentially increase mortality. However, there have been few studies examining whether HCV infection reduces survival after heart transplantation.

METHODS—We used data from the the U.S. Scientific Registry of Transplant Recipients to perform a multicenter cohort study evaluating the association between recipient pre-transplant HCV status and survival after heart transplantation. Adults undergoing heart transplantation between January 1, 1993 and December 31, 2007 were eligible to participate.

RESULTS—Among 20,687 heart transplant recipients (443 HCV-positive and 20,244 HCV-negative) at 103 institutions followed for a mean of 5.6 years, mortality was higher among HCV-positive than HCV-negative recipients (177 [40%] vs 6,367 [31.5%]; $p = 0.0001$). After matching on propensity score, hospital and gender, the hazard ratio (HR) of death for HCV-positive heart transplant recipients was 1.32 (95% confidence interval [CI] 1.08 to 1.61). Mortality rates were higher among HCV-positive heart transplant recipients at 1 year (9.4% vs 8.2%), 5 years (26.3% vs 22.9%), 10 years (53.1% vs 43.4%) and 15 years (74.8% vs 62.3%) post-transplantation. HRs did not vary by gender or overall number of heart transplantations performed at the center.

CONCLUSIONS—Pre-transplant HCV positivity is associated with decreased survival after heart transplantation.

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Keywords

heart transplantation; HCV; survival; mortality; outcome; cohort study

The effect of pre-transplant-acquired hepatitis C virus (HCV) infection on survival is poorly understood among patients who have undergone heart transplantation. It has been hypothesized that post-transplant immunosuppression could worsen survival among these patients by accelerating progression of HCV-associated liver fibrosis and shortening the time to hepatic decompensation.^{1–3} In addition, this immunosuppression might exacerbate HCV-associated inflammation that could promote cardiac vasculopathy.^{1–3}

Due to these concerns, there has been reluctance to list HCV-infected candidates for heart transplantation unless they achieve virologic cure with anti-viral therapy.⁴ However, the combination of HCV therapy with pegylated interferon plus ribavirin is not without risk when given to heart failure patients. Pegylated interferon can exacerbate cardiac decompensation or arrhythmias, and ribavirin can induce anemia that may precipitate cardiac decompensation or coronary ischemia.^{5–8} Given the limited number of available cardiac organ donors, the possibility that HCV infection might adversely affect survival, and the morbidity associated with anti-viral therapy in the setting of heart failure, it is important to determine the effect of previously acquired HCV infection on mortality after heart transplantation.

There have been very few studies examining the impact of HCV infection on survival after heart transplantation, and the existing studies are limited by the small numbers of HCV-seropositive patients, lack of adjustment for confounding variables, and inclusion of patients who acquired HCV after heart transplantation.^{2,9} It is therefore critical to evaluate whether HCV-positive heart transplant recipients have higher mortality compared to those without infection. Thus, we conducted this retrospective study to evaluate whether pre-transplant recipient HCV positivity is associated with decreased survival after heart transplantation.

Methods

Data source

We used data from the Scientific Registry of Transplant Recipients (SRTR), which collects information on all donors, wait-listed candidates and transplant recipients in the USA, submitted by members of the Organ Procurement and Transplantation Network (OPTN), as described elsewhere.¹⁰ The Health Resources and Services Administration (HRSA) of the U.S. Department of Health and Human Services provides oversight on activities of the OPTN and SRTR contractors. All U.S. organ transplant programs, organ procurement organizations and histocompatibility laboratories are required to submit transplant data to the OPTN to maintain membership in the United Network of Organ Sharing (UNOS). The OPTN monitors compliance with data submission and since 1991 has conducted on-site data audits every 3 years for heart transplantation programs.¹¹ Prior audits have identified error rates of <1%.¹²

The SRTR database incorporates information from the OPTN, the Social Security Administration Death Master File, Centers for Medicare and Medicaid Services and Surveillance Epidemiology and End Results. Data undergo regular quality assurance checks and validations. A comparison with the National Death Index showed that SRTR captures >99% deaths.¹⁰

Our study was approved by the institutional review board of the University of Pennsylvania. The requirement for written consent was waived.

Study design and subjects

We conducted a retrospective cohort study to compare survival between HCV-seropositive and HCV-seronegative heart transplant recipients. All heart transplant recipients in the USA, aged 18 years or older, who were transplanted between January 1, 1993 and December 31, 2007, were eligible and followed up until August 1, 2008. This period coincides with the initiation of routine screening of organ transplant candidates for HCV antibodies and ensured at least 7 months of follow-up for all patients.

Recipients were considered HCV-positive if a positive result was recorded for HCV antibody status and HCV-negative if a negative result was recorded for HCV status. HCV RNA results are not collected by the SRTR and were therefore unavailable.

Patients were excluded if they: (1) did not have their HCV serostatus recorded; (2) were cared for at institutions that did not perform heart transplantation in HCV-positive candidates during the study period, as these institutions may be different from those that did in ways that could possibly relate to survival; (3) underwent multi-organ transplantation; (4) were positive for hepatitis B surface antigen; (5) were positive for human immunodeficiency virus (HIV) antibody; (6) received hepatitis B–positive (i.e., positive hepatitis B surface antigen or DNA) or hepatitis C–positive (i.e., positive HCV antibody) hearts, because findings have demonstrated that survival among these transplant recipients is worse¹³; and (7) died, underwent another heart transplantation, or were lost to follow-up within 30 days of the initial transplantation— as it is unlikely that such events would be related to HCV infection.

Study end-points

The primary outcome was time to all-cause mortality. Death date was determined using the date of death reported to the SRTR. Causes of death were collected, particularly those related to cardiac vasculopathy (i.e., myocardial infarction, cardiac arrest, arterial embolism, coronary artery disease, atherosclerosis, cardiogenic shock, ventricular failure) and hepatic decompensation.

Patient follow-up was defined as time from transplantation until date of death or last follow-up on their transplant anniversary. Because follow-up forms are due annually near the transplant anniversary, we censored patients on their last expected transplant anniversary. Biases relating to counting extra time for patients who had follow-up forms turned in early were therefore avoided.

Data collection

Recipient characteristics collected included: age; gender; race; body mass index; cardiac output; etiology of cardiomyopathy (ischemic vs non-ischemic); life-sustaining measures (inotropes, ventricular assist device, total artificial heart, intra-aortic balloon pump, extracorporeal membrane oxygenation, ventilator use); co-morbidities (diabetes mellitus, renal failure requiring dialysis, chronic obstructive pulmonary disease, malignancy); and cytomegalovirus (CMV) serostatus.

Donor variables included: age; gender; race; body mass index; tobacco use; illicit drug use within the prior 6 months; comorbidities (prior myocardial infarction, diabetes mellitus, renal insufficiency); CMV serostatus; and human T-lymphotropic virus serostatus.

Peri-transplant variables included: year of transplantation; ischemic time; institution where transplantation occurred; and location immediately prior to transplant (at home or hospitalized).

Statistical analysis

The *t*-test or Wilcoxon's rank sum test and chi-square test or Fisher's exact tests were used to compare continuous and categorical variables, respectively, between HCV-positive and HCV-negative heart transplant recipients, depending on distribution of the data.

To address incomplete and missing data, multiple imputation was performed to generate 10 complete data sets.^{14–16} We used all available data, including outcomes, to impute missing values on covariates. Conducting a proper imputation by this method necessitates repeating all subsequent analytical steps 10 times. These steps included developing a propensity score, nearest neighbor matching on propensity score and stratified analysis of the resulting matched data sets.

Given the large number of potential confounders relative to the number of deaths, a propensity score was developed to balance, or control for, these confounders.^{17,18} All recipient, donor and peri-transplant variables in Table 1, with the exception of HCV status and death, were considered for inclusion in the propensity model. Due to low prevalence among the study cohort, we excluded recipient history of renal insufficiency requiring dialysis, chronic obstructive pulmonary disease, malignancy and ventilator use; and donor history of prior myocardial infarction, diabetes mellitus, malignancy and human T-lymphotropic virus serostatus. Using logistic regression, a conditional probability of being HCV-positive, given a set of covariates and without regard to survival, was assigned to each patient. Because certain institutions had a disproportionate number of males compared with females, gender was excluded from the propensity model and was controlled for through matching.

Once the propensity score was developed based on patient-level factors, HCV-positive heart transplant recipients were matched on hospital, gender and propensity score (using nearest neighbor matching) with up to 4 HCV-negative recipients using the gmatch algorithm as implemented in SAS, version 9.2 (SAS Institute, Inc., Cary, NC).¹⁹ The same number of matches did not vary within strata formed by gender and hospital. HCV-positive recipients who did not have any suitable HCV-negative matches were excluded to avoid bias from having patient-level differences between the HCV-positive patients and their HCV-negative matches.

Unadjusted patient survival was estimated using Kaplan–Meier methods. Cox proportional hazards analysis was performed using the propensity-matched cohorts to determine the hazard ratio (HR) and 95% confidence interval (CI) of death between HCV-positive and HCV-negative recipients, stratified by institution and year.²⁰ In keeping with the requirements of multiple imputation, results from these 10 analytic processes were combined to the appropriate 95% CIs that accounted for within- and across-imputation components of variance.¹⁶ Sub-analyses compared survival between HCV-positive and HCV-negative recipients stratified by gender and overall number of heart transplants performed at the centers (low: <200 heart transplants; medium: 200 to 399; high: ≥400).

Sensitivity analyses were performed to evaluate HRs of death between HCV-positive and HCV-negative recipients: (1) among institutions that performed heart transplants in larger numbers of HCV-positive recipients (≥5 and ≥10); and (2) assuming that all patients lost to follow-up had died. We also examined the effect of potentially unmeasured confounders on the relative hazard of death.²¹

Assuming a 10-year median survival among HCV-negative patients,^{30,31} an accrual time of 13 years and an unexposed:exposed ratio of 4:1, we estimated that 400 HCV-positive heart transplant recipients would provide 80% power to detect a relative hazard of death of 1.2 between HCV-positive and HCV-negative recipients.

Results

Study cohort

Between January 1, 1993 and December 31, 2007, 45,220 patients underwent heart transplantation at 103 institutions. Based on inclusion and exclusion criteria, 20,687 (443 HCV-positive and 20,244 HCV-negative) were included in the analyses (Figure 1).

Baseline characteristics for the study cohort are listed in Table 1. There were significant differences in age, ventilator use, chronic obstructive pulmonary disease status, CMV donor and recipient serostatus, and year of transplantation between the HCV-positive and HCV-negative heart transplant recipients (Table 1).

Recipient HCV status and survival

The mean duration of follow-up was 5.6 years (5.4 years for HCV-positive vs 5.6 years for HCV-negative; $p = 0.34$). In the eligible cohort, overall mortality was higher among HCV-positive recipients, with a more pronounced effect with greater time from transplant. At the end of follow-up, 229 (51.7%) HCV-positive heart transplant recipients were alive, 177 (40.0%) died, 33 (7.5%) were lost to follow-up and 4 (0.9%) were retransplanted. Among the HCV-negative recipients, 12,296 (60.7%) were alive, 6,367 (31.5%) died, 1,341 (6.6%) were lost to follow-up, and 240 (1.2%) were retransplanted.

Recipient HCV status and survival in propensity-matched patients

A comparison between propensity-matched patients in the first imputed data set is given in Table 2. In contrast to the entire cohort, the propensity-matched patients were well matched for factors included in the development of the propensity score except for year of transplantation.

Figure 2 shows Kaplan–Meier curves for the propensity-matched cohort (first imputed dataset). Using Kaplan–Meier methods, mortality rates were higher among HCV-positive heart transplant recipients at 1 year (9.4% vs 8.2%), 5 years (26.3% vs 22.9%), 10 years (53.1% vs 43.4%) and 15 years (74.8% vs 62.3%) post-transplantation. Results in all 10 imputed data sets were quantitatively and qualitatively similar. After combining all 10 data sets, recipient HCV status was independently associated with decreased survival after heart transplantation (HR 1.32; 95% CI 1.08 to 1.61; Table 3).

Among the patients who died, 19.7% did not have cause of death reported, or the cause of death was reported as other. In the HCV-positive group, 16.4% died from events related to cardiac vasculopathy and 3.9% died from hepatic decompensation (Table 4). In the HCV-negative group, 15.2% died from events related to cardiac vasculopathy and 0.4% died from decompensated liver disease (Table 4).

Additional analyses

Survival between HCV-positive and HCV-negative recipients did not differ by gender ($p = 0.9$) or overall number of heart transplants performed at the centers ($p = 0.3$) (Table 3).

The relative hazards of death between HCV-positive and HCV-negative recipients among institutions that performed heart transplants on ≥ 5 HCV-positive recipients ($n = 31$ centers;

HR 1.43; 95% CI 1.14 to 1.80) and ≥ 10 HCV-positive recipients ($n = 10$ centers; HR 1.36; 95% CI 0.98 to 1.89) did not differ from that of the entire propensity-matched cohort. Sensitivity analyses performed assuming that all patients lost to follow-up ($n = 1,374$) had died yielded a relative hazard of 1.25 (95% CI 1.04 to 1.49). Sensitivity analyses to evaluate the effect of potentially unmeasured confounders showed that $>10\%$ prevalence of an unmeasured confounder and a >2 -fold difference in the association of the unmeasured confounder and death between the HCV-positive and HCV-negative groups would be necessary to make our results non-significant.

Discussion

In this propensity-matched analysis, we found that recipient HCV positivity was associated with increased mortality after heart transplantation, with a more pronounced effect with greater time from transplant. Neither recipient gender nor number of heart transplants performed at the centers altered this relationship. This finding was robust to a number of sensitivity analyses.

Our results differ from two prior studies that reported no increased risk of death among HCV-positive patients after heart transplantation. A retrospective cohort study by Lake and colleagues compared 96 HCV-positive and 7,302 HCV-negative heart transplant recipients and found that survival was similar between groups, although more liver-related deaths occurred in the HCV-positive group.⁹ A retrospective cohort study by Fong and colleagues compared 224 HCV-positive and 10,406 HCV-negative heart transplant recipients and demonstrated no association between recipient HCV status and survival in adjusted analyses.²

Our results might differ from these studies due to their smaller number of HCV-positive heart transplant recipients, shorter observation period, different confounding variables adjusted for in analyses, and inclusion of patients who acquired HCV after heart transplant and deaths that occurred within the first month after heart transplant.

There are several potential explanations for the decreased survival, which is more pronounced with time from transplant, observed among the HCV-positive heart transplant recipients. Our findings suggest that post-transplant immunosuppression might accelerate progression of HCV-associated liver disease to hepatic decompensation.^{1,3,22} However, an alternative explanation is that immunosuppression might exacerbate the chronic inflammation associated with chronic HCV infection and predispose to cardiac vasculopathy.²³

The increased risk of death among HCV-positive heart transplant recipients has important clinical implications for the care of HCV-infected patients being considered for heart transplantation. Patients chronically infected with HCV infection should be evaluated to determine their candidacy to receive anti-HCV treatment. Combination therapy with pegylated interferon plus ribavirin can produce virologic cure in 45% to 52% of HCV genotype 1 patients and 78% to 82% of HCV genotype 2 and 3 patients.⁵ However, data regarding safety of treatment in this population is extremely limited. Consequently, treatment should be administered with caution among heart transplant candidates because interferon could exacerbate heart failure or arrhythmias and ribavirin-induced anemia could precipitate coronary ischemia.⁵⁻⁸ Although sustained virologic response to anti-HCV therapy prior to heart transplantation might reduce the risk of death post-transplant, no studies have evaluated whether virologic cure confers a survival benefit among HCV-infected heart transplant candidates administered prior anti-viral therapy. As new direct-

acting anti-viral agents for chronic HCV infection are developed, regimens with fewer cardiac-related toxicities might become available for this patient population.

The current study has a number of strengths. It is the largest study investigation on the impact of recipient HCV status on survival after heart transplantation. The effect of pre-transplant recipient HCV status on survival was isolated by excluding hepatitis B–infected recipients as well as recipients who received hearts from donors positive for hepatitis B or C. Further, our analyses controlled for many important confounding variables that might influence survival after heart transplantation by using a propensity-score approach, and our results were robust to multiple sensitivity analyses.

There are several potential limitations to this study. First, identification of HCV infection was based on positive HCV antibody tests, because HCV RNA was unavailable, and it is possible that HCV-positive patients may have been negative for HCV RNA, either because they spontaneously cleared or were treated with anti-viral therapy and achieved virologic cure. However, in the general population, studies have indicated that up to 86% of patients with positive HCV antibody tests are viremic.^{24–26} Consequently, although it would be advantageous to have an accurate assessment of HCV viremia, we do not believe that the conclusions would be substantially altered with this additional information, as a minority of patients would be HCV antibody–positive and RNA-negative. Furthermore, if a greater proportion of HCV antibody–positive patients were RNA negative, this would further increase concern about transplanting patients with HCV infection. Information on receipt of HCV therapy prior to transplantation was unavailable, preventing evaluation of the impact of anti-HCV therapy on survival.

Second, as in all non-randomized studies, the possibility for unknown and unmeasured confounding exists. However, our results remained robust after performing sensitivity analyses to assess the effect of potentially unmeasured confounders.²⁷

Third, like other studies using large databases, data accuracy cannot be directly validated and missing data can be problematic. These issues might be less of a concern in studies using the SRTR because participation is mandatory for all transplant centers in the USA, and a system of electronic edits is in place to minimize inappropriate data entries. Finally, our results might not be generalizable to centers outside the USA, where different HCV genotypes predominate, or to centers excluded from our study because they did not perform heart transplantation in HCV-positive individuals.

In conclusion, in this study we have demonstrated a survival disadvantage for HCV-positive heart transplant recipients as compared with HCV-negative patients. It is unknown whether this finding alone should influence eligibility for transplantation. Nevertheless, based on the HCV-infected patients' decreased post-transplant survival, it is reasonable to scrutinize more closely candidates with HCV infection. Anti-viral therapy against chronic HCV might be considered with caution in an attempt to achieve virologic cure prior to heart transplantation. Further prospective trials would be valuable to determine: (1) whether patients who are HCV-seropositive and RNA-negative have similar survival to those who are HCV-seropositive and RNA-positive; and (2) the optimal management of HCV-infected individuals with advanced heart failure.

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Figure 1.
Inclusion of subjects in the study.

Figure 2. Kaplan-Meier plot comparing survival between hepatitis C-positive and hepatitis C-negative heart transplant recipients in a propensity-score-matched cohort (i.e., results from first imputed data set). HCV, hepatitis C virus.

Table 1

Baseline Characteristics of Heart Transplant Recipients in the Study Cohort, by HCV Status

Variable	HCV-positive (n = 443)	HCV-negative (n = 20,244)	p-value
Median age (years, IQR)	52.7 (44.5, 60.0)	54.9 (46.8, 60.8)	0.006
Missing	0 (0)	0 (0)	
Race (n, %)			
White	329 (74.3)	15,834 (78.2)	0.07
Black	77 (17.4)	2,771 (13.7)	
Other	37 (8.3)	1,634 (8.1)	
Missing	0 (0)	5 (0.02)	
Gender			
Male	343 (77.4)	15,637 (77.2)	0.93
Female	100 (22.6)	4,607 (22.8)	
Missing	0 (0)	0 (0)	
Median body mass index (kg/m ² , IQR)	25.8 (22.9, 28.8)	25.8 (23.0, 29.1)	0.17
Missing	8 (1.8)	271 (1.3)	
Median cardiac output (liters/min, IQR)	4.3 (3.4, 5.4)	4.3 (3.4, 5.3)	0.60
Missing	74 (16.7)	3,702 (18.3)	
Reason for transplant			0.37
Non-ischemic cardiomyopathy	233 (53.0)	10,240 (50.8)	
Ischemic cardiomyopathy	207 (47.0)	9,925 (49.2)	
Missing	3 (0.7)	79 (0.4)	
Hospitalized prior to transplant	252 (56.9)	11,528 (57.0)	0.98
Missing	0 (0)	0 (0)	
Ventilated prior to transplant	14 (3.2)	1,080 (5.3)	0.04
Missing	0 (0)	0 (0)	
Inotrope use prior to transplant	158 (35.7)	7,270 (35.9)	0.91
Missing	0 (0)	1 (0.005)	
Defibrillator implanted prior to transplant	129 (35.0)	6,533 (37.4)	0.35
Missing	75 (16.9)	2,801 (13.8)	
Ventricular assist device, total artificial heart, or intra-aortic balloon pump	67 (15.1)	2,664 (13.2)	0.23
Missing	0 (0)	0 (0)	
Diabetes mellitus	68 (18.1)	3,441 (19.5)	0.50
Missing	67 (15.1)	2,564 (12.7)	
Dialysis	11 (2.7)	389 (2.0)	0.36
Missing	36 (8.1)	1,283 (6.3)	
Chronic obstructive pulmonary disease	1 (0.3)	7 (0.04)	0.04
Missing	77 (17.4)	3,208 (15.8)	
Malignancy (no., %)	13 (3.4)	718 (4.0)	0.54
Missing	62 (14.0)	2,480 (12.3)	
Median ischemic time (minutes, IQR)	180 (138, 222)	180 (140, 220)	0.71
Missing (no., %)	18 (4.1)	1,260 (6.2)	

Variable	HCV-positive (n = 443)	HCV-negative (n = 20,244)	p-value
Cytomegalovirus serostatus			
Donor ⁺ /recipient ⁺	108 (46.6)	4,197 (39.1)	0.02
Donor ⁺ /recipient [−]	38 (16.4)	2,331 (21.7)	
Donor [−] /recipient ⁺	61 (26.3)	2,590 (24.1)	
Donor [−] /recipient [−]	25 (10.8)	1,621 (15.1)	
Missing	211 (47.6)	9,505 (47.0)	
Orthotopic heart transplants, by year			
1993	33 (7.5)	1,291 (6.4)	0.01
1994	23 (5.2)	1,447 (7.2)	
1995	40 (9.0)	1,472 (7.3)	
1996	29 (6.6)	1,300 (6.4)	
1997	25 (5.6)	1,432 (7.1)	
1998	52 (11.7)	1,385 (6.8)	
1999	25 (5.6)	1,312 (6.5)	
2000	32 (7.2)	1,378 (6.8)	
2001	31 (7.0)	1,443 (7.1)	
2002	29 (6.6)	1,381 (6.8)	
2003	22 (5.0)	1,382 (6.8)	
2004	33 (7.5)	1,346 (6.7)	
2005	22 (5.0)	1,385 (6.8)	
2006	34 (7.7)	1,431 (7.1)	
2007	13 (2.9)	859 (4.2)	
Missing	0 (0)	0 (0)	
Donor median age (years, IQR)	27.0 (19.0, 38.0)	28.0 (20.0, 41.0)	0.12
Missing	1 (0.2)	10 (0.05)	
Donor race			
White	323 (73.1)	14,878 (73.7)	0.93
Black	53 (12.0)	2,428 (12.0)	
Other	66 (14.9)	2,885 (14.3)	
Missing	1 (0.2)	53 (0.3)	
Donor gender			
Male	315 (71.1)	14,282 (70.5)	0.80
Female	128 (28.9)	5,962 (29.5)	
Missing	0 (0)	0 (0)	
Donor median body mass index (kg/m ² , IQR)	25.1 (22.2, 28.4)	24.9 (22.3, 28.3)	0.49
Missing	52 (11.7)	1,986 (9.8)	
Donor renal insufficiency	64 (14.5)	2,655 (13.1)	0.41
Missing	0 (0)	0 (0)	
Donor prior myocardial infarction	2 (0.5)	132 (0.7)	0.60
Missing	0 (0)	42 (0.2)	
Donor diabetes mellitus	9 (2.2)	361 (2.0)	0.67
Missing	42 (9.5)	1,715 (8.5)	

Variable	HCV-positive (<i>n</i> = 443)	HCV-negative (<i>n</i> = 20,244)	<i>p</i> -value
Donor malignancy	9 (2.2)	328 (1.8)	0.48
Missing	41 (9.3)	1,655 (8.2)	
Donor cigarette use	131 (32.6)	5,938 (32.2)	0.87
Missing	41 (9.3)	1,809 (8.9)	
Donor illicit drug use within 6 months	116 (29.1)	4,983 (27.1)	0.38
Missing	44 (9.9)	1,846 (9.1)	
Donor human T-lymphotropic virus serostatus	0 (0.0)	7 (0.04)	0.70
Missing	40 (9.0)	1,754 (8.7)	

Data expressed as number (%), unless otherwise noted. HCV, hepatitis C virus infection; IQR, interquartile range.

Table 2Baseline Characteristics of Heart Transplant Recipients in Propensity Score-matched Cohort, by HCV Status^a

Variable	HCV-positive (n = 430)	HCV-negative (n = 1,662)	p-value
Median age (years, IQR)	52.7 (45.2, 60.0)	54.2 (46.3, 60.1)	0.29
Race (no., %)			
Black	72 (16.7)	275 (16.5)	0.92
Other	358 (83.3)	1,387 (83.5)	
Sex			
Male	339 (78.8)	1,301 (78.3)	0.80
Female	91 (21.2)	361 (21.7)	
Median body mass index (kg/m ² , IQR)	25.8 (22.9, 28.8)	25.5 (22.7, 29.0)	0.80
Median cardiac output (liters/min, IQR)	4.3 (3.4, 5.4)	4.2 (3.3, 5.2)	0.20
Reason for transplant			0.81
Non-ischemic cardiomyopathy	223 (51.9)	873 (52.5)	
Ischemic cardiomyopathy	207 (48.1)	789 (47.5)	
Hospitalized prior to transplant	224 (56.7)	922 (55.5)	0.64
Ventilated prior to transplant	14 (3.3)	68 (4.1)	0.43
Inotrope use prior to transplant	154 (35.8)	561 (33.8)	0.42
Defibrillator implanted prior to transplant	139 (32.3)	561 (33.8)	0.58
Ventricular assist device, total artificial heart, or intra-aortic balloon pump	62 (14.4)	236 (14.2)	0.91
Diabetes mellitus	76 (17.7)	278 (16.7)	0.64
Dialysis	11 (2.6)	38 (2.3)	0.74
Chronic obstructive pulmonary disease	1 (0.2)	0 (0)	0.21
Malignancy	12 (2.8)	53 (3.2)	0.67
Median ischemic time (min, IQR)	178 (137, 222)	184 (140, 220)	0.31
Cytomegalovirus serostatus			
Donor ⁺ /recipient ⁺	192 (44.7)	735 (44.2)	
Donor ⁺ /recipient ⁻	77 (17.9)	299 (18.0)	0.99
Donor ⁻ /recipient ⁺	118 (27.4)	454 (27.3)	
Donor ⁻ /recipient ⁻	43 (10.0)	174 (10.5)	
Number (%) of orthotopic heart transplants, by year			0.02
1993	32 (7.4)	106 (6.4)	
1994	23 (5.4)	138 (8.3)	
1995	39 (9.1)	118 (7.1)	
1996	26 (6.1)	104 (6.3)	
1997	24 (5.6)	116 (7.0)	
1998	52 (12.1)	107 (6.4)	
1999	25 (5.8)	102 (6.1)	
2000	30 (7.0)	114 (6.9)	
2001	31 (7.2)	120 (7.2)	
2002	29 (6.7)	109 (6.6)	
2003	22 (5.1)	117 (7.0)	

Variable	HCV-positive (<i>n</i> = 430)	HCV-negative (<i>n</i> = 1,662)	<i>p</i> -value
2004	32 (7.4)	107 (6.4)	
2005	22 (5.1)	118 (7.1)	
2006	31 (7.2)	119 (7.2)	
2007	12 (2.8)	67 (4.0)	
Donor median age (years, IQR)	27 (19, 38)	27 (19, 39)	0.84
Donor race			
Black	51 (11.9)	200 (12.0)	
Other	379 (88.1)	1,462 (88.0)	0.92
Donor Sex			
Male	305 (70.9)	1164 (70.0)	0.72
Female	125 (29.1)	498 (30.0)	
Donor median body mass index (kg/m ² , IQR)	25.0 (22.0, 28.2)	24.8 (22.3, 28.1)	1.00
Donor renal insufficiency	59 (13.7)	219 (13.2)	0.77
Donor prior myocardial infarction	1 (0.2)	9 (0.5)	0.41
Donor diabetes mellitus	9 (2.1)	31 (1.9)	0.76
Donor malignancy	8 (1.9)	23 (1.4)	0.47
Donor cigarette use	141 (32.8)	534 (32.1)	0.79
Donor illicit drug use within 6 months	119 (27.7)	428 (25.8)	0.42
Donor human T-lymphotropic virus serostatus	0 (0)	1 (0.06)	0.61

Data expressed as number (%), unless otherwise noted. HCV, hepatitis C virus; IQR, interquartile range.

^aResults from first imputed dataset.

Table 3

Relative Hazards of Death Between HCV-positive and HCV-negative Heart Transplant Recipients in the Propensity-matched Cohort

Model	Hazard ratio (95% confidence interval)
Overall	1.32 (1.08, 1.61)
Stratified by gender	
Male	1.31 (1.05, 1.64)
Female	1.35 (0.91, 2.00)
Stratified by heart transplant volume	
Low	1.24 (0.93, 1.66)
Medium	1.19 (0.88, 1.61)
High	1.67 (1.15, 2.42)

Table 4**Causes of Death, by HCV Status**

Cause of death	HCV-positive (n = 177)	HCV-negative (n = 6,367)
Acid/base or fluid/electrolyte disorder	1 (0.6)	8 (0.1)
Cardiovascular: cardiac vasculopathy	29 (16.4)	970 (15.2)
Cardiovascular: other	3 (1.7)	172 (2.7)
Cerebrovascular	3 (1.7)	207 (3.3)
Diabetes	0 (0.0)	9 (0.1)
Graft failure or non-compliance	20 (11.3)	860 (13.5)
Hematologic	0 (0.0)	18 (0.3)
Hemorrhage	1 (0.6)	63 (1.0)
Hepatic decompensation	7 (3.9)	23 (0.4)
Infection	21 (11.9)	962 (15.1)
Malignancy	19 (10.7)	774 (12.1)
Multiorgan failure	22 (12.4)	458 (7.2)
Pancreatitis	0 (0.0)	19 (0.3)
Pulmonary	7 (3.9)	305 (4.8)
Renal failure	4 (2.3)	196 (3.1)
Trauma	5 (2.8)	70 (1.1)
Unknown or other	35 (19.8)	1,253 (19.7)

Data expressed as number (%). HCV, hepatitis C virus.