Heart Transplantation Outcomes in Patients With Hepatitis C Virus Infection:
Potential Impact of Newer Antiviral Treatments After Transplantation

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This study found significant improvements in heart transplant
outcomes and survival in patients with hepatitis C virus.

More than 185 million people worldwide, including more than 4 million in the U.S., are infected with the hepatitis C virus (HCV).[1] Because of the indolent nature of the disease, actual prevalence is underestimated.[2,3] Detection of HCV in people already infected is estimated to continue to increase over the next decade.[4] Although primary manifestations of the disease are the result of liver damage, HCV infection is a systemic illness. In a study of more than 19,000 patients, HCV infection was identified as an independent risk factor for development of heart failure.[5] In the U.S., prevalence of HCV infection in patients with heart failure is reported to be as high as 15%, much higher than the general population prevalence of 1.8%.[6] When first identified in 1989, HCV infection was considered incurable. Clinical trials have since found a steady improvement in outcome, and now the disease is considered curable in up to 90% of cases.[7]

Clinical outcomes of heart transplantation (HTx) historically have been inferior in patients with HCV infection.[8,9] The authors hypothesized that the literature on HTx outcomes has not accounted for the improvements in HCV infection treatment options that have occurred since the 1990s. In the study reported here, United Network of Organ Sharing (UNOS) data on adult HTx was used to evaluate clinical outcomes of HCV infection over 4 treatment eras.

MATERIAL AND METHODS

The authors analyzed UNOS data on adult HTx from January 1991 to March 2014. Two groups were created: patients with HCV infection (HC+) and non-infected patients (HC–). Eligible patients were aged > 18 years. Hepatitis C virus status was defined with antibody testing at time of HTx. Patients with multi-organ transplantation or with hepatitis B virus or HIV infection were excluded. For comparison of post-HTx survival, the 23-year study period was divided into 4 eras reflecting the evolution in HCV infection treatment options in the U.S. (Table 1). The first medication was interferon α (IFN-α), which was used alone (first era, 1991-1997) and then with the newly introduced ribavirin (second era, 1998-2000). The combination of IFN-α and ribavirin increased sustained virologic response rates, but the rates of adverse effects (AEs), such as cytopenia and depression, were high, and many patients could not tolerate the extended (48-week) regimen.[10,11]

Peginterferon, a long-acting IFN introduced in 2001, significantly increased adherence to 2-drug treatment for HCV infection, and its use in combination with ribavirin marked the third era (2001-2010). The fourth era (2011-2014) began with the introduction of direct-acting antiviral agents and their remarkable results. Since 2014, direct protease inhibitors without IFN found a dramatic impact on HCV treatment: fewer

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AEs, shorter treatment (24 weeks), and high (> 90%) sustained virologic response.[7,12,13]

Statistical Analysis

Categoric variables were analyzed with the χ^2 test or the Fisher exact test and are reported as percentages. Continuous variables were analyzed with the Student t test or the Wilcoxon rank sum test and are reported as means, medians, and SDs. Statistical significance was set at $P < .05$. Survival curves were plotted with the Kaplan-Meier method, and comparisons made with log-rank tests. Analysis was performed with SAS Version 9.3 (Cary, NC).

RESULTS

Between January 1991 and March 2014, adult HTx was performed 36,589 times, including 778 times (2.1%) in patients with HCV infection. There was no significant difference in percentage of HC+ patients who underwent HTx over the 4 treatment eras (first, 2.1%; second, 2.9%; third, 2.1%; fourth, 1.6%) (Table 2). Mean patient age for the HC+ and HC– groups was comparable. Percentage of African American patients was higher in the HC+ group than in the HC– group (18.9% vs 15.0%), as was percentage of patients of other race (11.2% vs 9.2%; $P = .0008$).

Regarding indications for HTx, ischemic (and nonischemic) cardiomyopathy was similar in prevalence between the 2 groups, but the "other" heart failure etiologies (congenital heart disease, valvular heart disease, postpartum cardiomyopathy, restrictive heart disease) were more prevalent in the HC+ group (12.9% vs 9.7%; $P = .013$). The HC+ group also had higher rates of tobacco use history (42.2% vs 40.1%; $P = .002$) and hypertension (23.1% vs 20.9%; $P = .014$). Mean (SD) bilirubin level at time of transplantation for the HC+ and HC– groups was comparable: 1.12 (1) mg/dL and 1.11 (1) mg/dL, respectively ($P = .707$). Of the heart donor variables (Table 3), only tobacco use history was significantly higher in the HC+ group (23.5% vs 19.8%; $P = .008$).

Survival Data

Mean (SD) overall follow-up was 6.2 (5.3) years (median, 5 years; range, 0-23.3 years) for all patients; 5.6 (4.3) years (median, 5.05 years; range, 0-23.2 years) for HC+ patients; and 6.2 (5.3) years (median, 6.1 years; range, 0-23.2 years) for HC– patients.

HC+ patients' survival rates were 82.5% (1 year),

Table 1. Hepatitis C Virus Infection Treatment Eras

Treatment Era	Newly Available Treatment
1991-1997	Interferon α
1998-2000	Ribavirin
2001-2010	Peginterferon
2011-2014	Direct protease inhibitors
2014-present[a]	Interferon free direct-acting antivirals

[a]Not included in study period.

64.4% (5 years), and 42.1% (10 years), and HC– patients' rates were 87.2% (1 year), 73.4% (5 years), and 54.7% (10 years). The HC+ group's inferior survival at 1, 5, and 10 years was statistically significant ($P < .0002$) (Table 4).

During the first era (1991-1997), HC+ patients' survival rates were 81.0% (1 year), 73.3% (2 years), and 61.4% (5 years), and HC– patients' rates were 85.0% (1 year), 80.6% (2 years), and 70.3% (5 years) ($P < .05$). During the second era (1998-2000), HC+ patients' rates were 79.1% (1 year), 74.6% (2 years), and 62.0% (5 years), and HC– patients' rates were 85.4% (1 year), 81.7% (2 years), and 72.0% (5 years) ($P < .05$). During the third era (2001-2010), HC+ patients' rates were 83.6% (1 year), 78.6% (2 years), and 66.8% (5 years), and HC– patients' rates were 88.4% (1 year), 84.6% (2 years), and 75.4% (5 years) ($P < .05$).

Survival data for the fourth treatment era (2011-2014) were available only for 1 and 2 years. HC+ patients' survival rates were 89.01% (1 year) and 81.89% (2 years), and HC– patients' rates were 91.00% (1 year) and 86.00% (2 years). The inferior survival found for the HC+ group during the 3 preceding eras was not found this era, during which HC+ and HC– patients had comparable rates of survival at 1 year (Figures 1 and 2).

Survival 1 year after HTx was compared between the HC+ and HC– groups over the 4 treatment eras (Figures 3 and 4). The HC+ patients' survival after HTx improved from 81% during the earliest era (1991-1997) to 89% during the latest era (2011-2014), whereas HC– patients' survival improved from 85% to 91% ($P = .9$).

Table 2. Patients' Baseline Characteristics

Variable	Hepatitis C Virus Infection		P Value
	Yes (N = 778)	No (N = 35,811)	
Transplantations by period, n (%) 1991-1997 1998-2000 2001-2010 2011-2014	 226 (2.1) 135 (2.9) 324 (2.1) 93 (1.6)	 10,523 (97.9) 4,586 (97.1) 14,957 (97.9) 5,744 (98.4)	.002
Mean (SD) age, y	51.2 (11.1)	51.9 (11.8)	.094
Male sex, n (%)	608 (78.2)	27,350 (76.4)	.248
Mean (SD) body mass index, kg/m^2	26.1 (4.5)	26.3 (4.7)	.530
Race, n (%) White African American Other	 544 (69.9) 147 (18.9) 87 (11.2)	 27,143 (75.8) 5,366 (15) 3,302 (9.2)	.0008
Indications for heart transplantation, n (%) Ischemic cardiomyopathy Nonischemic cardiomyopathy Other[a]	 344 (44.2) 334 (42.9) 100 (12.9)	 16,077 (44.9) 16,243 (45.4) 3,491 (9.7)	.013
Pretransplantation morbidities, n (%) Hypertension Diabetes Tobacco use history Cerebrovascular disease Mean (SD) baseline creatinine level, mg/dL Mean (SD) total serum bilirubin mg/dL	 180 (23.1) 149 (19.2) 330 (42.2) 43 (5.5) 1.33 (0.61) 1.12 (1.4)	 7,001 (20.9) 6,828 (19.1) 14,356 (40.1) 1,707 (4.8) 1.31 (0.59) 1.11 (2.7)	 .014 .982 .002 .616 .305 .707
LVAD support at transplantation, n (%)	106 (13.6)	4,072 (11.4)	.209
IABP at transplantation, n (%)	39 (5)	1,974 (5.5)	.545
ICU admission before transplantation, n (%)	298 (37.1)	14,027 (39.2)	.299
On ventilator at transplantation, n (%)	9 (1.2)	877 (2.5)	.020
History of malignancy, n (%)	27 (3.5)	1,578 (4.4)	.450
UNOS listing status at transplantation, n (%) 1A 1B Status 2	 398 (51.2) 169 (21.7) 210 (28.2)	 18,432 (51.5) 8,973 (25.1) 8,351 (23.3)	.098
Mean (SD) total cold ischemia time, h	3.07 (0.97)	3.03 (0.98)	.265

Abbreviations: IABP, intra-aortic balloon pump; ICU, intensive care unit; LVAD, left ventricular assist device; UNOS, United Network of Organ Sharing.
[a]Congenital heart disease, valvular heart disease, postpartum cardiomyopathy, or restrictive heart disease.

Hepatic decompensation leading to death was uncommon, but the rate was significantly higher (P = .0001) in the HC+ group (2.8%) than in the HC– group (0.6%).

DISCUSSION

HCV infection is a risk factor for the development of cardiovascular illness and advanced heart failure. Given the worldwide prevalence of HCV infection, more HC+ patients will be evaluated for HTx in the future.[2-4] Significant progress has been made in HCV infection treatment since the virus was first described. What was once incurable now has up to a 90% cure rate with newer treatment options.[7,12,13] The present study findings showed consistent improvement in HC+ patients' post-HTx survival during each treatment era. During the latest era, HC+ and HC– patients' post-HTx survival was statistically similar.

It is possible that HC+ patients' improvement in post-HTx survival could have resulted from improvement in overall post-HTx survival.[14] Over the 23-year study period, the survival rates of both groups (HC+, HC–) improved, likely secondary to improved immunosuppression and perioperative care, but the magnitude of improvement was more pronounced in the HC+ group. HC+ patients' post-HTx survival improved from 81% during the earliest era (1991-1997) to 89% during the latest era (2011-2014), whereas HC– patients' survival improved from 85% to 91%. The improvement in HC+ patients' short-term survival over the study period was substantial but did not reach statistical significance (P = .9).

Over the study period, the percentage of HC+ patients who underwent HTx remained low, ranging from 2.9% during the second era (1998-2000) to 1.7% during the fourth era (2011-2014). Overall, only 2.2% of study patients were HC+ at time of transplantation—a rate similar to previously reported rates.[8,15] This rate likely represents a selection bias for HTx listing, in which patients with nearly normal liver function were selected for HTx, as evident by normal bilirubin levels in both groups. In the present study, a high proportion of HC+ patients were not white. This distribution also was noted in epidemiologic studies of HCV infection by ethnicity.[6] In the U.S., the highest prevalence of HCV infection was noted in African Americans and the lowest in whites. According to the U.S. census report, African Americans constitute 12% of the total U.S. population,[16] whereas 22% of HC+ patients are African American.[1]

It has been postulated that the immunosuppression that accompanies the post-HTx state accelerates

Table 3. Heart Donor Characteristics

Variable	Hepatitis C Virus Infection		P Value
	Yes (N = 778)	No (N = 35,811)	
Mean (SD) age, y	31 (12.3)	31.0 (12.3)	.887
Male sex, n (%)	569 (73.1)	25,217 (70.4)	.100
Mean (SD) donor body mass index, kg/m²	25.9 (4.9)	26 (5.0)	.681
Race, n (%)			.225
White	558 (71.7)	25,514 (71.3)	
African American	87 (11.2)	4,671 (13.0)	
Other	133 (17.1)	5,626 (15.7)	
Cause of brain death, n (%)			.801
Anoxia	92 (11.8)	3,887 (10.9)	
Cerebrovascular	199 (25.6)	9,108 (25.4)	
Head trauma	440 (56.5)	20,307 (56.7)	
Central nervous system tumor	6 (0.8)	320 (0.9)	
Other	41 (5.3)	2,181 (6.1)	
CPR before brain death, n (%)	28 (3.6)	1,165 (3.3)	.101
Social history, n (%)			
Tobacco use	183 (23.5)	7,106 (19.8)	.008
Illicit drug use	150 (19.3)	6,811 (19.0)	.128
Heavy alcohol use	128 (16.5)	4,950 (13.8)	.107
CDC high risk	28 (3.6)	1,575 (4.4)	.053

Abbreviation: CPR, cardiopulmonary resuscitation.

HCV disease progression and shortens HC+ patients' survival.[17,18] These concerns were not validated in the most recent studies of kidney, liver, and heart transplantation in HC+ patients.[15,19,20] Furthermore, where post-HTx cause of death was examined in HC+ patients, death was attributed primarily to post-HTx malignancy and bacterial sepsis but seldom directly to hepatic failure. In a study in which liver function was serially monitored after HTx in 11 HC+ patients, immunosuppression did not affect HCV disease progression, and there was no liver function impairment.[15] In the same study, the 3 more recent HTx patients (of the 11) had their serial HCV viral load monitored. Viral load remained steady in 2 of the patients and decreased in the third. Similarly, there has been a theoretical concern that heightened immunologic status in HC+ patients might lead to more frequent rejection episodes. However, this concern has not been substantiated in reported studies.[21,22] In the present study, the rate of graft failure as the cause of death

Figure 1. Survival of Patients With Hepatitis C Virus Infection by Treatment Era
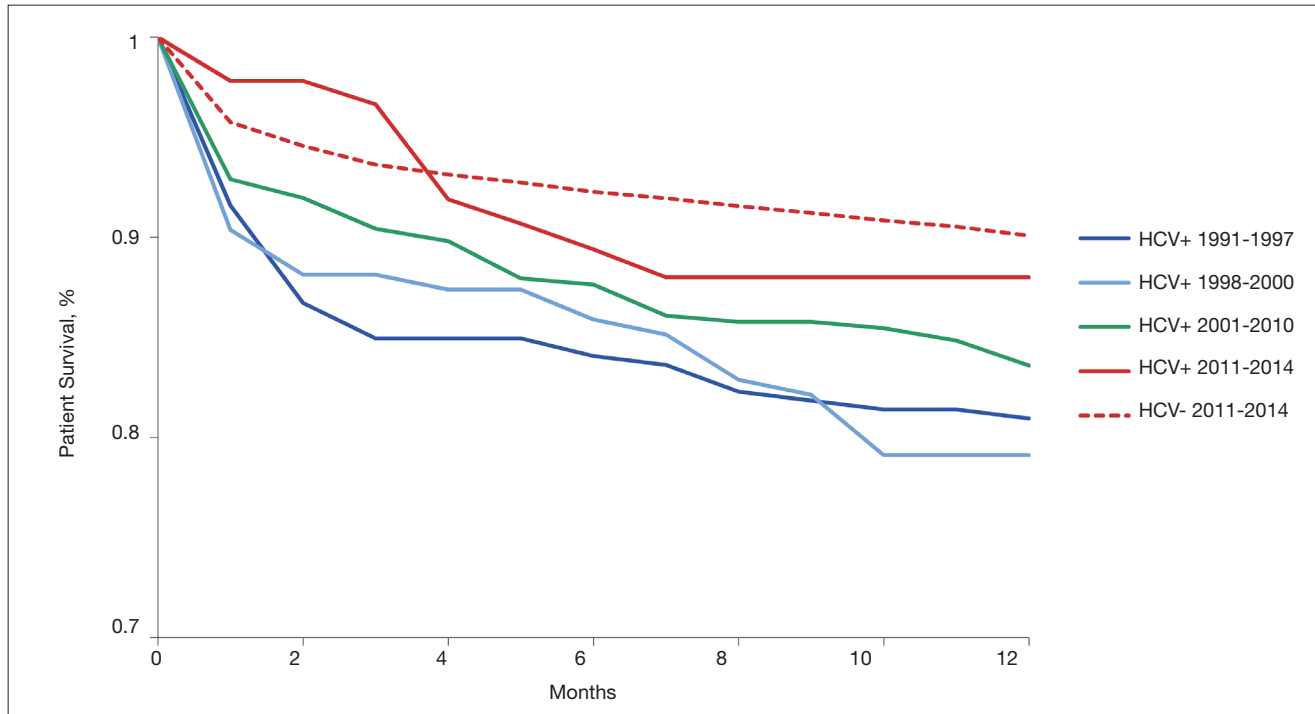
Abbreviation: HCV, hepatitis C virus.

Figure 2. Survival of Patients Without Hepatitis C Virus Infection by Treatment Era
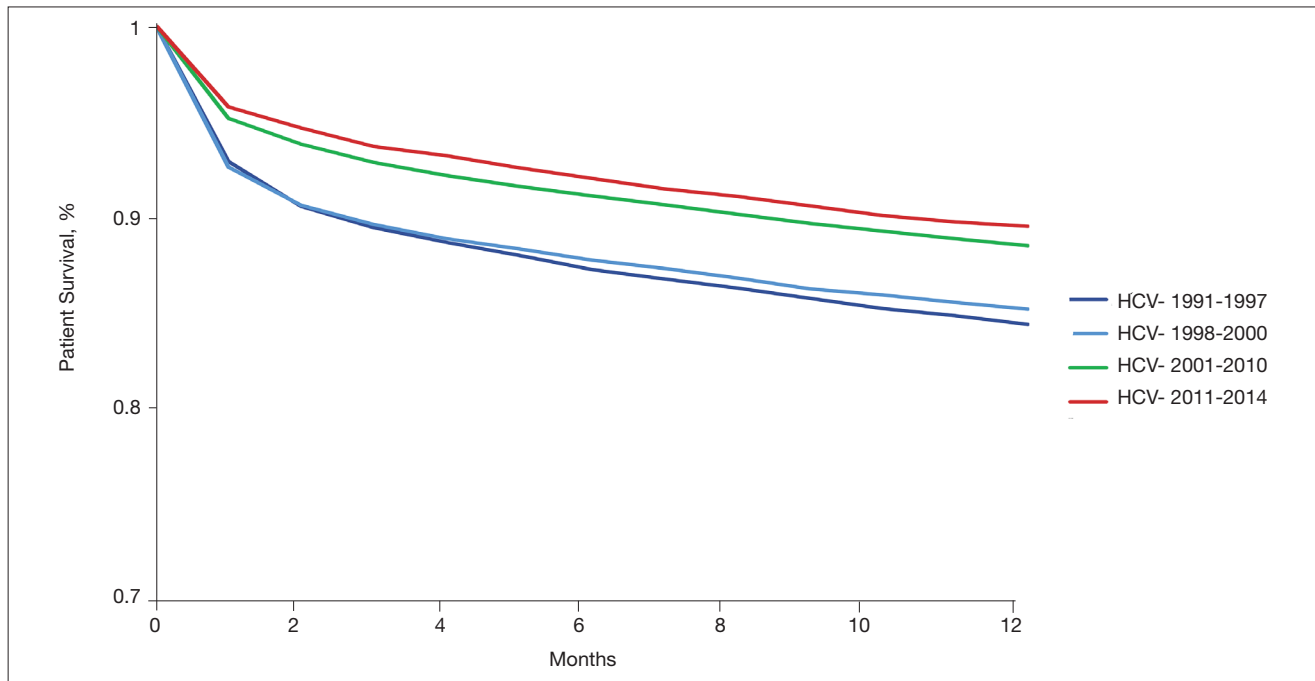
Abbreviation: HCV, hepatitis C virus.

was 11.2% in HC+ patients and 13% in HC– patients, though the difference was not statistically significant. Thus, concerns about HCV reactivation during immunocompromise or during increased allograft rejection were not substantiated.

Vasculopathy is a leading cause of morbidity and mortality after HTx and seems to be influenced by HC+. In a study of HC+ donor hearts transplanted to HC– patients, the prevalence of HCV infection in the recipients was 75% at a mean follow-up of 4.2 years.[23] Serial angiogram showed coronary vasculopathy in 46% of HC+ patients and 24% of HC– patients 3.2 years after HTx.[23] Similar concerns were raised in another small study, in which 2 of 4 HC+ patient deaths at 3.7-year follow-up were attributed to cardiovascular causes with features similar to those of transplantation vasculopathy.[24] Those findings contrast with the present findings of cardiovascular deaths in 17.6% of HC+ patients and 17.2% of HC– patients. Outcomes similar to the present outcomes were reported by Lee and colleagues: Post-HTx cardiovascular deaths occurred in 16.4% of HC+ patients and 15.2% of HC– patients.[8]

Survival data on HC+ patients who undergo HTx are mixed, with some studies finding similar short-term and midterm post-HTx survival[21,22] and others finding decreased survival.[8,9] It is difficult to interpret survival results from these studies, as some have included HCV infection that developed after HTx,[9] and others have excluded early postoperative deaths from analysis.[21] In addition, in the larger of these studies, which spanned 15 years, propensity matching was used for survival analysis. [8]

It is possible that the selection and treatment of HC+ patients who were awaiting or underwent HTx changed over the study period. Thus, it might not be accurate to compare HTx outcomes of patients without considering the significant progress that has been made in the management of HCV infection. Although the present study's aggregate (23-year) post-HTx survival results at 1, 5, and 10 years were similar to those reported in large series of HC+ patients who underwent HTx, the present early and intermediate survival results showed consistent improvements over time.[8,9] This improvement in survival of HC+ patients was not examined in previous studies.

In the present study, the distribution of causes of post-HTx deaths was diverse (Table 5). Although the leading causes of death were cardiovascular or were related to sepsis or multi-organ failure, deaths attributed to liver failure were uncommon. Only 2.8% of
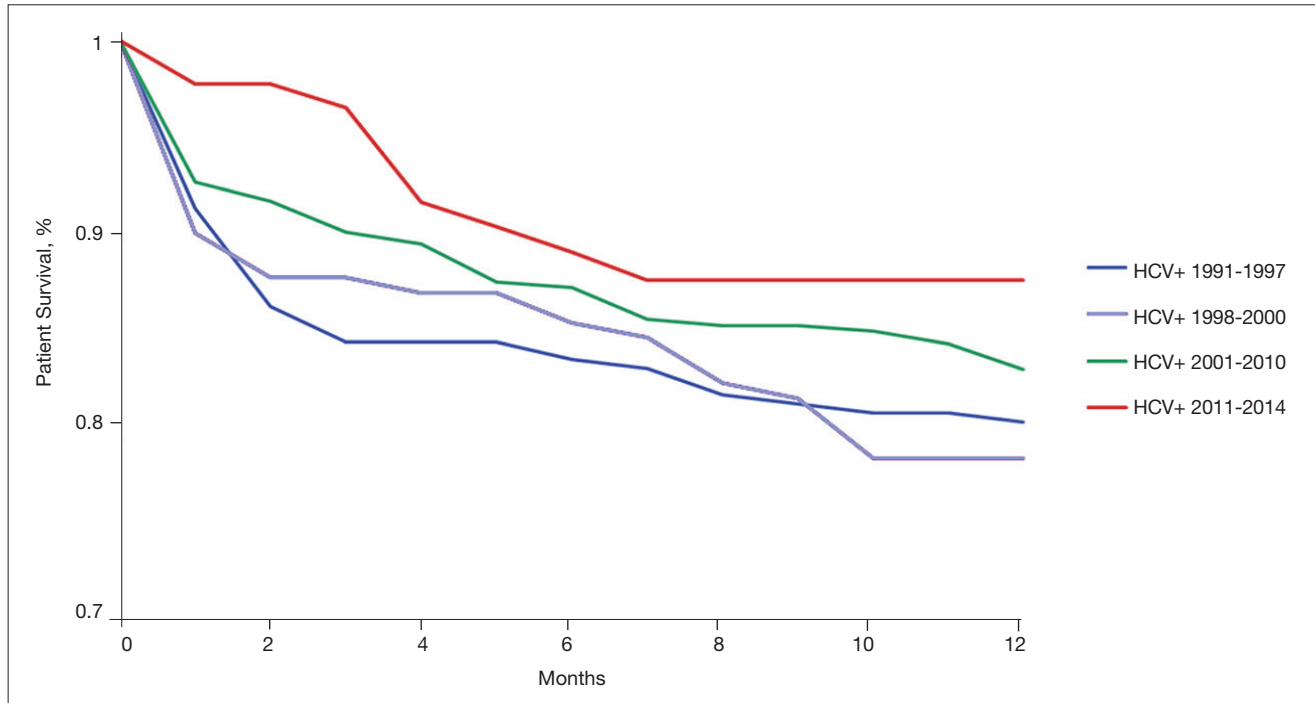
deaths in the HC+ group and 0.6% of deaths in the HC– group were attributed to liver failure ($P \le .001$). These findings are similar to the cause-specific mortality reported in the literature.[8,9,15,22] It is possible that these mortality results may be secondary to selection of patients with preserved liver function.

### Future of HCV Infection and Heart Transplantation

Modern diagnostic methods will be used to accurately assess HC+ patients for HCV disease burden, and treatment will be provided before HTx is performed. Historically, the major limitations to treating HC+ patients awaiting HTx have been the long (48 week) duration of therapy and the anemia that can exacerbate heart failure symptoms and shorten the safe HTx waiting time.[25] Most of the HCV

Table 4. Survival After Heart Transplantation by Serostatus and Transplantation Era[a]

Variable	Hepatitis C Virus Infection		P Value
	Yes, % (N = 778)	No, % (N = 35,811)	
Survival, y			
1	82.5	87.2	.0002
5	64.4	73.4	< .001
10	42.1	54.7	< .001
1 y survival by transplantation period			
1991-1997	81.0	85.0	.077
1998-2000	79.1	85.4	.064
2001-2010	83.6	88.4	.008
2011-2012	89.0	91.0	.608
2 y survival by transplantation period			
1991-1997	73.3	80.6	.006
1998-2000	74.6	81.7	.046
2001-2010	78.6	84.6	.003
2011-2012	81.9	86.0	.564
5 y survival by transplantation period			
1991-1997	61.4	70.1	.002
1998-2000	62.0	72.0	.015
2001-2010	66.8	75.4	.0005
2011-2012	NA	NA	—
10 y survival by transplantation period			
1991-1997	37.4	51.0	< .001
1998-2000	40.3	54.5	.001
2001-2010	46.9	57.7	.0003
2011-2012	NA	NA	—

Abbreviation: NA, not applicable.
[a]Data are percentages.

Figure 3. Survival Improvements in Patients With Hepatitis C Virus Infection by Treatment Era

Abbreviation: HCV, hepatitis C virus.

Figure 4. Survival Improvement in Patients Without Hepatitus C Virus Infection by Treatment Era
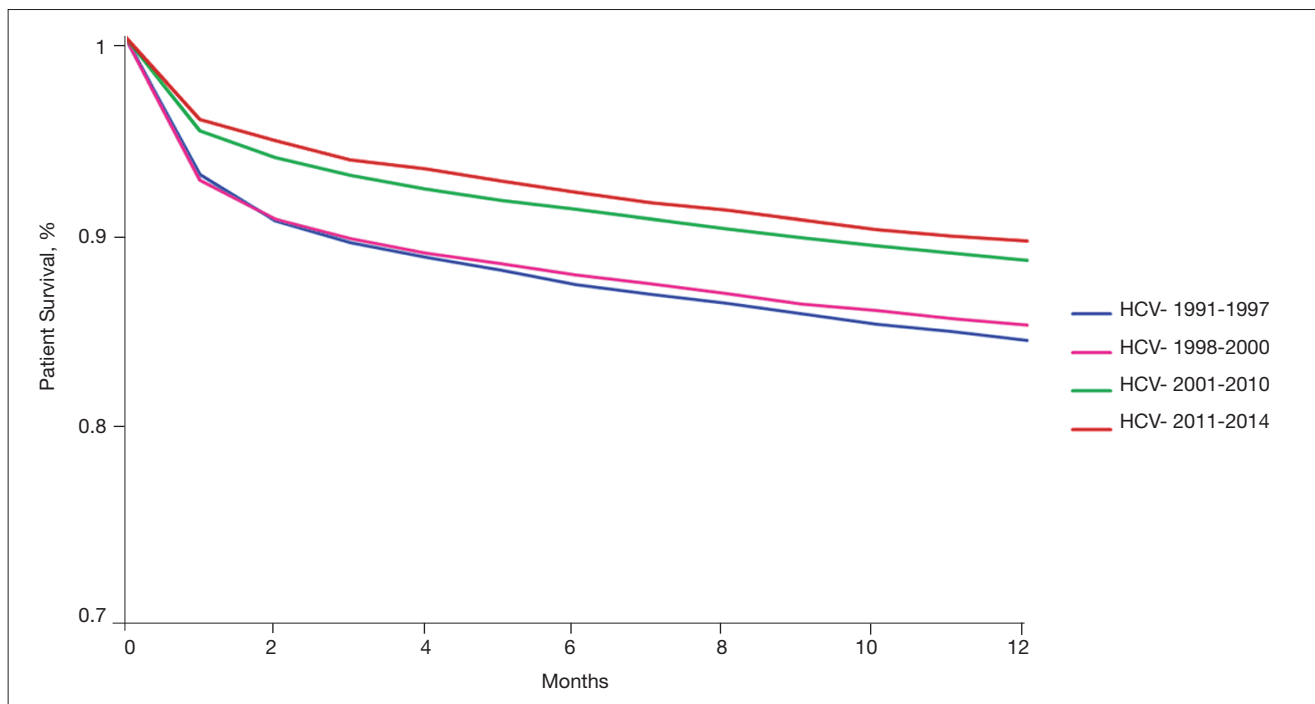
Abbreviation: HCV, hepatitis C virus.

treatment AEs have been attributed to use of IFN-α. Newer HCV treatments (direct-acting protease inhibitors without IFN) are of shorter duration (24 weeks) and have fewer AEs and higher cure rates. Most important, these treatments obtain similar cure rates irrespective of viral load, viral genotype, patient race, and previous HCV response status.[7,12,13]

Authors researching other solid-organ transplantation (eg, liver, kidney) have studied HCV pretreatment and found sustained virologic response before and after transplantation.[26,27] Although these studies were conducted before the advent of direct-acting protease inhibitors, the feasibility of treating HCV before transplantation has been demonstrated.

Limitations
The limitations of retrospective data analysis are applicable to the present findings. Although HTx is infrequently performed in HC+ patients, the authors used a large national database and a 23-year study period and thus were able to gather a significant number of patients and perform meaningful statistical analysis. HCV disease burden, which influences disease progression, is much better quantified with recent quantitative viral loads, but these were not available in the UNOS database. It should be noted that UNOS does not gather information on HCV genotypes or forms of treatment received, both of which influence treatment response and prognosis. It is therefore not possible to elucidate, from the UNOS database, the influences of virus genotype and treatment response on post-HTx outcomes.

CONCLUSION
The treatment of HCV infection has significantly evolved since the virus was identified in 1989. At first the disease was considered incurable, but now a > 90% cure rate is possible with newer treatment regimens. This study found significant improvements in post-HTx outcomes in HC+ patients between 1991 and 2014. Both HC+ and HC– patients have had similar post-HTx clinical outcomes in recent years. The noted improvements in post-HTx survival in HC+ patients may be secondary to better patient selection or more effective antiviral treatments. Future studies will provide the answers. ●

Table 5. Cause of Death by Serostatus[a]

| | Hepatitis C Virus Infection | | | |
| | Yes | | No | |
Causes of Death	n	%	n	%
Cardiovascular	87	17.6	3,190	17.2
Cerebrovascular	11	2.2	682	3.7
Graft failure	55	11.2	2,418	13
Hemorrhage	13	2.6	362	2
Hepatic decompensation	14	2.8	108	0.6
Infection	56	11.5	2,432	13
Malignancy	36	7.3	1,939	10.4
Multiple organ failure	51	10.3	1,457	7.8
Nonadherence	11	2.2	214	1.1
Pulmonary	30	6.1	1,124	6.1
Renal failure	23	4.7	985	5.3
Unknown/other	106	21.5	3,663	19.7

[a]All Ps < .0001.

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