

Impact of Hepatitis C Virus on Renal Transplantation: Association With Poor Survival

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ABSTRACT

Data concerning the effect of hepatitis C virus (HCV) infection on the long-term outcome of patient and allograft survival are conflicting. We performed a retrospective study including all renal transplant recipients who underwent the procedure at our center between July 1983 and December 2004. We compared HCV-positive ($n = 155$) versus HCV-negative ($n = 1044$) recipients for the prevalence of anti-HCV, patient/donor characteristics, and graft/patient survival. The prevalence of HCV-positive patients was 12%. The anti-HCV positive recipients displayed a longer time on dialysis ($P < .001$), more blood transfusions prior to transplant ($P < .001$), and a higher number of previous transplants ($P < .001$). There were no differences in the incidence of acute rejection between the two groups. Patient ($P = .006$) and graft survival ($P = .012$) were significantly lower in the HCV-positive than the HCV-negative group. Graft survival censored for patient death with a functioning kidney did not differ significantly between HCV-positive and HCV-negative recipients ($P = .083$). Death from infectious causes was significantly higher among the HCV-positive group ($P = .014$). We concluded that HCV infection had a significant detrimental impact on patient and renal allograft prognosis. Death from infectious causes was significantly more frequent among HCV-positive than the non-HCV population.

HEPATITIS C VIRUS (HCV) infection is relatively common among dialysis patients. Although there are marked geographical differences in prevalence, it is always higher than in the general population. The prevalence of HCV depends on the center, country, geographic origin of the recipient, race, history of intravenous drug abuse, modality and duration of dialysis therapy, retransplantation, presence of anti-hepatitis B core antigen, and number of blood transfusions. In Mediterranean countries, the prevalence of HCV infection among dialysis patients is usually higher than 20%.¹⁻³

With the improving results of organ transplantation, numerous studies have shown that liver dysfunction is a major cause of morbidity and mortality in immunosuppressed renal recipients. Liver disease is frequently associated with viral infections, usually hepatitis C virus.^{4,5} Liver failure is the cause of death in 8% to 28% of long-term graft survivors.^{2,5} The effects of immunosuppressive therapy on the natural history of HCV infection are unknown, and impact on patient and allograft survivals remains controversial. Some, but not all studies, have detected significant differences in patient survival between recipients with and

without anti-HCV antibodies.⁶⁻⁹ We analyzed the prevalence of HCV among our recipients and its impact on graft and patient survivals.

PATIENTS AND METHODS

From July 1983 to December 2004, 1297 end-stage renal disease patients underwent renal transplantation at our center. We retrospectively evaluated the clinical courses of all patients who displayed positive anti-HCV antibody who underwent primary or repeat grafts. Anti-HCV status was determined before or after transplantation by a second- or third-generation enzyme immunoassay, depending on the era of transplantation. In our center, the recent test only became available since 1990.

The outcome of 155 HCV-positive patients was compared with that of 1044 non-HCV patients who were recruited during the same period. Immunosuppression was similar in the two groups. Among

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hepatitis C-positive patients the use of polyclonal and monoclonal antibodies was reserved for immunologically high-risk patients. All patients had no clinical evidence of chronic active hepatitis or cirrhosis before transplantation.

Statistical analyses for group comparisons were chi-square or Student's *t* tests as appropriate. The survival functions of patient and graft as well as death-censored outcomes were studied using Kaplan-Meier analysis with the log-rank or the multiple comparison test. Values of *P* < .05 were considered significant. Cox's proportional hazards regression model was used to assess the independent effect of HCV infection on patient and graft survival, estimating hazard ratios (HR) of death or graft failure with their 95% confidence intervals (95% CI) after controlling for gender, age at transplantation date, previous time on dialysis, and number of renal transplants. Primary outcome analyses focused on patient survival and graft survival. In a first analysis, graft loss was defined as loss of graft function, resulting in the need to restart dialysis, of retransplantation, or death. Graft survival was performed without censoring data for patients who died with functioning grafts. An additional analysis was performed after censoring data on patients who died with a functioning allograft (graft survival censored for patient death).

Statistical inferences were derived using the SPSS software package, version 12.0 (SPSS Inc, Chicago, Ill).

RESULTS

The HCV serologic status was unknown in 98 (7.5%) patients, positive in 155 (12%), and negative in 1044 (80.5%). Patients with unknown HCV serologic status were excluded from further study. Fourteen of the HCV-positive patients (9%) were simultaneously hepatitis B surface antigen positive.

Table 1 summarizes the demographic data for HCV-positive and HCV-negative groups as well as the donor characteristics. Time on dialysis previous to the transplant

Table 1. Demographic Characteristics of HCV-Positive and HCV-Negative Patients

	HCV+ (n = 155)	HCV- (n = 1044)	<i>P</i>
Age (y)	40.2 ± 11.5	37.7 ± 13.5	.018
Gender, male (%)	57.4	59.7	.656
Number of Renal Transplants 1/≥2	128/27	955/89	<.001
Duration of dialysis (mo)	90.3 ± 59.3	42.1 ± 39.2	<.001
Number of blood transfusion	9.8 ± 12.8	2.7 ± 4.7	<.001
Donor age (y)	28.3 ± 14.5	31.9 ± 15.6	.006
Donor gender, male (%)	76.6	70.9	.188
Number of donor cadaver/living	154/1	1112/32	.146
Cold ischemia (h)	24.2 ± 4.5	23.6 ± 4.7	.215
Acute rejection (%)	26.5	25.4	.853
Occurrence of acute tubular necrosis	71 (45.8%)	339 (32.5%)	.001
HLA A mismatch	1.19 ± 0.66	1.11 ± 0.68	.187
HLA B mismatch	1.27 ± 0.66	1.21 ± 0.69	.303
HLA DR mismatch	0.60 ± 0.65	0.58 ± 0.62	.697
Total HLA mismatch	3.03 ± 1.27	2.87 ± 1.31	.156

P-values shown are the differences between the two groups.

Table 2. Prevalence of Anti-HCV and Time of Onset of Chronic Dialysis Therapy

Onset of Dialysis (year)	HCV+ (n = 155), %	HCV- (n = 1044), %
before-1977	7.10	0.57
1978-1982	23.87	3.93
1983-1987	38.06	15.90
1988-1992	18.06	26.92
1993-1997	9.03	29.21
1998 or later	3.88	23.47

was significantly higher among the HCV-positive than the HCV-negative group (90.3 ± 59.3 vs 42.1 ± 39.2 months, *P* < .001). The number of blood transfusions prior to transplantation was larger among HCV-positive patients: 9.8 ± 12.8 vs 2.7 ± 4.7 (*P* < .001). The HCV-positive recipients included a higher number of retransplants (*P* < .001) and more frequent occurrence of acute tubular necrosis (ATN) (*P* = .001). HCV-positive recipients were also older (40.2 ± 11.5 vs 37.7 ± 13.5 years, *P* = .018) and their donors younger (28.3 ± 14.5 vs 31.9 ± 15.6 years, *P* = .006) compared with the HCV-negative group. No significant differences were observed in patient or donor gender, cadaver/living source, cold ischemia time, or HLA mismatch.

There was no significant difference in the incidence of acute rejection between the groups: 26.5% in HCV-positive group vs 25.4% in HCV-negative group (*P* = .853).

Analyzing the groups according to the year the patients started dialysis (Table 2) showed that most HCV-positive patients started dialysis before the availability of tests for HCV: 87% of HCV-positive recipients began dialysis before 1993 versus 47.3% of the HCV-negative group.

Actuarial patient survivals at 1, 5, and 10 years were 97.4, 90.5, and 83.6% for the HCV-positive group and 97.3, 95.2, and 88.7% for the HCV-negative group, respectively (Fig 1). Actuarial graft survivals at 1, 5, and 10 years were 88.9, 78.6, and 64.9% for HCV-positive patients and 90.1, 84.3, and

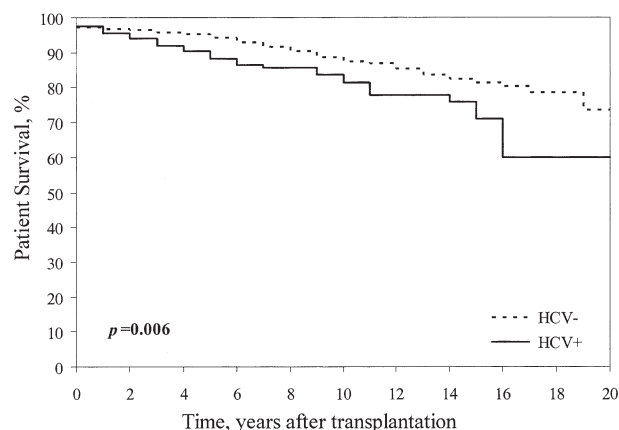


Fig 1. Kaplan-Meier estimate of the cumulative probability of patient survival.

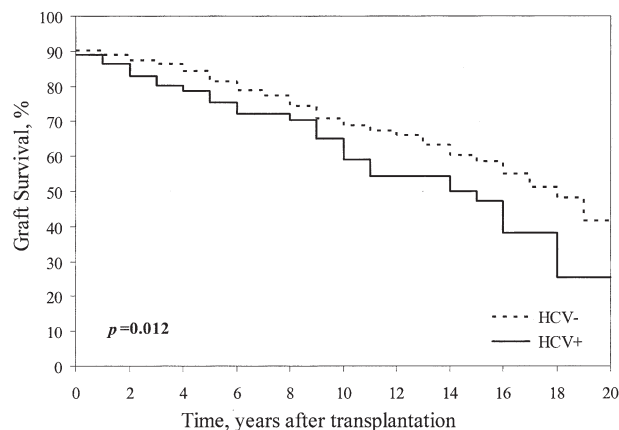


Fig 2. Kaplan-Meier estimate of the cumulative probability of graft survival.

70.9% for HCV-negative patients, respectively (Fig 2). When observations were censored for patient death with a functioning kidney, actuarial graft survival at 1, 5, and 10 years was 89.6, 83.8, and 75.4% for the HCV-positive group and 91.7, 87.2, and 79.0% for HCV-negative group, respectively (Fig 3).

Figures 1, 2, and 3 show patient, graft, and censored graft survival curves for the HCV-positive and HCV-negative groups. Patient ($P = .006$) and graft survivals ($P = .012$) in the HCV-positive group were significantly lower than those in the HCV-negative group. Graft survivals censored for patient death with a functioning kidney (death-censored graft survival) did not differ significantly between the HCV-positive and HCV-negative recipients ($P = .083$).

In a multivariate analysis with renal allograft survival as a dependent variable using Cox's proportional hazards model, infection with HCV was an independent predictor of graft failure ($P = .025$; HR = 1.382; 95% CI = 1.041–1.835), as well as occurrence of ATN ($P < .001$; HR = 1.973; 95% CI = 1.575–2.472) and acute rejection ($P < .001$; HR = 1.734; 95% CI = 1.379–2.181). Gender, age at time of grafting, prior time on dialysis and number of transplants were excluded from the model. Similar results were obtained for death-censored graft survival as the dependent variable. In relation to patient survival, infection with HCV ($P = .019$; HR = 1.606; 95% CI = 1.081–2.385); ATN ($P < .001$; HR = 1.846; 95% CI = 1.313–2.595), and recipient age ($P < .001$; HR = 1.050; 95% CI = 1.034–1.065) were significant independent predictors of a poor outcome. Gender, time on dialysis, occurrence of rejection, and number of grafts were not significant independent predictors of patient death.

During the 21 years of follow-up, 138 patients died in the two groups. A significant difference was observed in the mortality between the two groups. Thirty-three (21.3%) HCV-positive patients died, versus 105 (10.1%) in the HCV-negative group ($P = .001$). Death in the HCV-positive recipients resulted from infections ($n = 11$), cardiovascular complications ($n = 6$), hepatic complications ($n = 2$), malignancy ($n = 3$), and other etiologies ($n = 11$).

Death from infectious causes was significantly higher among the HCV-positive group (33.3% vs 12.4%, $P = .014$) with no apparent increase in mortality rate due to chronic liver disease among the HCV-positive group ($P = .286$).

Sixty-two HCV-positive patients lost their kidneys after a mean follow-up of 7.9 ± 5.3 years. The loss of organs was mainly due to acute or chronic rejection (51.6%; $n = 32$) and death with a functioning kidney (33.9%; $n = 21$).

DISCUSSION

In our Portuguese renal transplant center, the prevalence of HCV infection is 12%, a figure that is consistent with prevalence at the time of transplant reported by other centers, namely, 6% to 49% HCV-positive subjects by ELISA-2.^{2,6,8,10}

Several studies have reported that the number of blood units transfused prior to the transplant, duration of dialysis prior to the transplant, as well as the year in which the patient enters renal replacement were risk factors for HCV infection.^{1,7,11} For many years, blood transfusions have been the main source of HCV infection in this patient population. The introduction of screening of blood products for anti-HCV has virtually eliminated transmission of HCV in blood transfusions. However, the management of dialysis patients, transplant candidates, and recipients already infected with HCV remains an important clinical problem. Our results showed that anti-HCV-positive recipients had a longer time on dialysis, more blood transfusions prior to the transplant, and a higher number of previous transplants. They also entered early in the renal replacement therapy programs, with 87% of HCV-positive recipients beginning dialysis before 1993 versus 47.3% of the HCV-negative group. Most HCV-positive recipients entered dialysis before the availability of anti-HCV tests.

HCV disease is a major problem. Some authors believe that immunosuppression facilitates HCV replication and aggravates liver lesions. Transplantation of a patient previously infected with HCV is associated with increased virus proliferation, resulting in a 1.8- to 30.3-fold increase in the

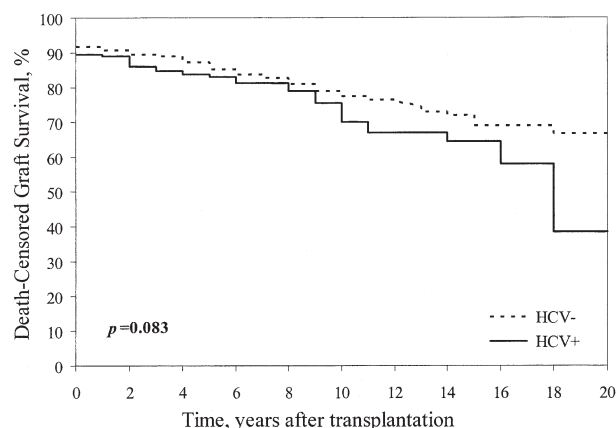


Fig 3. Kaplan-Meier estimate of the cumulative probability of death-censored graft survival.

viral load, higher alanine aminotransferase levels, and fewer HCV-positive patients with normal alanine aminotransferase levels.^{1,6,10,12} However, an increased viral titer may not be associated with an increased risk of posttransplantation liver disease.^{6,10,12} In our study, the long-term outcome of HCV-positive patients was worse than that of non-HCV subjects. According to the literature, the poor outcome is related primarily to a high morbidity and mortality from liver disease^{1,5,13} and infection.^{1,6,12,13} Liver failure is the cause of death in 8% to 28% of long-term transplant survivors.^{2,5} In addition, an unusual form of liver disease, termed fibrosing cholestatic hepatitis, has been described in a few patients with HCV infection who undergo renal transplantation.¹⁴ Among our HCV-positive recipients, the leading cause of death was infectious; we found that patients with HCV infection showed a significant increased risk of infectious death compared with subjects not infected with HCV. However, contrary to previous reports, we did not find an increased mortality due to liver complications among our HCV-positive recipients.

The incidence of acute rejection in patients infected by HCV remains controversial. Some, but not all, authors have reported a higher frequency of acute rejection among patients infected with HCV when compared with non-HCV patients.^{1,3,9,15} In the present study we were not able to find any significant differences in the incidence of acute rejection among patients with versus without anti-HCV.

Certain factors, such as pretransplant liver pathology, HCV genotypes, HCV viral load, and type of immunosuppression, may influence outcomes of HCV-positive patients.¹ In the Mediterranean countries, HCV genotype 1b has been described to be the most frequent, and to also be associated with severe forms of the disease. However, the clinical course of chronic liver disease in these areas has been described to be similar to the other parts of the world.³ The outcome of HCV disease and response to antiviral therapy with interferon may differ with viral genotype. Genotype 1b is associated with a poor response to interferon therapy^{1,16} and more severe chronic liver failure.¹ Interferon therapy is only recommended during the dialysis or predialysis period, as this therapy has been associated with an increased incidence of acute rejection.³ Several studies on interferon therapy in dialysis patients have confirmed a good response to interferon among this subset of patients, although it has also been associated with more frequent side effects than in the general population.^{1,16} We did not examine the various genotypes or viral load in our patients. However, all patients included on the waiting-list had no clinical sign of liver disease, including near normal values of liver enzymes. Most candidates had undergone a liver biopsy to establish for normal liver histology; we only accepted subjects with minimal changes or mild chronic hepatitis. ALT level was not a reliable parameter to evaluate the severity of the hepatic lesion because transaminase levels did not correlate well with liver histology. Liver biopsies represented the gold standard to define the severity of liver involvement and define the prognosis. Liver

biopsy was also useful as an indication for interferon treatment prior to transplantation.³

Co-infection with hepatitis B and C in these recipients has been described to lead to a more aggressive liver disease than that in patients with only HCV infection.^{1,2,9} Fourteen patients had co-infection with hepatitis B and C, but we did not find a significant difference in the long-term survival rates of patient and grafts.

Several investigators have reported a negative influence of HCV infection on patient survival,^{6,7} while others did not find any impact on long-term patient or graft survival.^{8,9} Our results showed a significant decrease in long-term patient survival rates and increased mortality among HCV-positive patients. The graft survival rate was also significantly decreased, indicating that HCV infection was associated with poorer long-term graft survival. However, we did not observe a significant difference in graft survival when censored for patient death with a functioning graft, suggesting that the lower graft survival among HCV-positive patients reflected lower patient survival. Some authors have attributed the lower graft survival to the development of HCV-associated glomerulonephritis in the graft.^{1,17} The main cause of graft loss in our HCV-positive patients was acute or chronic rejection. In the absence of a renal biopsy, we cannot dismiss the possibility of HCV-associated glomerulonephritis in some patients. Infectious death was significantly lower in the non-HCV group, so that the lower HCV-positive patient survival may have resulted from infectious death.

In addition, multivariate analysis confirmed that HCV infection was an independent predictor of graft failure with a relative risk of 1.382 (CI = 1.041–1.835) and of death-censored graft survival, even after adjusting other clinically important variables. Also, among our recipients, the presence of HCV infection was associated with a 1.606-fold (CI = 1.081–2.385) increased risk of death. These findings confirm previous studies showing that HCV infection was associated with an increased mortality after transplantation.^{6,18}

HCV-positive patients seem to show lower long-term survival rates when compared to HCV-negative recipients, nevertheless renal transplantation remains the best option for end-stage renal disease patients with HCV infection. Some reports have suggested that HCV-positive recipients have a net long-term survival advantage compared with HCV-positive patients on the waiting list for transplantation due to the high cardiovascular mortality of this cohort on dialysis.^{1,13,18} So the possible deleterious effect of immunosuppression on the clinical course of HCV infection seems to no outweigh its long-term beneficial effect on survival and quality of life in end-stage renal disease patients.

In summary, HCV in renal recipients showed a significant long-term negative impact on patient and renal allograft prognosis. Consistent with the literature, death from infectious causes was significantly more frequent than among the non-HCV population.

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