Patient and Graft Survival of Kidney Allograft Recipients With Minimal Hepatitis C Virus Infection
A Case-Control Study

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Introduction: The impact of pretransplant hepatitis C virus (HCV) infection on the outcome of kidney transplantation is controversial. This study was designed to determine the impact of pretransplant minimal HCV infection on the patient and graft survival at a single center in southwest of Iran.

Materials and Methods: We designed a historical cohort study on 337 kidney transplant recipients and selected 35 patients with HCV infection and a histological activity index score less than 4 (*minimal HCV infection*). A group of kidney recipients with negative anti-HCV antibody were compared with the anti-HCV-positive patients in terms of acute allograft rejection, graft loss, mortality, causes of death, and patient and graft survival. The controls were matched for age, sex, donor source, pretransplant dialysis duration, and panel reactive antibodies test. All of the participants had a follow-up period of at least 5 years.

Results: There were no significant differences in terms of early and late acute allograft rejection episodes between the groups. Although patient and graft survival rates were lower in HCV-positive patients at 2 and 5 years, the differences between the two groups were not significant. The main causes of death among patients with and without HCV infection were sepsis and cardiovascular events, respectively.

Conclusion: Our findings suggest that pretransplant minimal HCV infection had no detrimental effect on the short-term patient and graft survival. However, we suggest that kidney transplant recipients with minimal HCV infection be monitored for severe systemic bacterial infections.

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INTRODUCTION

Hepatitis C virus (HCV) is a common pathogen that causes chronic hepatitis in patients with end-stage renal disease. The effect of HCV infection on patient survival after kidney transplantation has been a subject of debate, with some but not all studies finding an increased risk of death among patients with a positive anti-HCV antibody before transplantation.[1-5] Notwithstanding the outstanding amount of research worldwide, to the best of our knowledge, there has been limited information on the prognosis of HCV-infected patients who received kidney transplantation in Iran.[2,6] The prevalence of HCV infection among patients undergoing hemodialysis in our community is still high, especially in the southwest of Iran.[7]

Determination of the severity of hepatitis in patients undergoing kidney transplantation is not a

routine procedure in transplant centers. However, it seems that pretransplant liver biopsy in HCV-infected patients may increase the accuracy of the staging of liver disease and improve patient selection for kidney transplantation. Our aim was to compare the outcomes of the patient and the kidney allograft between kidney transplant recipients with and without HCV infection.

MATERIALS AND METHODS

We designed a historical cohort study to evaluate the posttransplant impact of chronic HCV infection on the patients who received a kidney transplant at Ahwaz Jundishapur University's Transplantation centers. The research ethics committee of the university approved the study protocol. A total of 337 patients had received a kidney allograft between May 1997 and December 2001. We selected patients with HCV infection and a histological activity index (HAI) score[8] less than 4 (*minimal HCV infection*) and a matched group of kidney recipients with negative anti-HCV antibody.

All of the patients had routinely been tested for anti-HCV antibody before transplantation using the 2nd or 3rd generation of enzyme-linked immunosorbent assay. Serum HCV RNA was also assayed with a combined reverse transcript polymerase chain reaction assay (Amplicor HCV test; Roche Diagnostic System Inc, Branchburg, New Jersey, USA) with a detection sensitivity of 10 to 100 copies per milliliter. The HCV-infected patients had been further evaluated by liver biopsy for severity of liver disease before transplantation. Patients with an HAI score of 4 or higher were excluded from our study. We also excluded those with a positive hepatitis B virus (HBV) surface antigen, because hepatitis B infection may affect the clinical course of HCV infection. Of note, none of our patients was co-infected by the human immunodeficiency virus. The control group was selected from among kidney recipients with negative HCV and HBV tests. Stratified randomization was used to select a group matched for age, sex, donor source, pretransplant dialysis duration, and panel reactive antibodies test with the patients with minimal HCV infection.

All of the patients had received their allografts from a living (related or unrelated) donor. Immunosuppressive therapy comprised cyclosporine (initiation dose of 3.5 mg/kg/d), prednisolone (5 mg/d to 10 mg/d), and azathioprine (100 mg/d) or mycophenolate mofetil (2 g/d). Episodes of acute allograft rejection were treated by methylprednisolone, 1 g/d, intravenously for 3 days. Physical examination and biochemical tests including serum HCV RNA level and liver function tests were performed every other month.

Transplantation outcomes were reviewed at the 1st, 2nd, and 5th years of the posttransplant follow-up period, and data on death, cause of mortality, chronic allograft nephropathy, and graft loss were collected. Survival time was defined as the time between the date of transplantation and death, the most recent follow-up date, or the end of the study period. Graft failure was defined as return to dialysis after transplantation and did not include death with a functioning graft (death-censored analysis). Acute rejection was determined according to clinical diagnosis or pathological evidence.

The collected data were coded in Microsoft Access 2000 database software (Microsoft Corp, Redmond, Washington, USA) and statistical analyses were done by the SPSS software (Statistical Package for the Social Sciences, version 11.0, SPSS Inc, Chicago, Ill, USA). The Fisher exact test, chi-square test, Mann Whitney U test, and Student t test were used to make univariate comparisons. The Kaplan–Meier method and log rank test were used for patient and graft survival analyses. Continuous variables were demonstrated as mean $\pm$ standard deviation or median, where appropriate. The criterion for statistical significance was a P value less than .05.

RESULTS

Patients

Thirty five kidney recipients with a positive anti-HCV antibody or a positive HCV RNA were selected. They had minimal liver involvement and a negative HBV surface antigen. There were 9 seropositive patients for HCV, 7 of whom

with an HAI score higher than 4 and 2 with a positive HBV surface antigen, all of whom were excluded. All of the patients had a minimum follow-up period of 5 years, and none of them were lost to follow up in either group. The control group consisted of a matched group of 35 kidney recipients without any positive tests for HCV or HBV. There were no significant differences between the patients and the control group of kidney recipients in terms of age, sex, etiology of kidney disease, duration of follow-up, and duration of hemodialysis, or donor source. The main demographic and clinical features of the transplant patients are shown in Table 1.

Table 1. Characteristics of Kidney Transplant Recipients With Positive Anti-Hepatitis C Virus Antibody and a Matched Group of Kidney Recipients

Characteristics	HCV Positive	HCV Negative
Number of patients	35	35
Mean age, y	38.0 ± 8.4	37.4 ± 7.6
Sex		
Male	21 (60.0)	20 (57.1)
Female	14 (40.0)	15 (42.9)
Donor source		
Living related	8 (22.9)	9 (25.7)
Living unrelated	27 (77.1)	26 (74.3)
Duration of dialysis, y	2.2 ± 1.2	2.2 ± 1.1
Median follow-up, y	7.2	7.4
Median PRA, %	20	20

*Values in parentheses are percents. HCV indicates hepatitis C virus and PRA, panel reactive antibody.
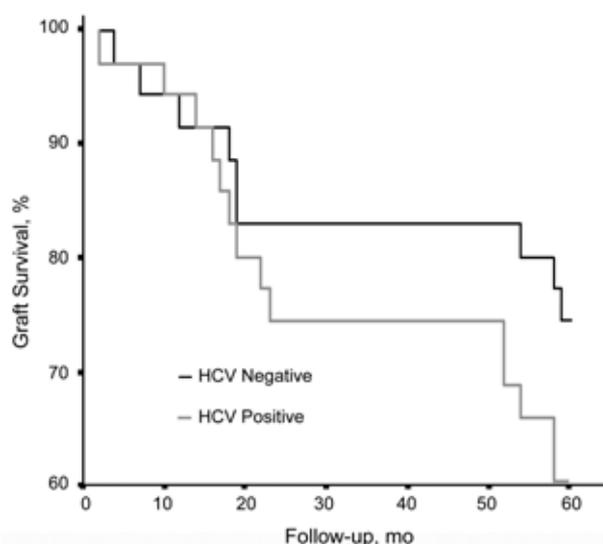

Figure 1. Graft survival rates for kidney transplant recipients with and without positive anti-hepatitis C virus (HCV) antibody.

Graft Outcome

During the follow-up period, 7 patients (20.0%) in the anti-HCV-positive group and 5 (14.3%) in the control group experienced acute allograft rejection within the first posttransplant year ($P = .38$). There were 2 cases of acute rejection during the second posttransplant year, both of which were among the anti-HCV-positive recipients ($P = .25$).

The kidney allograft survival rates were comparable; the 1-, 2-, and 5-year graft survival rates in the anti-HCV-positive patients were 94%, 74%, and 60%, respectively. In the anti-HCV-negative transplant recipients, these rates were 94%, 83%, and 74%, respectively ($P = .92$, $P = .35$, and $P = .65$, respectively). The mean graft survivals were 47.8 ± 3.3 months and 51.7 ± 3.0 months for the kidney recipients in the anti-HCV-negative and anti-HCV-positive groups, respectively ($P = .21$; Figure 1).

After the fifth year of follow-up, 6 anti-HCV-positive patients (17.1%) and 4 anti-HCV-negative patients (11.4%) were on dialysis. The remaining kidney recipients showed stable kidney function with normal or nearly normal serum creatinine levels.

Patient Outcome

There was no clinical or laboratory evidence of decompensation of liver disease in the anti-HCV-positive group. Ten patients (28.6%) in the anti-HCV-positive group and 5 (14.3%) in the anti-HCV-negative group died during the follow-up period ($P = .12$). Sepsis was the prominent cause of death in the patients of the anti-HCV-positive group. In contrast, this complication was not frequent in the kidney recipients of the control group; however, the differences between the two groups in causes of death were not significant (Table 2).

The 1-, 2-, and 5-year patient survival rates in the anti-HCV-positive patients were 97%, 84%, and 68%, respectively. In the anti-HCV-negative transplant recipients, these rates were 97%, 87%, and 84%, respectively ($P = .19$, $P = .34$, and $P = .75$, respectively). The mean patient survival rates were 52.6 ± 2.7 months and 55.7 ± 2.2

Table 2. Main Causes of Death in Kidney Transplant Recipients With and Without Positive Anti-Hepatitis C Virus (HCV) Antibody

Cause of Death	HCV Positive (%)	HCV Negative (%)
Cardiovascular events	2 (5.7)	3 (8.6)
Sepsis	6 (17.1)*	1 (2.9)
Gastrointestinal bleeding	1 (2.9)	0
Sudden death	1 (2.9)	0
Unknown	0	1 (2.9)

*P value was .053 for sepsis (Fisher exact test).
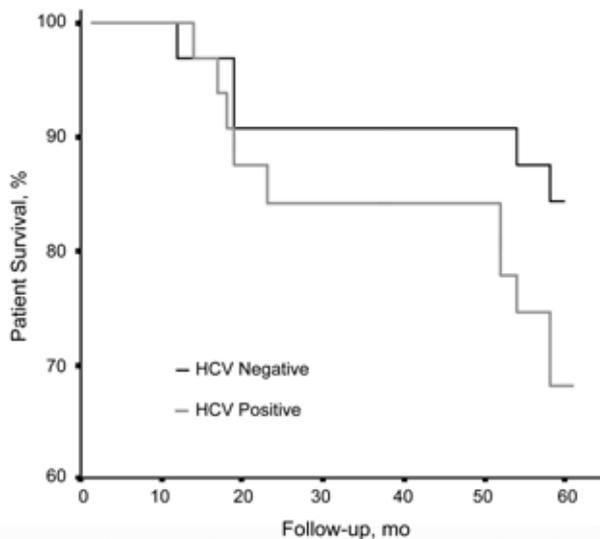
Figure 2. Patient survival rates for kidney transplant recipients with and without positive anti-hepatitis C virus (HCV) antibody.

months for the kidney recipients in the anti-HCV-negative and anti-HCV-positive groups, respectively (P = .54; Figure 2).

DISCUSSION

The impact of HCV infection on survival figures after kidney transplantation remains controversial.[3-6,9-14] It has been demonstrated that hepatic failure plays an important role as the cause of death in patients surviving more than 5 posttransplant years.[15] However, some reports have indicated similar patient and graft survival in HCV-positive and HCV-negative kidney recipients.[3,14] Results of our study demonstrate that the patient and graft survival were comparable between HCV-positive and HCV-negative patients at the first year of transplantation, and although the 2- and 5-year survival rates were lower in HCV-positive than in HCV-negative patients, there were no significant

differences between the two groups. Also, there were no significant differences in the frequency of early or delayed acute allograft rejection between the two groups.

Ozdemir and associates found a higher graft failure rate due to chronic rejection in HCV-positive than in HCV-negative transplant recipients (68.0% versus 47.8%; P = .001).[13] However, our data showed that although the anti-HCV-positive recipients had a higher rate of graft loss, there was no significant difference between the two groups. Sabet and colleagues published a study from Iran,[6] in which they demonstrated that graft loss was seen in 5% of the HCV-positive and none of the HCV-negative patients.[6] The 2-year graft survival was lower in both HCV-positive and HCV-negative patients in our study compared with that in Sabet and coworkers' study. Hestin and colleagues[14] demonstrated that 1- and 5-year graft survival rates were comparable in the recipients with and without a seropositive HCV. Interestingly, they found that HCV infection was associated with proteinuria, a factor that had worsened graft survival independently.

According to a study on a large group of 73 707 recipients, Meier-Kriesche and coworkers found that while graft survival was worse, patient survival of HCV-positive recipients was slightly superior to that of HCV-negative patients. In this study, cardiovascular-related death was less frequent, while gastrointestinal-related and infection-related deaths were more frequent in the HCV-positive patients.[3] Our study showed no significant difference in mortality rate between the two groups, and the major causes of death were similar to this study. Contrary to Meier-Kriesche and colleagues' study, a report by Gentil and associates was indicative of that graft survival was significantly lower in HCV-positive transplant recipients. Their study was on a cohort of 335 cadaveric allograft recipients who received a 4-drug immunosuppressive regimen. In this study, the comparison results revealed significant difference between the patients with and without HCV infection. Their 1-, 5-, and 10-year patient survival rates were 96%, 87%, and 72%, respectively.[4] Results of this study are different to ours, but it should

be noted that all of our patients received their allografts from living donors and were on a triple-drug immunosuppressive regimen. Data from one large study on 33 479 kidney allograft recipients showed a significantly higher risk of mortality in HCV-positive patients (adjusted hazard ratio, 1.23; 95% confidence interval, 1.01 to 1.49; P = .04).[5] However, seropositivity was associated with African-American race, male gender, cadaveric donor source, increased duration of pretransplant dialysis, previous transplant, recipient age, etc. Patients with HCV infection are more likely to have longer dialysis duration and they are usually older than other patients at transplantation. Thus, a lower patient survival rate might be related to these factors rather than HCV infection. Such a bias was noted by Gentil and colleagues, as well[4]; their group of seropositive patients had longer dialysis duration and more frequent blood transfusions. Our matched group of HCV-negative kidney recipients did not have such differences with the HCV-positive patients.

Meier-Kriesche and colleagues reported that acute rejection within the first 6 months after allograft transplantation was significantly more frequent in HCV-positive compared with HCV-negative recipients.[3] Ozdemir and colleagues noted that there was no significant difference between HCV-positive and HCV-negative patients in early acute graft function, but late acute rejections was significantly more frequent in HCV-positive recipients.[13] In contrast, Corell and coworkers demonstrated a significantly lower rate of acute rejection in 118 HCV-positive recipients (28%) compared with 229 HCV-negative recipients (40%). They suggested that it could be explained by the reduction of T-helper cells and altered T-cell proliferative responses to mitogens in HCV-positive recipients.[16] Although our study showed a higher rate of early and late acute rejections in HCV-positive patients, the difference was not significant.

Controversy exists regarding the short-term and long-term impact of HCV infection on the outcome of kidney allograft transplantation and an exact conclusion could not be made from the published papers. Differences in the results

of these studies may be due to differences in immunosuppressive regimens, study design, diagnostic method of HCV infection, variation in HCV genotypes, duration of pretransplant dialysis, and age of allograft recipients. Although in most of these studies long-term survival rates are lower in HCV-positive graft recipients comparing with HCV-negative recipients, regarding the similar short-term graft and patient survival and comparable long-term survival rates—as reported by the present study, renal transplantation remains the best choice for patients with end-stage renal disease and HCV infection with regard to the lower survival rate of HCV-positive patients on maintenance dialysis.[10]

CONCLUSION

Our data suggest that minimal HCV infection per se has no adverse effect on short-term and long-term graft and patient survival, and HCV antibody-positive recipients do not have an increased risk of death after transplantation compared with HCV-negative recipients. Since sepsis was slightly more frequent as the cause of death in HCV-positive patients, we suggest that kidney transplant recipients with minimal HCV infection be monitored for severe systemic bacterial infections. These conclusions were based on the comparison of two matched groups. However, a larger sample size is required to further confirm the results.

CONFLICT OF INTEREST

None declared.

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