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## Research Article

# The Impact of Hepatitis C Virus Infection on the Clinical Course, Short Term and Long-Term Outcome in Renal Transplant Recipients – A Prospective and Retrospective Study

## Abstract

**Background:** Hepatitis C (HCV) Infection is not uncommon in patients on maintenance hemodialysis (around 10% in our dialysis population). It is also known to increase morbidity and mortality in Renal Allograft Recipients more so in post-transplant period with various studies quoting mixed results.

**Aim:** To find the impact of HCV infection on graft and patient survival and to compare the incidence of rejection, infections, liver dysfunction, NODAT (New Onset Diabetes after Transplantation) in HCV infected and negative patients.

**Setting and Design:** Retrospective and prospective institutional based study.

**Method:** HCV RNA positive patients without portal hypertension/abnormal liver scan were included in the study. Patients were divided into three groups on the basis of whether or not they received anti HCV treatment and how they responded to it.

**Results and Conclusion:** Patients who are anti-HCV positive before transplantation have a significantly increased risk of post-transplant liver disease. Most of the literature quotes a relative risk of 5 and an incidence of 19%-64% for post-transplant liver disease. (Vs. 1%-30% for general population) In our study 15% of patients had deranged liver function post-transplant however none of these patients showed any sign of decompensation. Conflicting results surround the question as to whether post-transplant liver disease is associated with decreased survival. As an example, three studies failed to detect significant differences in patient survival between recipients with and without anti-HCV prior to renal transplantation. The same fact is also highlighted in our study where in there were no graft loss and the patient survival were comparable to our regular cohort at 1 and 5 year post transplant. Rejection rate were higher compared to regular cohort particularly in modern era. As such renal transplant is a safe and viable option in HCV + patients with or without anti HCV treatment pretransplant medically, financially, socially and physically.

## Introduction

Viral hepatitis is prevalent in patients with end stage renal disease (ESRD) on renal replacement therapy (RRT) because the patients are exposed to the transmission risk factors such as blood transfusion and nosocomial factors, etc. Nevertheless, there has been a decrease in the prevalence of hepatitis B infection after the application of vaccination program, isolation of infected patients and common use of erythropoiesis-stimulating agents.

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 [1,2].

Even though there has been significant amount of research worldwide, to the best of our knowledge, there has been limited information on the prognosis of HCV-infected patients who have had received kidney transplantation in India [3-6]. The prevalence of HCV infection among patients undergoing haemodialysis in our country is at around 10%

which is considered to be high. Renal transplantation (RTx) is considered as the treatment of choice in HCVinfected ESRD patients compared to dialysis treatment [5,6].

However, the impact of HCV infection on graft and patient survival after RTx remains controversial. Several studies suggest that HCV infection could worsen both graft and patient survival rates [7] and increase the risk of post-transplant infections, sepsis and diabetes mellitus [8,9]. On the other hand, some studies have documented that HCV infection did not influence patient or graft survival significantly [10-12].

The purpose of this study is to determine the effect of HCV infection on patient-graft survival and liver function in renal allograft recipients.

### Objectives of the study

To determine the impact of HCV infection on graft and patient survival, at al., 1, 3, 6, 12 months interval post-transplant and to compare the outcome with HCV negative patients undergoing transplantation.

To determine the transplant related events (rejection, infections, hospital readmission, liver diseases, and new onset diabetes after transplant [NODAT]) in HCV infected patients as compared to the HCV negative patients.

## Material and Methods

### Study area

The study was conducted in the Department of Nephrology and Transplantation at Rabindranath Tagore International Institute of Cardiac Sciences, (RTIICS) Kolkata which is a tertiary care multispecialty hospital with the highest number of renal transplant in eastern India.

### Study population

HCV RNA positive end stage renal disease (ESRD) patient who have presented themselves for renal transplantation in Department of Nephrology, RTIICS, Kolkata, were taken for the study. The study group comprised both males and females from Eastern India and adjoining states.

### Inclusion criteria

1. AGE: No age bar for transplantation. (This study has patients above 18 years of age only)
2. SEX: Both males and females were selected for the study.
3. Patients with ESRD having hepatitis C virus infection.
4. Patient or family member must give informed consent.

### Exclusion criteria

1. Patients who are positive for Human Immuno-deficiency virus (HIV) or Hepatitis B virus infection (HBsAg).

2. Patients with abnormal liver scan (Fibro scan score 3, 4).
3. Patients with portal hypertension as determined by upper gastro intestinal. Endoscopy and ultrasonography of abdomen.
4. Informed consent not given by patient or family member.

### Sample size and sample technique

The medical reports of the patients were evaluated retrospectively as well as prospectively.

HCV infected prospective transplant patients were offered HCV treatment with GFR appropriate doses of Pegylated Interferon - 2a (once weekly) and oral Ribavirin (once daily). However, refusal to take HCV treatment on part of the patient or, inadequate response to the therapy was not a criterion for refusal of transplantation. Patients were grouped into three groups as under (Figure 1).

1. Those who took HCV treatment and responded to it adequately.
2. Those who had inadequate treatment or have had inadequate response to the treatment.
3. Those who refused HCV related treatment.

### Data collection technique and tools

The period of data collection was from January 2008 to February 2014. As both prospective and retrospective data was collected; duration of follow up was atleast 12 months post transplantation in the prospective arm and in the retrospective arm the mean duration of follow up was 18±7 months was done. These three groups mentioned above were then compared to the historical HCV negative transplant recipients of the centre. The control group was selected from recipients who were HCV-negative and matched for age, sex, donor type, pretransplantation dialysis duration, cytotoxic antibody status, and immunosuppressive regimen.

Physical examination and biochemical tests including liver function tests and renal function test were performed at the

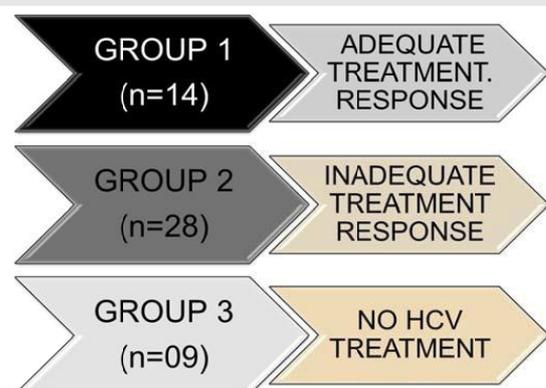


Figure 1: The sample size of each group mentioned above was 14, 28 and 09 respectively.

time of discharge, one month, 3 months, 6 months and one year post-transplant. HCV RNA status (quantitative) was also done at the time of discharge and subsequently at 3, 6 and 12 months post-transplant.

Transplantation outcomes were reviewed at 1st, 3rd, 6th and 12th month of the posttransplant follow-up period, and data on death, infection, rejections, hospital readmission, NODAT and graft loss were collected. Duration of follow up was at least one year posttransplantation with a mean follow up of  $18 \pm 7$  months in retrospective arm.

All of the patients have had received their renal allograft from a living (related or non near related) donor. Immunosuppressive therapy comprised tacrolimus (initiation dose of 0.15mg/kg/d) or cyclosporine (initiation dose of 2-3 mg/kg/d), prednisolone (20 mg/d), and mycophenolate mofetil (1.5 g/d). Episodes of acute allograft rejection were treated by methylprednisolone, 500 mg/d, intravenously for 3 days.

Acute rejection was diagnosed based on clinical and/or histological findings. Clinical acute rejection was considered when serum creatinine level increased by more than 25-30% of basal values after excluding other non-immunological causes and if there was a response to anti-rejection therapy.

Graft loss was defined as return of the patient to dialysis or patient death.

In the assessment of graft function, serum creatinine level (mg/dl) and estimated glomerular filtration rate (GFR) (ml/min/1.73m<sup>2</sup>) with the modified four variables Modification of Diet in Renal Disease (MDRD) equation was taken into account. The standard creatinine based equation estimating GFR which uses Age, Sex, Race and Serum Creatinine (Jaffe' or enzymatic method). The criterion of pathologic proteinuria was defined as urinary protein > 300mg/24 hours.

Post-operative liver function was assessed by doing liver function tests (LFT), Ultrasonography of upper abdomen, anti HCV antibody and HCV RNA. LFT included total and unconjugated bilirubin, SGPT, SGOT, albumin, globulin, alkaline phosphatase and GGT.

Anti-HCV antibodies was detected in sera by third generation enzyme immunoassays (CobasCore Anti-HCV, Roche Diagnostics), and HCV RNA was measured in the plasma samples by quantitative polymerase chain reaction (PCR) assays (CobasAmplicor HCV monitor and CobasTaqMan HCV, Roche Diagnostics). Both these tests were done in every patient presenting for transplant because of high false negativity of anti HCV antibodies in ESRD patients.

## Data analysis

The collected data were coded in Microsoft Access 2007 database software (Microsoft Corp, Redmond, Washington, USA) and statistical analyses were done by the SPSS software (Statistical Package for the Social Sciences, version13.0, 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 0.05.

## Results

Among 51 patients in our study group who were HCV +ve there were 40 males (78.43%) and 11 females (21.56%). Likewise the maximum numbers of patients were in the age group of 30-60 years which comprised about 71%. The highest average aged patient belonged to group 1 followed by 2 and 3 respectively. The most common cause of renal failure across the three groups was chronic glomerulonephritis (CGN) followed by diabetes and hypertension. Among 51 patients we had only one patient of ADPKD who was also HCV+ve.

The minimum and maximum period for which the patient was on hemodialysis prior to transplant was 3 and 48 months respectively and the mean duration was  $25 \pm 22$  months.

The duration for which patients took anti HCV treatment ranged from 1 to 24 months with a mean of  $12.5 \pm 10$  months.

The most common genotype encountered was 3 followed by 1 and 2.

Highest number of deaths was observed in patients not receiving any induction therapy; however infections were more common in the induction group. A total of 5 patients died of sepsis (9.8%). 3 out of 5 deaths occurred in group 2 and 2 deaths in group 3 who received no anti HCV treatment.

Interestingly the maximum number of rejection was observed in group 2 who received anti HCV treatment for some duration but did not respond to it. The incidence of NODAT was 17.6% and all cases were seen in patients taking tacrolimus. Further most of these cases occurred in Group 2 patients.

In our regular cohort incidence of NODAT was 14.92%.

Death rate in our study was 3.92%, 5.88% and 9.8% at 1, 3 and 5 years respectively.

Consequently patient survival rates at 1, 3 and 5 years were 96.02%, 94.12% and 90.1% respectively. Number of death was equally distributed among Group 2 and 3 but was null in Group 1 which received adequate treatment and responded to it favourably.

Patient survival in our regular cohort at 1, 3 and 5 years was 98%, 92.5% and 88% respectively.

Incidence of acute rejections was 17.6% (AMR 44.44%; ACR 55.56%) in our study and the same in our regular cohort of HCV-ve patients was 7.62% (AMR 14.8%; ACR 85.2%).

Among the HCV+ve patients who received induction, the rejection rate was 12% (AMR 100%; ACR 0%) and among those HCV+ve patients who did not received induction the rejection

rate was 23.07% ( AMR 16.67% and ACR 83.33%). In our regular cohort the rejection rate among induction group and non-induction group was 5.05% (AMR 13.08%; ACR 76.42%) and 9.32% (AMR 11.8%; ACR 88.2%) respectively.

We had one graft loss among 51 patients in our study (1.96%) and about 1.91% in our regular cohort.

On comparing the variables of patient survival, graft survival, infections, incidence of NODAT and effect of transplantation (liver enzymes, renal function tests, viral load) among the three groups it was not found to be statistically significant.

However when comparing it to our regular cohort the incidence of infection was indeed higher as was the acute rejection rate (17.6% Vs. 7.62) and incidence of NODAT (17.6% vs. 14.2%) but which again was not statistically significant.

These results have been tabulated as shown in tables 1-3.

### Conclusions

Our data suggest that HCV infection per se has no adverse effect on short-term and long-term graft and patient survival.

Rate of acute rejection was comparable among HCV+ve patients receiving or not receiving anti HCV treatment, though rejection rate was higher when compared to HCV-ve cohort. Incidence of other complications like infection, NODAT, hospitalization and liver failure was not statistically significant among the HCV+ve group. However it was higher when compared to the regular cohort. Since sepsis was slightly more frequent as the cause of death in HCVpositive patients, kidney transplant recipients with HCV infection should be monitored for severe systemic bacterial infections.

Renal transplantation is still plausible in patients not responding adequately or not undergoing anti HCV treatment prior to transplant since survival rates are better in patients undergoing transplantation then those who remain on hemodialysis. These conclusions were based on comparison of the three subgroups with the historical HCV-ve cohort.

### Recommendations

The recommendations from our study are as under; Induction therapy decreases the incidence of acute rejections even in HCV+ve patients (not responding to or not undergoing anti HCV treatment); thus induction should be considered in such patients. Further induction therapy also reduces the total cumulative dose of anti-rejection therapy if the patients do develop rejections in future. (As patients who had induction therapy also had less rejection episodes 12.0% vs. 23.07%).

Infection rate in HCV+ve patients are higher as compared to negative cohort. Thus they should be monitored meticulously post-transplant.

Renal transplantation may be considered in HCV+ve patients [who do not respond to or who are unable to undertake anti HCV treatment (due to financial constraints)] without added risk to the outcomes.

Incidence of NODAT is higher in HCV+ve patients on tacrolimus immunosuppression; hence cyclosporine should be considered in such patients.

Since liver disease can develop later in life post-transplant (>5 years) a 10-20 years follow-up of these patients should be prudent.

**Table 1:** Incidence of NODAT, Death, Rejections, Infections across Various Groups.

	INDUCTION		TAC/CYA		NODAT	DEATHS	REJECTIONS		INFECTIONS
	YES	NO	TAC	CYA			AMR	ACR	
<b>GROUP 1 (n=14)</b>	11	03	13	01	02	00	01	00	EPTB-2;HERPES ZOOSTER1;ARDS/LRTI-1
<b>GROUP 2 (n=28)</b>	12	16	16	12	06	03 (AT 6,9,48 MONTHS)	02	05	HERPES2;MILIARY TB-1;MUCOR-1
<b>GROUP 3 (n=09)</b>	02	07	05	04	01	02 (AT 36,45 MONTH)	01	00	LRTI-1
<b>HCV +VE (n=51)</b>	25 (49%)	26 (51%)	34 (66.6%)	17 (33.4%)	9 (17.6%)	05	17 .6% 04 (44.4%)	05 (55.5%)	--
<b>HCV-VE (n=1278)</b>	79%	21%	97%	3%	14.92%	22% (at the end of 5 years)	07 .6% 14.8%	85.2%	

TAC= Tacrolimus; CYA= Cyclosporine; NODAT=New Onset Diabetes after Transplant; AMR=Antibody mediated rejections; ACR= Cell mediated rejection; EPTB= Extra pulmonary tuberculosis; ARDS= Acute respiratory distress syndrome; LRTI= Lower respiratory tract infection; MUCOR= Mucormycosis.

**Table 2:** Trend of Viral Load in Three Groups Post-transplant period.

	VIRAL LOAD (Log <sub>10</sub> (x)) (IU/ML)					Mean difference (from transplant to 12 months)	P value*
	PRE TRANSPLANT	POST TRANSPLANT					
		IMMEDIATE	3 MONTHS	6 MONTHS	12 MONTHS		
<b>GROUP 1</b>	0	2.58	3.03	3.33	3.65	3.12	
<b>GROUP 2</b>	6.71	6.74	6.79	6.89	6.91	6.84	0.013
<b>GROUP 3</b>	6.78	6.82	7.09	7.17	7.17	6.91	0.009

Mean difference = mean during 1<sup>st</sup> year post transplant period.

**Table 3:** Trends of Serum Creatinine in Three Groups Post-transplant period.

	CREATININE					Mean difference (from transplant to 12 months)	P value*
	DISCHARGE	PTX1	PTX3	PTX6	PTX12		
<b>GROUP 1</b>	1.53	1.59	1.31	1.25	1.30	-0.23	
<b>GROUP 2</b>	1.45	1.39	1.41	1.32	1.36	-0.14	0.70
<b>GROUP 3</b>	1.55	1.33	1.25	1.19	1.18	-0.37	0.70

PTX = Post transplant months; 1,3,6,12 months respectively.

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