

Hepatitis C Virus Antibody Status and Survival After Renal Transplantation: Meta-Analysis of Observational Studies

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The natural history of hepatitis C virus (HCV) among patients after renal transplantation (RT) remains incompletely defined. We conducted a systematic review of the published medical literature on the impact of hepatitis C antibody status on survival of patients who received RT. We used the random effects model of DerSimonian and Laird to generate a summary estimate of the relative risk (RR) for mortality and graft loss with HCV seropositivity across the published studies.

We identified eight clinical trials (6365 unique patients); six (75%) were cohort studies and two (2/8 = 25%) controlled trials, respectively. Pooling of study results demonstrated that presence of anti-HCV antibody was an independent and significant risk factor for death and graft failure after RT; the summary estimate for RR was 1.79 (95% CI, 1.57–2.03; homogeneity test, $p = 0.0427$) and 1.56 (95% CI, 1.35–1.80; homogeneity test, $p = 0.0192$), respectively. As a cause of death, hepatocellular carcinoma (HCC) and liver cirrhosis were significantly more frequent among anti-HCV positive than anti-HCV negative RT patients.

This meta-analysis demonstrates that RT recipients with anti-HCV antibody have an increased risk of mortality and graft failure compared with HCV antibody negative patients.

Key words: Anti-HCV antibody, hepatitis C virus, meta-analysis, mortality, renal transplantation, survival

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Introduction

The natural history of hepatitis C virus (HCV) infection after renal transplantation (RT) remains incompletely understood (1). HCV infection is still highly prevalent both in developed and less-developed countries (1,2) among patients with end-stage renal disease (ESRD), including RT recipients, despite the screening of blood products for HCV. Chronic liver disease (CLD) is a frequent complication after RT, representing the fourth most frequent cause of death in some series (3), and HCV is the most important cause of CLD (4) in renal transplant patients.

Controversy continues about the natural history of HCV infection in patients even with normal kidney function. Defining the natural history of HCV remains difficult for several reasons: the disease has a very long duration (5), and determining its onset may be difficult. Additional factors can modify the course including coinfection with hepatitis B (HBV), human immunodeficiency virus (HIV) and alcohol use. Because treatment is widely used, future natural history studies of chronic HCV may not be possible as easily documented onset of infection, that is post-transfusional HCV, no longer occurs (6).

Assessing the natural history of hepatitis C among RT recipients is even more problematic because of additional characteristics of this population (7). Nephrologists have been reluctant to perform liver biopsy due to concern about abnormalities in platelet function in uremia. Aminotransferase activity is lower in patients with chronic renal failure than nonuremic population, and this may hamper recognition of HCV-related liver disease (8). Although third-generation anti-HCV testing is specific and sensitive in patients with ESRD, earlier versions of anti-HCV testing have been less reliable in ESRD patients because of the blunted humoral immune response that occur with renal disease: a small proportion of ESRD patients have HCV viremia in serum, but lacked detectable anti-HCV (9). However, it is a concern that the immunosuppressive therapy affects the course of HCV infection after RT (1).

Liver-related mortality is an important cause of death rate after RT but survival among kidney transplant recipients, although improved compared to ESRD patients remaining on dialysis, is several times lower than nonuremic patients (1–4); this may obscure long-term adverse consequences of hepatitis C after RT.

Mortality is an identifiable complication of liver disease and a reliable end-point in the natural history of HCV-associated liver disease. The goal of our study was to synthesize the available evidence on the impact of hepatitis C virus seropositivity on mortality after RT by performing a systematic review of the literature with a meta-analysis of clinical trials.

Materials and Methods

Search strategy and data extraction

Electronic searches of the National Library of Medicine's (Bethesda, MD, USA) MEDLINE database, Current Contents, Cochrane Library and manual searches of selected specialty journals were performed to identify all pertinent literature. It had been previously demonstrated that a MEDLINE search alone might not be sensitive enough (10). Four MEDLINE database engines (Ovid, PubMed, Embase and GratefulMed) were used. The key words 'hepatitis C', 'renal transplantation', 'mortality', 'natural history' and their synonyms were used. Reference lists from qualitative topic reviews and published clinical trials were also searched. Our search was limited to human studies that were published in the English literature. Data extraction was conducted independently by two investigators (F.F., V.D.) and consensus was achieved for all data. Studies were compared to eliminate duplicate reports for the same patients, which included contact with investigators when necessary. Eligibility and exclusion criteria were prespecified.

Criteria for inclusion

We included reports evaluating ESRD patients who underwent RT. Both case-control trials and cohort studies were considered eligible for inclusion in the analysis. HCV infection was defined by testing for anti-HCV antibody in serum. Information on anti-HCV antibody status was registered at the time of enrollment. Patient outcome collected included death, graft survival and loss to follow-up.

Ineligible studies

Studies were excluded if they reported inadequate data on survival. Trials that were only published in abstract form or as interim reports were excluded; letters and review articles were not considered for this analysis.

End-points of interest

The primary end-point was the adjusted relative risk (aRR) and 95% CI of all-cause mortality among RT recipients who were anti-HCV positive relative to those not infected. The aRR of all-cause mortality was specified by Cox proportional hazard analysis in each study. Cox proportional hazard analysis was used to estimate the independent effect of HCV serology status on patient survival after adjustment for differential follow-up time and distribution of potential confounders (e.g. recipient age at RT, gender, race, renal replacement years prior RT, cadaveric or living graft, diabetes mellitus, cause of donor death, proteinuria and serum creatinine after RT).

The secondary end-point was the aRR and 95% CI of graft failure among RT recipients who were anti-HCV seropositive relative to those not infected. The aRR of graft loss was specified by Cox proportional hazard analysis in

each study. Cox proportional hazards regression was used to assess the effect of HCV serology status per se on graft failure after adjustment for differential follow-up time and distribution of potential confounders (e.g. recipient age, last panel reactive antibodies, acute rejection, triglycerides, proteinuria and serum creatinine after RT).

An additional end-point was the relative risk (RR) and 95% CI of death rate due to liver disease among anti-HCV positive RT recipients relative to those who were anti-HCV negative.

Source of support

This meta-analysis was not supported by any pharmaceutical company, governmental agency or other grants.

Statistical methods

A summary estimate of the aRR of all cause mortality in anti-HCV seropositive to anti-HCV negative patients was generated by use of a random-effect approach, as described by DerSimonian and Laird (11) and a fixed effect model (12). The chi-square test statistics was used to test for homogeneity of the RR across studies. A two-sided p value of <0.05 was considered statistically significant.

Results

Literature review

Our electronic and manual searches identified 371 articles, of which 124 were considered potentially relevant and were selected for full text review. One hundred and fourteen reports were excluded. Ten reports (13–22) fulfilled the inclusion criteria; the trials by Pereira et al. (study 1 and 2) were addressed in three reports (13–15), the series by Morales et al. was reported in two papers (21,22). A total of eight clinical trials (with 6365 unique patients) were included in our meta-analysis. A complete list of the 124 reports reviewed is available from the authors on request. There was a 100% concordance between reviewers with respect to final inclusion and exclusion of studies reviewed based on the predefined inclusion and exclusion criteria.

Study design of clinical trials

Studies reported by Legendre et al. (16), Gentil et al. (17), Lee et al. (18), Bruchfeld et al. (20) and Morales et al. (21,22), described outcomes (death rate and graft loss) in RT recipients according to anti-HCV antibody status after RT (anti-HCV positive vs. anti-HCV negative patients). The report by Pereira et al. (13,15) included 29 recipients who had received donor organs (kidneys [n = 19], hearts [n = 6] and livers [n = 4]) from 13 anti-HCV positive cadaver organ donors (study group) and 74 recipients of organs (kidneys [n = 57], hearts [n = 6] and livers [n = 11]) from 37 randomly selected anti-HCV negative cadaver organ donors (control group). Another study by Pereira et al. (14,15) described 103 randomly selected recipients of kidneys from anti-HCV negative donors; testing of pretransplantation stored sera revealed positive results by anti-HCV ELISA in 23 (22%), 80 (78%) seronegative recipients constituted the control group. In Breitenfeldt's report (19), RT recipients who acquired HCV infection after transplantation were compared

with those who had been infected already before transplantation and with noninfected patients.

The diagnosis of HCV was based on the presence or absence of serum anti-HCV antibody by enzyme-linked immunoadsorbent assay (ELISA) in the eight clinical trials included in the study. First-generation assays were used during 1990–1991, second-generation during 1991–1997 and third-generation from 1997 onward. Bruchfeld et al. (20) confirmed serological assays by detection of HCV viremia (HCV RNA) with polymerase chain reaction (PCR) in 36 (71%) of 57 patients; 6 ELISA-positive patients tested repeatedly negative by PCR and had normal liver enzymes: they were classified as noninfected. Breitenfeldt et al. (19) and Gentil et al. (17) confirmed all anti-HCV positive patients by immunoblot techniques. No confirmation of ELISA results was made in the other reports (13–16,18,21,22).

Patient characteristics of clinical trials

Shown in Table 1 are some salient demographic characteristics of subjects in the eight clinical trials. Two (25%) studies were from centers in North America, one (12.5%) from Asia and five (62.5%) from Western Europe.

Baseline characteristics of the patients participating in these studies for this meta-analysis are shown in Table 2–4. The mean age of subject cohorts ranged from 38 ± 1 to 51 years of age. The gender distribution ranged from 52.9% to 71.5% male. The average follow-up ranged between 56.9 ± 36.5 and 130 months.

Pereira et al. (13–15), Legendre et al. (16), Gentil et al. (17), included only RT recipients from cadaver organ donors. No donor information was given by Lee et al. (18) and Morales et al. (21,22). In the report by Breitenfeldt et al. (19), there were 19 (2.6%) of 927 living donor kidneys, 2.1% (15/727) and 3.1% (4/130) in anti-HCV negative and anti-HCV positive patients, respectively (n.s.). Bruchfeld et al. (20) included 30.6% (175/571) living-donor kidneys,

31.5% (164/520) and 21.5% (11/51) among anti-HCV negative and anti-HCV positive RT recipients, respectively (n.s.).

An immunosuppressive regimen including micophenolate mofetil (with cyclosporine or tacrolimus) was less frequent in anti-HCV positive than anti-HCV negative recipients in the study by Morales et al. (21,22). Immunosuppressive treatment was given irrespective of hepatitis C antibody status in the reports by Bruchfeld et al. (20) and Breitenfeldt et al. (19). No clear information on this point was reported in the other studies (13–16,18).

Death rate in study groups

Table 5 reports the numbers of deaths and graft failures. Univariate analysis demonstrated that the death rate was significantly higher in anti-HCV positive than anti-HCV negative recipients in four (57.1%) of seven studies (16,17,19,20). Three (60%) of five surveys showed a significantly higher percentage rate of graft loss in anti-HCV positive than anti-HCV negative RT recipients (17,19,20).

As shown in Table 6, cardiovascular disease was a common cause of death over follow-up in three (75%) of four studies. No significant difference occurred between anti-HCV positive and anti-HCV negative patients by univariate analysis.

Table 7 shows causes of death ascribed to liver disease (liver cirrhosis and hepatocellular carcinoma [HCC]) in anti-HCV positive and anti-HCV negative patients. In three (37.5%) of eight studies, the frequency of death due to liver disease was significantly higher in anti-HCV positive than HCV-negative patients by univariate analysis (16,20,21). In the majority of the other reports (4/5 = 80%), the death rate due to liver disease was greater in anti-HCV positive than anti-HCV negative RT recipients but the limited number of patients precluded reaching statistical significance (13,15,17,19).

Table 8 reports the frequency of death due to infection. Univariate analysis demonstrated no significant difference between anti-HCV positive and anti-HCV negative patients after RT.

All included studies used Cox proportional hazard models to adjust for differential follow-up times and distribution of potential confounders in isolating the effect of HCV serology status per se on all cause mortality. The resulting adjusted risk ratio (RR) calculated in each study is shown in Table 9. The presence of anti-HCV antibody in serum after RT was an independent prognostic factor for mortality in the majority of studies, although sometimes of borderline statistical significance.

The adjusted risk ratio (aRR) calculated in each study of graft failure in anti-HCV positive versus anti-HCV negative patients after RT is shown in Table 10. Graft survival

Table 1: Baseline characteristics of studies included in analysis

Authors	Number of patients	Country of origin	Type of study	Reference year
Pereira B.J.G. et al. (study 1)	103	U.S.	C, R	1997
Pereira B.J.G. et al. (study 2)	103	U.S.	C, R	1997
Legendre Ch. et al.	499	France	Co, R	1998
Gentil M.A. et al.	320	Spain	Co, R	1999
Lee W.C. et al.	477	Taiwan	Co, R	2001
Breitenfeldt M.K. et al.	927	Germany	Co, R	2002
Bruchfeld A. et al.	571	Sweden	Co, R	2004
Morales J.M. et al.	3.365	Spain	Co, R	2004

C, controlled trial; P, prospective study; R, retrospective study; Co, cohort study.

Table 2: Baseline characteristics of studies included in analysis

Authors	Age, years	Gender, Male (%)	Mean follow-up after RT (months)
Pereira B.J.G. et al. (study 1)	40 (22)/48 (23)	20 (69%)/46 (62%)	68 (2–107)/70 (0–112)
Pereira B.J.G. et al. (study 2)	51 (21) /43 (19)	13 (57%)/50 (63%)	68 (1–104)/83 (1–112)
Legendre Ch. et al.	38 ± 1	69 (61.6%)/240 (62%)	79 ± 2/81 ± 5
Gentil M.A. et al.	39.2±11.9/39.6 ± 12.0	50 (58.8%)/144 (61.3%)	62.6 ± 35.5/56.9 ± 36.5
Lee W.C. et al.	38.6 ± 11.5	90 (59.6%)/190 (58.3%)	72 ± 84
Breitenfeldt A. et al.	40 ± 12/42 ± 13	93 (71.5%)/484(63%)	110.4 ± 52.8
Bruchfeld A. et al.	45.4 ± 13.7 / 45.5 ± 13.8	27 (52.9%)/340 (65.4%)	130
Morales J.M. et al.	n.a.	n.a.	n.a.

Figures are given for anti-HCV positive/anti-HCV negative patients when appropriate. Data for continuous variables are presented as median (inter-quartile range) by Pereira et al. n.a. = not available.

Table 3: Baseline characteristics of the studies included in the analysis

Authors	HBsAg pos.	Anti-HCV pos.	Prior renal transplant
Pereira B. J. G.. et al. (study 1)	1/24 (4%)/1/63 (2%)	21/92 (22.8%)	7/29 (24%)/5/74 (6.7%)
Pereira B.J.G. et al. (study 2)	0/22 (0%)/0/71 (0%)	23/103 (22.3%)	5/23 (21.7%)/8/80 (10%)
Legendre Ch. et al.	0	112/499 (22.4%)	0
Gentil M.A. et al.	2 (1.9%)/9 (3.9%)	85/320 (26.5%)	9/85 (10.6%)/10/235 (4.3%)
Lee W.C. et al.	62 (12.9%)	155 (31.6%)	n.a.
Breitenfeldt M.K. et al.	37 (3.9%)	160/927 (17.2%)	0
Bruchfeld A. et al.	0	51/561 (8.9%)	12/51 (23.5%)/53/520 (10.2%)
Morales J.M. et al.	76 (2.2%)	513/3365 (15.2%)	0

Figures are given for anti-HCV positive/ anti-HCV negative patients when appropriate. Data for continuous variables are presented as median (inter-quartile range) by Pereira et al. n.a. = not available.

Table 4: Baseline characteristics of the studies included in the analysis

Authors	Diabetes mellitus	Positive blood transfusion history	Time on dialysis prior RT
Pereira B.J.G. et al. (study 1)	n.a.	10 (19%)/10 (33%)	34 (54%)/14 (18%)
Pereira B.J.G. et al. (study 2)	n.a.	10(13%) / 7 (10%)	27 (81%)/16 (18%)
Legendre Ch. et al.	n.a.	n.a.	153±7/122 ± 3
Gentil M.A. et al.	5/85 (5.9%)/26/235 (11.6%)	15.8 ± 23.3/7.6 ± 13.2	67.4 ± 53.3/41 ± 32.0
Lee W.C. et al.	2/151 (1.3%)/18/326 (5.5%)	n.a.	27.9 ± 27.8
Breitenfeldt M.K. et al.	n.a.	6 ± 13.4/4.5 ± 7.8	5.4 ± 4.2/3.8 ± 3.4
Bruchfeld A. et al.	7/51 (13.7%)/98/520 (18.8%)	n.a.	5.7 ± 6.4/2.3 ± 3.6
Morales J.M. et al.	n.a.	n.a.	n.a.

Figures are given for anti-HCV positive and anti-HCV negative when appropriate. n.a. = not available.

was calculated after censoring for death by Morales et al. (21) and Breitenfeldt et al. (19). In the other studies (13–15,17,18,20), death with a functioning graft was considered as graft failure. No such information was provided by Legendre et al. (16).

Summary estimates of outcome

Based on the aRR and confidence bounds in Table 9, the summary estimate for aRR of mortality with anti-HCV

across the identified studies was 1.79 with a 95% CI of 1.57–2.03 (Fixed Effects Model). A test for homogeneity of the RRs across the eight studies gives a two-sided p value of 0.0427: the homogeneity assumption was borderline rejected. Thus, there is some evidence that there is not one underlying risk ratio, even though they were adjusted using a Cox model which would tend to make them comparable. The random effects confidence bounds are wider than those calculated by fixed effects model (Table 9).

Table 5: Death rate and graft loss over follow-up

Authors	Anti-HCV positive		Anti-HCV negative	
	Death	Graft loss	Death	Graft loss
Pereira B.J.G. et al. (study 1)	37.9% (11/29)	58.6% (17/29)	36.1% (26/72)*	57.5% (42/73)†
Pereira B.J.G. et al. (study 2)	40.9% (9/22)	54.5% (12/22)	20.5% (16/78)*	43% (34/79)†
Legendre Ch. et al.	13.4% (15/112)	n.a.	4.9% (19/387)**	n.a.
Gentil M.A. et al.	15.3% (13/85)	36.5% (31/85)	4.7% (11/235)***	17.9% (42/235)††
Lee W.C. et al.	20.5% (31/151)	n.a.	14.1% (46/326)*	n.a.
Breitenfeldt M.K. et al.	29.2% (38/130)	51.5% (67/130)	20.6% (164/797)****	40.6% (324/797)†††
Bruchfeld A. et al.	56.9% (29/51)	74.5% (38/51)	32.7% (170/520)****	47.7% (248/520)††††
Morales J.A. et al.	n.a.	n.a.	n.a.	n.a.

n.a. = not available.

Anti-HCV positive versus anti-HCV negative patients; *n.s., **p = 0.01, ***p = 0.003, ****p = 0.001.

Anti-HCV positive versus anti-HCV negative patients; †n.s., ††p = 0.001, †††p = 0.025, ††††p = 0.0001.

Table 6: Deaths from cardiovascular diseases in the studies included in the analysis

Authors	Deaths from cardiovascular diseases (study group)	Anti-HCV positive	Anti-HCV negative
Pereira B.J.G. et al. (study 1)	n.a.	n.a.	n.a.
Pereira B.J.G. et al. (study 2)	n.a.	n.a.	n.a.
Legendre Ch. et al.	n.a.	n.a.	n.a.
Gentil M.A. et al.	29.2% (7/24)	38.5% (5/13)	18.2% (2/11)*
Lee W.C. et al.	5.2% (4/77)	0 (0/31)	8.7% (4/46)*
Breitenfeldt M.K. et al.	26.7% (54/202)	34.2% (13/38)	25.0% (41/164)*
Bruchfeld A. et al.	51.7% (103/199)	44.8% (13/29)	52.3% (89/170)*
Morales J.M. et al.	n.a.	n.a.	n.a.

n.a. = not available.

Anti-HCV positive versus anti-HCV negative patients: *n.s.

Table 7: Deaths from liver disease in the studies included in the analysis

Authors	Deaths from liver disease (study group)	Anti-HCV positive	Anti-HCV negative
Pereira B.J.G. et al. (study 1)	9% (3/33)	22.2% (2/9)	4.2% (1/24)*
Pereira B.J.G. et al. (study 2)	8% (2/25)	11% (1/9)	6% (1/16)*
Legendre Ch. et al.	20.6% (7/34)	40% (6/15)	5.3% (1/19)**
Gentil M.A. et al.	12.5% (3/24)	15.4% (2/13)	9% (1/11)*
Lee W.C. et al.	35% (27/77)	32.2% (10/31)	36.9% (17/46)*
Breitenfeldt M.K. et al.	2.5% (5/202)	2.6% (1/38)	2.4% (4/164)*
Bruchfeld A. et al.	1% (2/199)	6.9% (2/29)	0% (0/170)***
Morales J.M. et al.	n.a.	13.85%	0.6%**

n.a. = not available.

Anti-HCV positive versus anti-HCV negative patients: **p = 0.040, ***p = 0.01, *n.s.

Because there are only eight trials, we could not explore potential sources of variation across studies (i.e. sensitivity analysis). The qualitative presentation of descriptive data has been provided in Table 2–5.

The summary estimate for aRR of graft loss with anti-HCV antibody across the selected studies was 1.56 with a 95%

CI of 1.35–1.80 (Fixed Effects Model). A test for homogeneity of the RRs across the eight studies gives a two-sided p value of 0.0192.

Figures 1 and 2 show the estimated log RR for each study ± two SEs, that is, the 95% CIs. We use the log RR scale since the CIs are only symmetric on this scale.

Table 8: Deaths from infections in the study groups included in the analysis

Authors	Deaths from infections (study group)	Anti-HCV positive	Anti-HCV negative
Pereira B.J.G. et al. (study 1)	39.4% (13/33)	11.1% (1/9)	50% (12/24)*
Pereira B.J.G. et al. (study 2)	48% (12/25)	78% (7/9)	31.2% (5/16)*
Legendre Ch. et al.	17.6% (6/34)	27% (4/15)	10.5% (2/19)*
Gentil M.A. et al.	37.5% (9/24)	30.8% (4/13)	45.4% (5/11)*
Lee W.C. et al.	41.5% (32/77)	51.6% (16/31)	34.8% (16/46)*
Breitenfeldt M.K. et al.	14.8% (30/202)	13.1% (5/38)	15.2% (25/164)*
Bruchfeld A. et al.	16% (32/199)	17.2% (5/29)	15.9% (27/170)*
Morales J.M. et al.	n.a.	n.a.	n.a.

n.a. = not available.

Anti-HCV positive versus anti-HCV negative patients: *n.s.

Discussion

Controversy persists regarding the impact of HCV infection on renal transplant recipients. Numerous studies have evaluated the effect of HCV on graft and patient survival after RT; initial studies mostly focused on 5-year survival rates and generally failed to show a difference between anti-HCV positive and anti-HCV negative patients (23–28). However, liver disease develops late after RT (6); and the majority of surveys with large size and adequate follow-up have recently demonstrated a detrimental effect of HCV on patient and graft survival (29–31). A recent report suggested that patients with anti-HCV antibodies had better survival when compared with patients without anti-HCV antibody with up to 15-year follow-up (32).

It is somewhat difficult to reconcile these varying results; these were all single center or regional surveys, and center-specific factors have been invoked to reconcile the conflicting results. Batty et al. (33) in a historical cohort analysis (33 479 RT in the United States) found that mortality was significantly linked to HCV seropositive status (aRR, 1.23 [95% CI; 1.01–1.49], $p < 0.04$), but the data from the US-RDS database (73 707 adult primary solitary RT recipients) demonstrated that the overall patient survival was not any worse in hepatitis C positive versus hepatitis C negative RT recipients (34).

Mortality is a reliable end-point in the natural history of HCV after RT but other outcomes have also been addressed in HCV-infected renal allograft recipients. In a case-control, retrospective survey Zylberberg et al. (35) found that the yearly progression rate of hepatic histological activity and fibrosis was significantly higher in the RT recipients as compared with the immunocompetent group. In contrast, Alric and coworkers (36) found that in most HCV-infected patients progression of liver fibrosis after RT is slow. In their prospective trial, progression of liver fibrosis per year was significantly lower for RT recipients than for matched patients with HCV and normal renal function.

In order to better characterize the outcome for RT recipients who are HCV positive, we undertook a meta-analysis of observational studies giving adjusted estimates of all cause mortality which may be the most readily available and reliable end point in assessing the natural history of HCV after RT. We observed that the aRR of all-cause mortality and graft failure was significantly higher for seropositive HCV recipients after RT. We used the aRR that had been obtained by the Cox regression model in each study; this approach takes into account both differential follow-up time as well as differential distribution of covariates in order to isolate the effect of HCV serology status per se.

Three single-center studies have additionally evaluated the effect of HCV on patient and graft survival and performed Cox's model (32,37,38). They were excluded by this meta-analysis for different reasons—the crude aRR value was not shown (32,37); alternatively, the HCV seropositive group was divided into a chronic hepatitis and a nonchronic hepatitis group (38). Two of them demonstrated an impact of HCV on death rate (37,38).

Our findings are consistent with accumulating evidence from other sources. A recent survey from the United States Renal Data System (USRDS) observed an independent and significant association between seropositive anti-HCV status donor status and patient mortality after RT (aRR 2.66 [95% CI, 1.38–5.13], $p < 0.003$) (39). Kasiske et al. (40) have identified 11 659 Medicare beneficiaries who received their first kidney transplant in 1996–2000, and demonstrated that the post-transplant diabetes mellitus (PTDM) was associated with death-censored graft failure and mortality. Using Cox's analysis, HCV infection was a significant risk factor for PTDM (aRR, 1.33 [95% CI, 1.15–1.55], $p < 0.0001$). Stehman-Breen et al. (41) retrospectively found that HCV in kidney-pancreas transplant patient results in an increased risk of kidney allograft failure (aRR, 5.1 [95% CI, 1.7–15.4], $p < 0.002$) and death (aRR, 3.7 [95% CI, 1.5–20], $p < 0.01$).

Table 9: Anti-HCV positive versus anti-HCV negative patients: aRR of all-cause mortality homogeneity test (fixed effects model) $p = 0.0427$

Authors	Adjusted relative risk	95% CI	p
Pereira B.J.G. et al. (study 1)	1.00	0.49–2.02	0.25
Pereira B.J.G. et al. (study 2)	2.6	1.15–5.90	0.001
Legendre Ch. et al.	2.80	1.4–5.7	0.0001
Gentil M.A. et al.	3.1	1.2–7.8	0.001
Lee W.C. et al.	1.569	0.751–1.113	0.1148
Breitenfeldt M.K. et al.	1.93	1.031–3.425	0.0453
Breitenfeldt M.K. et al. ¹	1.00	n.a.	0.25
Bruchfeld A. et al.	2.23	1.48–3.34	0.0001
Morales J.M. et al.	1.505	1.121–2.021	0.0065
Overall fixed effects	1.79	1.57–2.03	
Overall random effects	1.93	1.40–2.65	

aRR: adjusted relative risk by Cox proportional hazard model.
 Pereira (1): aRR adjusted for time on dialysis, prior transplants, age, type of organ.
 Pereira (2): aRR adjusted for age, time on dialysis, prior transplants.
 Legendre: aRR adjusted for age, time on dialysis, gender and transplantation year.
 Gentil: aRR adjusted for donor age, donor gender, cause of brain death, recipient age, recipient gender, time on dialysis, underlying nephropathy, number of prior transplants, pretransplant transfusions, peak and immediate pretransplant immunization, number of HLA AB and HLA mismatches, cold ischaemia time and pretransplant clinical liver disease.
 Bruchfeld: aRR adjusted for age, gender, diabetes, prior transplant, type of transplant (cadaveric vs. living graft) and time on dialysis.
 Breitenfeldt: aRR adjusted for time on dialysis, HBsAg positivity, age, acute rejection, HBV/HCV coinfection and HCV post-RT.
 Breitenfeldt¹: aRR adjusted for time on dialysis, HBsAg positivity, age, acute rejection, HBV/HCV coinfection and HCV at RT.
 Lee: aRR adjusted for gender, dialysis mode, time on dialysis, HBV, hypertension, diabetes mellitus and hepatoma.
 Morales: aRR adjusted for recipient age, cause of death, serum creatinine levels at 3 months, proteinuria at 3 months, serum creatinine and proteinuria increase from 3 months to 1 year.

In this meta-analysis, the increased mortality in anti-HCV positive patients was at least partially related to an increase in liver-related death; the frequency of HCC and liver cirrhosis as causes of death was significantly higher among anti-HCV positive than -negative patients after RT in many studies included in this systematic review. RT recipients have a significant increase in viral load after transplantation (42), related to immunosuppression after RT; also, a link between liver deterioration and high viraemia has been suggested (1,2,6).

No other differences (including infections) in causes of death occurred between anti-HCV positive and -negative groups. Cardiovascular and infectious diseases remain important causes of death among RT recipients (1,2,4) and

Table 10: Anti-HCV positive versus -negative patients: aRR of graft loss homogeneity test (fixed effects) $p = 0.0192$

	Adjusted relative risk	95% CI	p
Pereira B.J.G. et al. (study 1)	0.95	0.54–1.67	0.25
Pereira B.J.G. et al. (study 2)	1.30	0.66–2.58	0.35
Legendre Ch. et al.	n.s.	n.s.	n.s.
Gentil M.A. et al.	3.0	1.8–5.0	0.001
Lee W.C. et al.	1.25	0.751–1.322	0.3058
Breitenfeldt M.K. et al.	1.00	n.s.	0.25
Bruchfeld A. et al.	1.96	1.37–2.79	0.0002
Morales J.A. et al.	1.585	1.274–1.973	0.0001
OVERALL Fixed Effects	1.56	1.35–1.80	
OVERALL Random Effects	1.57	1.09–2.27	

aRR: adjusted relative risk by Cox proportional hazard model.
 Pereira: aRR adjusted for time on dialysis, age, number of prior transplants and type of organ transplanted.
 Gentil: aRR adjusted for donor age, donor gender, cause of brain death, recipient age, recipient gender, time on dialysis, underlying nephropathy, number of prior transplants, pretransplant transfusions, peak and immediate pretransplant immunization, number of HLA AB and HLA DR mismatches, year of transplantation, cold ischaemia time and pretransplant clinical liver disease.
 Bruchfeld: aRR adjusted for age at transplantation, gender, diabetes mellitus, prior transplants, type of transplant (cadaveric vs. living graft) and time on renal replacement therapy.
 Breitenfeldt: aRR adjusted for HBsAg, HBV and HCV coinfection, acute rejection, age at transplantation, time on dialysis, HCV after transplantation and HCV at transplantation.
 Lee: aRR adjusted for gender, dialysis mode, time on dialysis, diabetes mellitus, hypertension, HBsAg and hepatoma.
 Morales: aRR adjusted for recipient age, last panel reactive antibodies, acute rejection, serum creatinine levels and proteinuria at 3 months, serum creatinine and proteinuria increase from 3 months to 1 year, use of angiotensin II receptor blockers (ARB II) and angiotensin-converting enzyme inhibitors (ACEI).

this diagnosis was common in all the clinical trials included in our study.

An accelerated loss of the graft in HCV-positive renal transplant recipients has been related to an increased frequency of *de novo* immune-mediated glomerular lesions, especially type 1 membranoproliferative glomerulonephritis, after RT (43). Thus, an additional rationale to treat HCV-infected patients is to potentially prevent post-transplant HCV-related glomerulonephritis, as recently indicated (44).

This meta-analysis is potentially biased by numerous issues. First, all the clinical studies enrolled in the current meta-analysis were retrospective, observational studies. In fact, although much has been learned about the course of HCV in the immunosuppressed renal allograft recipient, the available data is of limited nature due to the lack of carefully controlled studies that provide pretransplant baseline data and sequential follow-up, including liver histology. Prospective studies of patients who are identified as HCV-infected during the pretransplant evaluation are in progress, all

Figure 1: Estimated logRR (all-cause mortality) for each study and 95% CIs. The vertical line represents the summary logRR.

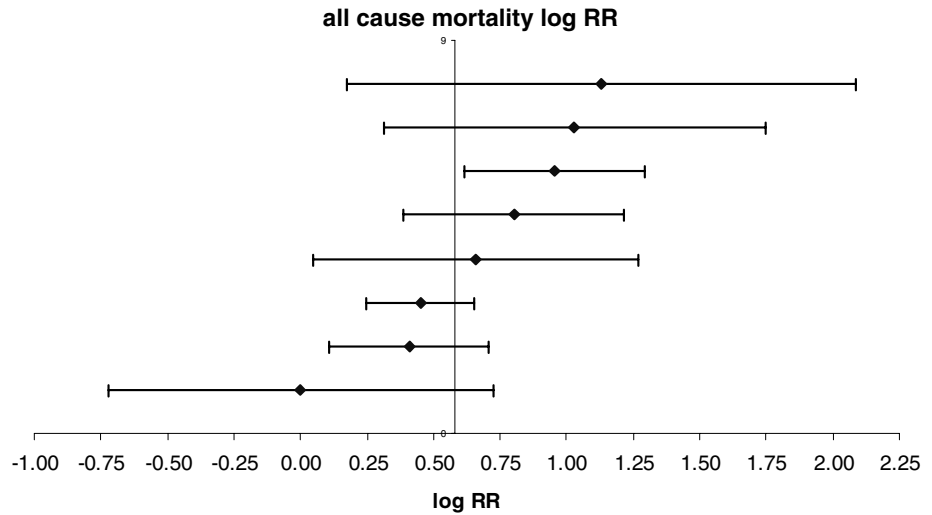
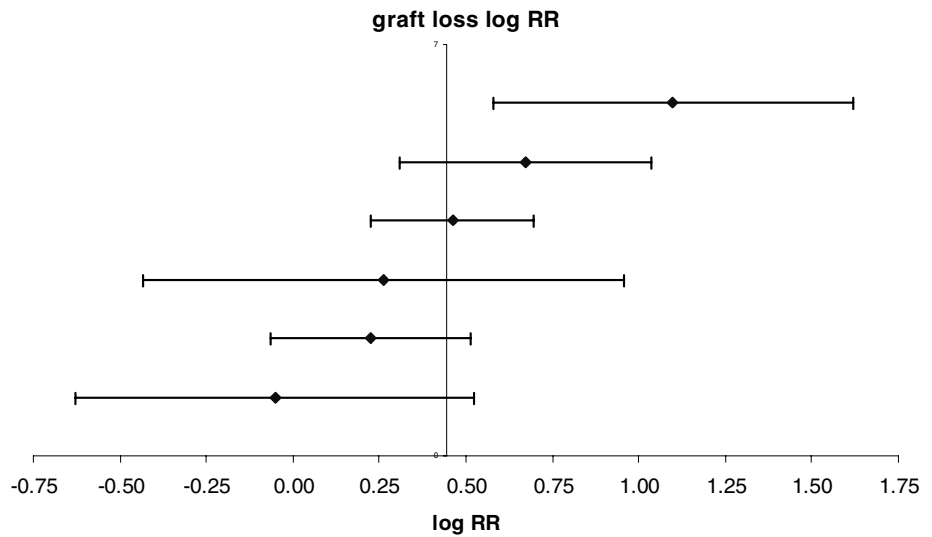


Figure 2: Estimated logRR (graft loss) for each study and 95% CIs. The vertical line represents the summary log RR.



patients undergoing through virologic evaluation and baseline pretransplant liver biopsy. Follow-up liver biopsies will be made in a significant number of patients. Second, the observational nature of all the clinical studies included in this meta-analysis may give incomplete information on additional unmeasured confounders that could introduce bias into the analysis. Incomplete information was available in these studies about confounding factors affecting hepatocarcinogenesis in nonuremic patients with hepatitis C (6), for example alcohol consumption, occult HBV infection, HIV status and increased hepatic iron content. However, it is unlikely that the alcohol consumption was more excessive in anti-HCV positive patients after RT; also, the link between hepatocarcinogenesis and occult HBV infection in general population is still controversial (6). HIV prevalence is very low among RT recipients in developed countries. Third, anti-HCV antibody was assessed only at entry, anti-HCV negative patients might have become positive during the study period, and vice versa. On the other hand, the

frequency of *de novo* HCV after RT in developed countries is extremely low (1,2); it has been reported that only 8.1% of anti-HCV seropositive dialysis patients became negative during the follow-up due to resolution of infection (45). Thus, it is unlikely that repeat anti-HCV testing during the follow-up might have affected the results. Fourth, individual data from each study (e.g. 'patient-level data') were not available; thus, it was impossible to perform our own adjustments. Based on the RR reported in each study, we have calculated our summary estimate for RR of mortality with anti-HCV across the studies. However, we used aRR obtained by Cox model in each study- this approach takes into account both differential follow-up time as well as differential distribution of covariates in order to isolate the effect of HCV seropositive status per se. Finally, as with all meta-analyses, this study has the potential limitation of publication bias; negative trials are less likely to be published. To limit the possible effect of publication bias, we used several strategies for identifying studies to include

published and unpublished studies. Inclusion criteria, established a priori, were chosen to increase the likelihood that high-quality studies would be included.

Although our meta-analysis links the HCV seropositive status with diminished patient and graft survival after RT, transplantation of HCV positive kidneys is associated with improved survival for dialysis patients receiving such a transplant compared to remaining in the renal waiting list and dialysis dependent. A recent analysis of Medicare beneficiaries included in the RT waiting list suggested that transplantation from a hepatitis C positive donor is associated with improved survival compared to staying on the waiting list (aRR 0.76; 95% CI, 0.60–0.96) (46). Of patients receiving HCV positive donor kidneys, 52% were themselves HCV antibody positive. Transplantation of all deceased donor kidneys was also associated with a survival advantage, and the benefit was larger (46).

In conclusion, this meta-analysis demonstrates that HCV seropositive patients have lower patient and graft survival than seronegative patients after RT. Mortality due to HCC and liver cirrhosis are at least partially responsible for this finding. The higher risk of death in HCV seropositive patients has been linked to enhanced viral replication which supports worsening of liver disease after RT. Prospective trials with extended follow-up may help to better define the natural history of HCV in this population.

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