

## Meta-analysis: effect of hepatitis C virus infection on mortality in dialysis

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### SUMMARY

**Background:** The natural history of hepatitis C virus infection among patients on long-term dialysis treatment remains incompletely understood. Efforts to elucidate the natural history of hepatitis C virus in this population are difficult because of the slowly progressive nature of hepatitis C virus with often an unrecognized onset in patients whose life-expectancy is substantially diminished by end-stage renal disease.

**Aim:** To conduct a systematic review of the published medical literature concerning the impact of hepatitis C virus infection on the survival of patients receiving chronic dialysis. The relative risk of mortality was regarded as the most reliable outcome end-point.

**Methods:** We used the random effects model of DerSimonian and Laird to generate a summary estimate of the relative risk for mortality with hepatitis C virus across the published studies.

**Results:** We identified four clinical trials (2341 unique patients); three (75%) of them were prospective, cohort

studies; the fourth was a case-control study. Pooling of study results demonstrated that presence of antihepatitis C virus antibody was an independent and significant risk factor for death in patients on maintenance dialysis. The summary estimate for relative risk was 1.57 with a 95% confidence interval (CI) of 1.33–1.86. A test for homogeneity of the relative risks across the four studies gave a *P*-value of 0.77. As a cause of death, hepatocellular carcinoma and liver cirrhosis were significantly more frequent among antihepatitis C virus-positive than -negative dialysis patients.

**Conclusions:** This meta-analysis demonstrates that antihepatitis C virus-positive patients on dialysis have an increased risk of mortality compared with hepatitis C virus-negative patients. The excess risk of death in hepatitis C virus-positive patients may be at least partially attributed to chronic liver disease with its attendant complications. Clinical trials with extended follow-up are currently under way to assess the effect of hepatitis C virus treatment on the excess risk of mortality in this population.

### INTRODUCTION

The consequences of hepatitis C virus (HCV) infection in dialysis population remain incompletely understood. HCV infection remains highly prevalent both in

developed<sup>1–4</sup> and less-developed countries<sup>2, 5–7</sup> despite advances in knowledge in this area. HCV plays a key role in the development of liver disease and hepatic malignancy in dialysis patients.<sup>2, 8</sup>

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,<sup>9</sup> and timing its onset may be difficult relying

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on potential exposures. Additional factors can modify the course including co-infection with hepatitis B virus (HBV), human immunodeficiency virus (HIV) and alcohol use. Because treatment is widely used, future natural history studies of chronic HCV may not be performed in the future particularly as easily documented onset of infection, e.g. post-transfusional, no longer typically occurs.<sup>10, 11</sup>

Assessing natural history of hepatitis C among patients on maintenance dialysis is more problematic because of additional characteristics of this population.<sup>2</sup> Nephrologists are usually reluctant to perform liver biopsy in dialysis patients because of abnormalities in platelet function in end-stage renal disease (ESRD). Aminotransferase activity is lower in dialysis than non-uraemic patients, and this may hamper recognition of HCV-related liver disease.<sup>2</sup> Anti-HCV testing has not been reliable in dialysis patients because of the blunted humoral immune response that occur with renal disease; a small proportion of patients with ESRD have HCV viraemia in serum, but lacked detectable anti-HCV with earlier generation enzyme-linked immunosorbent (ELISA) assays.<sup>12</sup> Liver-related mortality in dialysis patients is usually low; also, mortality in the dialysis population is several times higher than non-uraemic patients;<sup>13</sup> this may obscure the long-term consequences of hepatitis C in dialysis patients.

Mortality is an identifiable complication of liver disease and a reliable end-point in the natural history of HCV-associated liver disease. The primary goal of this study was to synthesize the available evidence on the impact of HCV infection on mortality in dialysis population 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) MEDLINE database, Current Contents, and manual searches of selected speciality journals were performed to identify all pertinent literature. It had been previously demonstrated that a MEDLINE search alone may not be sensitive enough.<sup>14</sup> Four MEDLINE database engines (Ovid, PubMed, Embase and GratefulMed) were used. The keywords 'hepatitis C', 'survival', 'dialysis', 'mortality' and 'natural history' 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 surveys evaluating patients with ESRD undergoing maintenance dialysis [haemodialysis (HD) and peritoneal dialysis (PD)]. 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 status was registered at the time of enrolment. 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 as abstracts 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% confidence interval (CI) of all-cause mortality among dialysis patients 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. The Cox proportional hazard analysis was used to estimate the independent effect of HCV status on survival after adjustment for differential follow-up time and distribution of potential confounders (e.g. age, gender, race, time on dialysis, transplantation, history of previous transplants and diabetes mellitus).

The secondary end-points were the RR and 95% CI of death rate because of liver disease and infection among dialysis patients who were anti-HCV-positive relative to those not infected. Each study presented these data in a form that could be used to construct a 2 × 2 contingency table.

*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-positive to anti-HCV-negative patients was generated by use of a random-effect approach, as described by DerSimonian and Laird.<sup>15</sup> The chi-square test statistics was used to test for homogeneity of the aRR across studies. A two-sided *P*-value of <0.05 was considered statistically significant.

**RESULTS**

*Literature review*

Our electronic and manual searches identified 214 articles, of which 132 were considered potentially relevant and were selected for full text review. Four studies<sup>16–20</sup> fulfilled the inclusion criteria and 128 were excluded. Two papers issued the same study.<sup>16, 20</sup> The list of the 132 references is available from the authors on request.

A total of 2341 unique patients was included in our meta-analysis. 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.

*Patient characteristics*

Shown in Table 1 are some salient demographic characteristics of subjects enrolled in the included clinical trials. Two (50%) studies were from centres in North America and two (50%) from either Western Europe or Asia. Baseline characteristics of the patients participating in the studies included in this

meta-analysis are shown in Table 2. The mean age of subject cohorts ranged from 40 to 57.2 years of age. The gender distribution ranged from 53 to 60.5% male. The average follow-up ranged between 3 and 8 years. As listed in Table 3, the majority of the patients included in this study did not undergo renal transplantation (RT) over the follow-up, with the exception of the study by Pereira *et al.*<sup>17</sup>

*Death rate in study groups*

Table 3 reports the number of deaths over follow-up. Univariate analysis demonstrated that the death rate over follow-up was significantly higher in anti-HCV-positive than -negative patients in three of the four included studies.<sup>17–19</sup>

As shown in Table 4, cardiovascular disease was a common cause of death over follow-up in the four studies. No significant difference occurred between anti-HCV-positive and -negative patients by univariate analysis.

Table 5 shows the causes of death ascribed to liver disease [liver cirrhosis and hepatocellular carcinoma (HCC)] in anti-HCV-positive and anti-HCV-negative patients over follow-up. The frequency of deaths as a result of liver disease was higher in anti-HCV-positive than HCV-negative patients by univariate analysis.

Table 6 reports the frequency of death because of infection over follow-up. Univariate analysis demonstrated no significant difference between anti-HCV-positive and -negative patients.

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 status on all-cause mortality. The resulting adjusted risk ratio calculated in each study has been reported in Table 7. Presence of anti-HCV antibody in serum was an independent prognostic factor for mortality in all the studies, although sometimes of borderline statistical significance.

Table 1. Baseline characteristics of studies included in analysis

Authors	Number of patients	Country of origin	Type of study	Dialysis type	Reference year
Pereira <i>et al.</i> <sup>17</sup>	496	USA	CCS, R	HD, PD	1998
Stehman-Breen <i>et al.</i> <sup>16</sup>	200	USA	CS, P	HD, PD	1998
Nakayama <i>et al.</i> <sup>18</sup>	1470	Japan	CS, P	HD	2000
Espinosa <i>et al.</i> <sup>19</sup>	175	Spain	CS, P	HD	2001

CCS, case-control study; R, retrospective; CS, cohort study; P, prospective; HD, haemodialysis; PD, peritoneal dialysis.

Table 2. Baseline characteristics of studies included in analysis

Characteristics	Pereira <i>et al.</i> <sup>17</sup>	Stehman-Breen <i>et al.</i> <sup>16</sup>	Nakayama <i>et al.</i> <sup>18</sup>	Espinosa <i>et al.</i> <sup>19</sup>
Mean follow-up (months)	73	37	72	96
Gender, male (%)	276 (55.6)	116 (58)	890 (60.5)	93 (53)
Race, Caucasian (%)	373 (75)	89 (44.5)	0	175 (100)
Anti-HCV rate (%)	223 (45)	44 (22)	276 (18.8)	57 (32.5)
Age (years)*	40	51.8/57.2	54.7/55.6	52.7/53.4
Diabetes mellitus	94 (18.9%)	65 (32.5%)	221 (15%)	8 (4.6%)
HBsAg rate (%)	8/379 (2.1)	5 (2.5)	22 (1.5)	8 (4.6)
HBsAg-positive/ anti-HCV-positive (%)	NA	1 (2.3)	3 (1.1)	2 (3.5)
Positive blood transfusion history	254/286 (88%)	108 (54%)	799 (54%)	NA
Dialysis modality, HD	411/479 (86%)	195/200 (97.5%)	100%	100%
Intravenous drug use	NA	13/200 (6.5%)	NA	NA
HIV-positive patients	NA	1/200 (0.5%)	NA	NA
Prior renal transplantation	NA	NA	NA	24/175 (11.4%)

\* Figures are given for anti-HCV-positive/anti-HCV-negative when appropriate.

HCV, hepatitis C virus; HD, haemodialysis; HIV, human immunodeficiency virus; NA, not available.

Authors	Anti-HCV-positive		Anti-HCV-negative	
	Death	Subsequent RT	Death	Subsequent RT
Pereira <i>et al.</i> <sup>17</sup>	84/223 (38)	111 (50)	70/273 (26)*	191 (70)
Stehman-Breen <i>et al.</i> <sup>16</sup>	24/44 (54.5)	1 (2.2)	90/156 (57.6)**	18 (11.5)
Nakayama <i>et al.</i> <sup>18</sup>	91/276 (33)	1 (0.3)	277/1194 (23.1)***	5 (0.4)
Espinosa <i>et al.</i> <sup>19</sup>	34/57 (59.6)	9 (15.8)	47/118 (39.8)****	33 (28)

Death from all causes in the studies included in the analysis: anti-HCV-positive vs. anti-HCV-negative subjects: \*  $P = 0.005$ , \*\*  $P = \text{NS}$ , \*\*\*  $P = 0.0001$ , \*\*\*\*  $P = 0.020$ .

Values in parentheses expressed as percentage.

HCV, HCV, hepatitis C virus; RT, renal transplantation.

Table 3. Mortality and subsequent transplantation in dialysis patients over follow-up

Authors	Deaths from cardiovascular diseases (study group)	Deaths from cardiovascular diseases	
		Anti-HCV-positive	Anti-HCV-negative
Pereira <i>et al.</i> <sup>17</sup>	NA	NA	NA
Stehman-Breen <i>et al.</i> <sup>16</sup>	44% (50/114)	44% (40/90)*	41% (10/24)
Nakayama <i>et al.</i> <sup>18</sup>	73% (129/368)	32% (29/91)*	36% (100/277)
Espinosa <i>et al.</i> <sup>19</sup>	30% (24/81)	26% (9/34)*	32% (15/47)

NA, not available; HCV, hepatitis C virus.

Anti-HCV-positive vs. anti-HCV-negative patients: \*N.S.

Table 4. Deaths from cardiovascular diseases in the studies included in the analysis

### Summary estimates of outcome

Based on the aRR and confidence bounds reported in Table 7, the summary estimate for aRR of mortality with anti-HCV across the identified studies was 1.57

with a 95% CI of 1.33–1.86. A test for homogeneity of the RRs across the four studies gives a two-sided  $P$ -value of 0.77, i.e. the homogeneity assumption was not rejected. Because there are only four studies, we could not explore potential sources of variation across

Table 5. 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 <i>et al.</i> <sup>17</sup>	9% (12/133)	14.4% (11/76)*	2% (1/57)
Stehman-Breen <i>et al.</i> <sup>16</sup>	NA	NA	NA
Nakayama <i>et al.</i> <sup>18</sup>	2.4% (9/368)	8.8% (8/91)**	0.4% (1/277)
Espinosa <i>et al.</i> <sup>19</sup>	4.9% (4/81)	12% (4/34)***	0% (0/47)

NA, not available; HCV, hepatitis C virus.  
 Anti-HCV-positive vs. anti-HCV-negative patients: \*P = 0.031, \*\*P = 0.0001, \*\*\*P = 0.059.

Table 6. Deaths from infections in the study groups included in the analysis

Authors	Deaths from infections (study group)		
	Anti-HCV-positive	Anti-HCV-negative	
Pereira <i>et al.</i> <sup>17</sup>	28.5% (38/133)	29% (22/76)*	28% (16/57)
Stehman-Breen <i>et al.</i> <sup>16</sup>	18% (21/114)	25% (6/24)*	17% (15/90)
Nakayama <i>et al.</i> <sup>18</sup>	13.6% (50/368)	14% (13/91)*	13% (37/277)
Espinosa <i>et al.</i> <sup>19</sup>	13.5% (11/81)	8.8% (3/34)*	17% (8/47)

NA, not available; HCV, hepatitis C virus.  
 Anti-HCV-positive vs. anti-HCV-negative patients: \*N.S.

Table 7. Anti-HCV-positive vs. -negative patients: aRR of all-cause mortality

Authors	aRR	95% CI
Pereira <i>et al.</i> <sup>17</sup>	1.41	1.01–1.97
Stehman-Breen <i>et al.</i> <sup>16</sup>	1.97	1.16–3.33
Nakayama <i>et al.</i> <sup>18</sup>	1.57	1.23–2.00
Espinosa <i>et al.</i> <sup>19</sup>	1.62	1.05–2.49

aRR: adjusted relative risk by Cox proportional hazard model.  
 Stehman-Breen *et al.*<sup>16</sup>: aRR adjusted for anti-HCV, time on dialysis, age, transplantation, race, diabetes, dialysis modality, intravenous drug use, and gender.  
 Espinosa *et al.*<sup>19</sup>: aRR adjusted for anti-HCV, age, male gender, diabetes mellitus as cause of ESRD, history of previous transplants, time on dialysis, and transplantation over the follow-up.  
 Nakayama *et al.*<sup>18</sup>: aRR adjusted for anti-HCV, age, time on dialysis, gender and diabetes.  
 Pereira *et al.*<sup>17</sup>: aRR adjusted for diabetes, number of prior transplants, gender, race, anti-HCV, transplantation and age.  
 HCV, hepatitis C virus; CI, confidence interval.

studies (i.e. sensitivity analysis). The qualitative presentation of descriptive data has been provided in Table 2.

**DISCUSSION**

Numerous cross-sectional surveys<sup>21–31</sup> estimated the point prevalence of liver disease in dialysis patients with HCV. In general, the reported proportion of patients with cirrhosis or advanced fibrosis has ranged from 5

and 32%. Furthermore, there was no demonstrable association between aminotransferase activity or HCV viraemia and severity of histopathological changes on liver biopsy suggesting that liver biopsy is the most accurate tool for assessing severity of hepatitis C. Unfortunately, duration of HCV infection was not easily established and no follow-up biopsies were obtained in these series. Assessment of natural history of HCV in dialysis patients must consider the incidence and consequences of liver disease over time.

Adjusted estimates of all-cause mortality may be the most readily available and reliable end-point in assessing the natural history of HCV among dialysis patients. Our meta-analysis aimed to clarify the impact of HCV status on survival in the dialysis population. We demonstrated that the overall RR for death in anti-HCV-positive patients was significantly higher than anti-HCV-negative patients on maintenance dialysis. Liver disease has been implicated in the higher risk of death in infected HCV patients<sup>32–34</sup> with the additive effect of altered immunity because of uraemia in subjects with ESRD.<sup>35</sup>

Our findings are consistent with accumulating evidence from other sources. A recent survey (DOOPS study) on patients undergoing dialysis in three continents reported an independent and significant association between positive anti-HCV antibody and mortality (RR: 1.17, P < 0.0159).<sup>36</sup> Also, mortality risk was

additionally associated with anti-HCV antibody status in the latest multicentre survey ( $n = 206\ 134$  dialysis patients) performed by the Japanese Society for Dialysis.<sup>1</sup>

In this meta-analysis, the increased mortality in anti-HCV-positive patients was at least partially related to an increase in liver-related death rate: the frequency of HCC and liver cirrhosis as causes of death was significantly higher among anti-HCV-positive than anti-HCV-negative dialysis patients in all the surveys included in this systematic review. No other differences (including infections) in causes of death occurred between anti-HCV-positive and -negative groups. The most important cause of death in all dialysis patients remain cardiovascular diseases<sup>13, 36</sup> and this diagnosis was the most frequent cause of death in all the clinical trials included in our meta-analysis.

This meta-analysis is potentially biased by numerous findings. First, all the clinical studies enrolled in the current meta-analysis were observational studies and, as such, there may be additional unmeasured confounders that could introduce bias into the analysis. Incomplete information was available in these studies about confounding factors affecting hepatocarcinogenesis in non-uraemic patients with hepatitis C,<sup>10</sup> e.g. alcohol consumption, occult HBV infection, HIV infection, and increased hepatic iron content. However, it is unlikely that the alcohol consumption was more excessive in anti-HCV-positive dialysis patients; also, the link between hepatocarcinogenesis and occult HBV infection in patients with normal kidney function is still controversial.<sup>10</sup> HIV prevalence is usually very low among patients on dialysis in developed countries. Secondly, anti-HCV antibody was assessed only at entry, anti-HCV-negative patients might have become positive during the study period, and vice versa. However, the frequency of *de novo* HCV infection among patients on maintenance dialysis in developed countries is low approximately 1% per year;<sup>2</sup> 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.<sup>37</sup> Thus, it is unlikely that repeat anti-HCV testing during the follow-up might have affected the results. Thirdly, 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 infection *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. One approach to this problem is to obtain data from as many sources as possible. We have limited the likelihood of publication bias through extensive efforts to identify all published and unpublished studies.

In conclusion, this meta-analysis demonstrates that HCV-positive patients have lower survival than -negative patients on dialysis. Mortality because of HCC and liver cirrhosis are at least partially responsible for this finding. The higher risk of death in HCV-positive patients has been linked to chronic liver disease and the additive affect of altered immunity secondary to chronic liver disease itself and uraemia. Clinical trials with extended follow-up may help to define the natural history of HCV in this population.

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