Survival Advantage of Kidney Transplantation Over Dialysis in Patients With Hepatitis C: A Systematic Review and Meta-Analysis

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Background. The clinical outcomes of hepatitis C infection in kidney transplantation and maintenance dialysis patients remain controversial. Here, we conducted a systematic review and meta-analysis that aimed at comparing 5-year mortality rates between waiting list and kidney transplantation patients with hepatitis C infections.
Methods. We searched Medline, EMBASE, and Scopus databases published since inception to June 2011 and found nine studies with 1734 patients who were eligible for pooling. Eligible studies were cohort studies that analyzed adult end-stage renal disease patients with hepatitis C virus infection and compared death rates between waiting list and kidney transplantation. The crude risk ratio of death along with its 95% confidence interval was estimated for each study. Data were independently extracted by two reviewers.
Results. The pooled risk ratio of death at 5 years by using a random-effect model was 2.19 (95% confidence interval, 1.50–3.20), which significantly favored the kidney transplantation when compared with the waiting list. There was evidence of heterogeneity of death rates across studies (χ^2=22.6; *df*=8; *P*=0.004). From the metaregression model, age and male gender could be the source of heterogeneity or variation of treatment effects. A major cause of death in the waiting list was cardiovascular diseases, whereas infection was a major cause in the transplant group. There was no evidence of publication bias suggested by an Egger test.
Conclusions. This systematic review suggested that hepatitis C virus–infected patients who remain on dialysis are at higher risk of death when compared with those who received kidney transplantations.

Keywords: Hepatitis C infection, Systematic review, Kidney transplant, Waiting lists, Dialysis.

(*Transplantation* 2013;95: 943–948)

Hepatitis C virus (HCV) infection is a global problem. HCV infection is also common in the end-stage renal disease (ESRD) population (*1*), with the prevalence of 8% to 51% in dialysis and 7% to 40% in kidney transplant patients (*2*). The prevalence in the dialysis population is also higher than in the general population (*2–4*). Most patients had been infected before their transplantations while they were still on dialysis treatments (*4–7*). Liver failure and hepatocellular carcinoma are the major long-term complications in chronic HCV-infected patients (*8, 9*). As a result, the risk of death for dialysis patients with HCV infection is higher when compared with dialysis patients without HCV infection (*9–11*). This has also been supported by the results of meta-analyses that showed that the risks of death were approximately 57% and 79% higher in dialysis and transplant patients with HCV infection than dialysis and transplant patients without HCV infection (*12, 13*), respectively.

The clinical courses of HCV infection in ESRD patients are varied. It is challenging whether HCV-infected patients should receive kidney transplantation or should remain on maintenance dialysis. Although many studies have compared the clinical outcomes between these patients, results were in conflict due to insufficient powers (*14–16*). We, therefore, performed a systematic review and meta-analysis by pooling relevant studies to compare 5-year survival rates between waiting list and kidney transplantation patients with HCV infections.

RESULTS

We identified 400 publications from three databases. Twenty-two publications were removed due to duplications leaving 378 titles and abstracts for screening. Three hundred

The authors declare no funding or conflicts of interest.
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Received 11 September 2012. Revision requested 27 September 2012.
Accepted 21 December 2012.

ISSN: 0041-1337/13/9507-943
DOI: 10.1097/TP.0b013e3182848de2

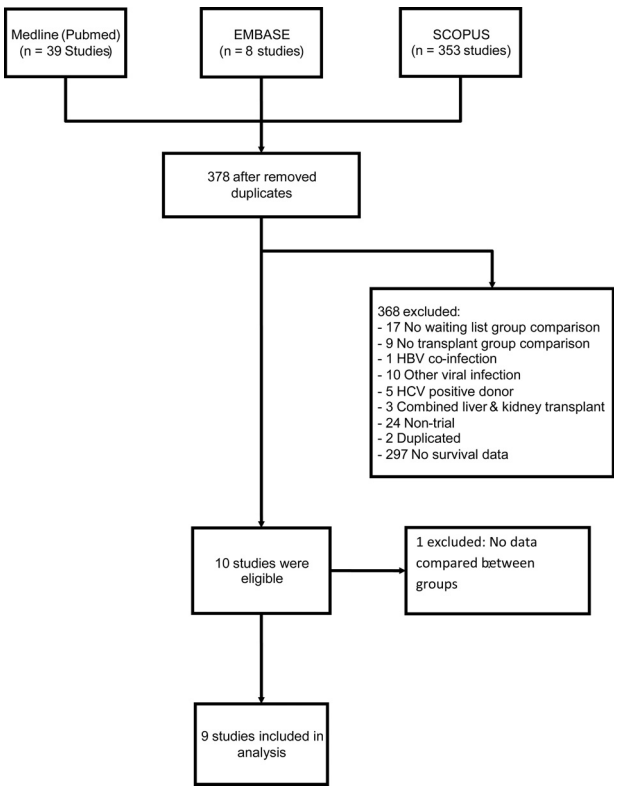

FIGURE 1. Study selection flow diagram.

sixty-eight articles were later excluded with reasons that have been described in Figure 1, leaving 10 studies (*10, 14–22*) eligible for full article review. One additional study was excluded due to no data comparison between hemodialysis and kidney transplantation in HCV-infected patients (*22*). Nine studies were finally included in the analysis with the total number of 1068 and 666 HCV-infected patients as waiting list and kidney recipients, respectively. None of the enrolled studies included patients with mixed HCV and HIV infection.

The characteristics of included studies have been described in Table 1. All included studies were retrospective cohorts, except the study of Maluf et al. (*18*), which was a prospective cohort. All studies had follow-up times from 5 to 20 years, except one study (*15*), which had a duration of follow-up for 4 years. There were only two studies (Scott et al. (*20*) and Roth et al. (*21*)) that reported the loss to follow-up rates as 0.3% to 2.2% in waiting list group and 0.8% to 11.8% in the kidney transplantation group, respectively. Four studies were conducted in the United States, two studies in Europe, and two studies in Asia Pacific countries. The diagnosis of HCV infection was mainly based on positive anti-HCV antibody by enzyme-linked immunosorbent assay 2, except the study by Sezer et al. (*17*), which used polymerase chain reaction technique, and Lezaic et al. (*19*), which used recombinant immunoblot assays. No confirmation of enzyme-linked immunosorbent assay tests was reported in the other studies. The mean age of patients ranged from 38.9 to 54.6 years in the waiting list group and 33.4 to 48.0 years in the kidney transplant group. The percentage of males varied from 48% to 69% among those in the waiting list group and 43% to 82% among those in the kidney transplant group. Only five studies (*16, 18–21*) reported the prevalence of diabetes mellitus, which ranged from 8% to 42% in the waiting list group and 2% to 43% in the kidney transplant group. Five studies (*14–17, 21*) reported the duration of dialysis, which varied from 31.6 (0–318) to 58.7±6.1 months among the waiting list group and 23±31 to 41 (0–246) months among the kidney transplant group.

TABLE 1. Characteristics of included studies

Author and year	Setting	Study design	Years of follow-up	Group	Number	Age, mean (SD)	Sex, n (%) male
Knoll 1997 (*15*)	USA	Retrospective	4	HCV/W	25	43 (11)	13 (52)
				HCV/KT	33	40 (10)	27 (82)
Pereira 1998 (*10*)	USA	Retrospective	6	HCV/W	112	NA	NA
				HCV/KT	111	NA	NA
Huo 2001 (*14*)	Taiwan	Retrospective	14	HCV/W	52	53 (17)	35 (67)
				HCV/KT	30	37 (15)	13 (43)
Sezer 2004 (*17*)	Turkey	Retrospective	5	HCV/W	30	38.9 (15)	18 (60)
				HCV/KT	22	33.4 (9.8)	14 (63.64)
Bloom 2005 (*16*)	USA	Retrospective	10	HCV/W	177	47.4 (0.7)	108 (61)
				HCV/KT	138	NA	78 (56.52)
Maluf 2007 (*18*)	USA	Prospective	5	HCV/W	52	NA	NA
				HCV/KT	43	46.9	35 (81.40)
Lezaic 2008 (*19*)	Serbia	Retrospective	15	HCV/W	83	54.6 (15.2)	40 (48.19)
				HCV/KT	39	36.2 (10.5)	27 (69.23)
Scott 2010 (*20*)	Australia	Retrospective	12	HCV/W	362	51.96	244 (67.4)
				HCV/KT	140	43	101 (72.1)
Roth 2011 (*21*)	USA	Retrospective	20	HCV/W	175	47.6 (12.76)	121 (69.1)
				HCV/KT	110	48 (12.74)	75 (68.2)

HCV, hepatitis C infection; KT, kidney transplantation; NA, not available; W, waiting list.

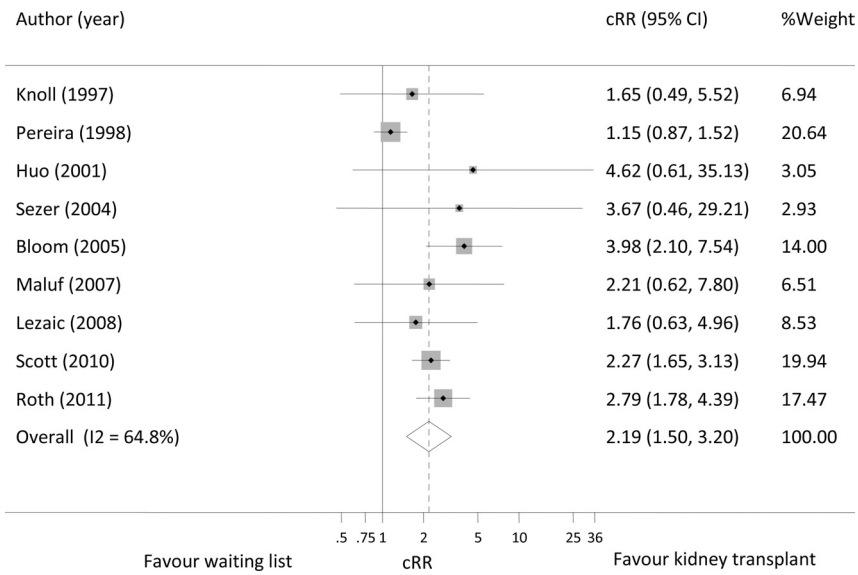

FIGURE 2. Forest plot of overall mortality and 95% CI of cRR of death comparing waiting list and kidney transplant groups. Vertical dashed line represents the pooled RR. CI, confidence interval; cRR, crude risk ratio; RR, risk ratio.

Data from nine studies were used to compare death rates between waiting list and transplant groups (Table 2). We could extract death rates at 5 years and then calculated risk ratios (RRs) for all studies, except one study (*15*) that had a follow-up time for 4 years. For this study, death rates at 3 years were used to calculate RR based on the assumption that the hazard ratio (HR) was constant overtime. There was evidence of heterogeneity of death rates; in other words, death rates were moderately varied across studies (χ^2=22.6; *df*=8; *P*=0.004) with the estimated degree of variability I^2 of 64.8%. The pooled RR of death at 5 years was 2.19 (95% confidence interval [CI], 1.50–3.20), which significantly favored kidney transplantation (Fig. 2). From this, it could be interpreted that patients with HCV infection who remained on a waiting list had 2.19 times higher risk for death than those patients who received kidney transplantation. The number needed to treat was estimated and it was found that treating eight patients (95% CI, 5–11) by kidney transplantation can prevent one extra death when compared with treating by maintenance dialysis in the waiting list group.

The major causes of death were explored and have been described in Table 3. The estimated causes of death from cardiovascular disease, infection, and liver disease were 53.5% (range, 40%–84%), 16% (range, 7%–60%), and 3% (range, 0%–14%), respectively, in the waiting list groups and 40.5% (range, 0%–50%), 40.5% (range, 0%–100%), and 2.5% (range, 0%–50%), respectively, in the transplant groups. This suggested that the waiting list group had higher risk of cardiovascular diseases, lower risk of infection, and similar risk of liver disease when compared with the transplant group.

The source of heterogeneity or variation of treatment effects was explored by fitting the mean age and percent of

TABLE 2. Number of patients who had died at 5 years and calculated cRR of death

	Waiting list		Kidney transplant			
Author and year	**Dead**	**Alive**	**Dead**	**Alive**	**cRR**	**95% CI**
Knoll[a] 1997 (*15*)	5	20	4	29	1.650	0.493–5.521
Pereira[b] 1998 (*10*)	112		111		1.15	0.87–1.52
Huo 2001 (*14*)	8	44	1	29	4.615	0.606–35.132
Sezer 2004 (*17*)	5	25	1	21	3.667	0.460–29.214
Bloom 2005 (*16*)	51	126	10	128	3.976	2.096–7.543
Maluf 2007 (*18*)	8	44	3	40	2.205	0.623–7.804
Lezaic 2008 (*19*)	15	68	4	35	1.762	0.626–4.961
Scott 2010 (*20*)	188	174	32	108	2.272	1.650–3.129
Roth 2011 (*21*)	80	95	18	92	2.794	1.777–4.391
Pooled	1068		666		2.19	1.50–3.20

[a] Data were extracted at 3 years.
[b] No report of the number of patients who remain alive or dead.
CI, confidence interval; cRR, crude risk ratio.

TABLE 3. Comparison of deaths from infection, cardiovascular disease, and liver disease in HCV-positive patients in the included studies

	Waiting list group			Kidney transplant group		
Author	Infection or sepsis (%)	Cardiovascular disease (%)	Liver disease (%)	Infection or sepsis (%)	Cardiovascular disease (%)	Liver disease (%)
Knoll (*15*)	16	84	0	50	50	0
Pereira (*10*)	29	NA	14	NA	NA	NA
Huo (*14*)	25	56	6	0	50	50
Sezer (*17*)	60	40	0	100	0	0
Bloom (*16*)	NA	NA	NA	NA	NA	NA
Maluf (*18*)	NA	NA	NA	NA	NA	NA
Lezaic (*19*)	9	50	3	40	0	0
Scott (*20*)	15	51	2	14	43	5
Roth (*21*)	7	68	4	41	38	7
Pooled median	16	53.5	3	40.5	40.5	2.5

HCV, hepatitis C virus; NA, not available.

males into a metaregression model. This suggested that the mean age and percentage of males could reduce the degree of variation from 64.8% to 7.2% and 43.0%, respectively. As a result, age might be a source of heterogeneity and a subgroup analysis was therefore performed. The mean age was categorized into two groups according to the average age of 45.1 years (range, 36.6–49.5). Pooling within age groups of 45 years or less and more than 45 years were homogenous (I^2=0% for both groups) with the pooled RR (95% CI) of 1.19 (0.91–1.56) and 2.57 (2.04–3.23), respectively. This suggested that the risk of death between waiting list and transplant groups was not statistically different in patients who were aged younger than 45 years. However, the risk was approximately 2.5-fold higher in the former than the latter groups in patients who were aged 45 years or older. As a result, kidney transplantation may benefit ESRD patients with HCV infection who are older than 45 years. There was no evidence of publication bias suggested by an Egger test (coefficient=1.17; SE=0.95; *P*=0.260).

DISCUSSION

Whether HCV-infected ESRD patients should receive kidney transplants or remain in maintenance dialysis is very challenging. This may be related to the fact that immunosuppressive therapy after transplantation can induce flares of HCV infection and lead to increase liver-related morbidities and mortalities, although information regarding this issue is limited. Therefore, we have performed a systematic review and meta-analysis that aimed at assessing the impacts of kidney transplantation on HCV patient survival. The pooled numbers were 666 and 1068 patients in kidney transplant and waiting list patients, respectively. Our results have suggested a potential benefit of kidney transplantation over waiting list approximately 55% lower risk of death at 5 years without evidence of reporting bias.

Our study also suggested the survival advantage from kidney transplantation over dialysis, particularly in HCV patients aged 45 years or older. This might be explained by older-aged patients were more likely to have cardiovascular events from their deterioration of underlying diseases plus gradual decline of renal function (*23, 24*). We have also found that cardiovascular disease was the leading cause of overall death followed by infection and liver diseases. For comparison, deaths from cardiovascular diseases in our waiting list group patients were considered to be higher when compared with the kidney transplant recipients (~40.5% vs. 30%) (*25*). In contrast, deaths from infectious complications in the waiting list patients were lower when compared with the kidney transplant recipients (20% vs. 40.5%) (*25*). The results from our and prior studies (*26, 27*) suggest more efforts to reduce infectious complications after kidney transplantation are required.

Because a functioning kidney allograft should provide more glomerular filtration rate than maintenance dialysis, it is possible that the survival benefit may result from improved clearance of uremic toxins, lower inflammatory responses, and/or oxidative stress (*28*). In addition, left ventricular hypertrophy tends to lessen after kidney transplantation, which may decrease the risk of mortality from coronary heart disease (*28, 29*).

Our study was the first systematic review with meta-analysis that compared survival benefit between kidney transplantation and waiting list in HCV-infected patients. Pooling of the published information has been performed systematically; thus, there was less selection bias. The result from our study supports the concept that kidney transplantation is not contraindicated in HCV-infected ESRD patients.

Our study has some limitations. First, our pooling was based on cohort studies, not a randomized control trial. We extracted treatment effects (i.e., RR or HR) from individual studies, in which some studies had been adjusted for confounding effects via statistical analyses, whereas some other studies had not. To minimize confounding bias in pooling data, a multivariate analysis by adjusting for the same confounders across studies should be performed, but doing this would require efforts to ask for sharing individual patient data. Second, we could not retrieve data for the severity of HCV infection (liver biopsy, HCV viral load, and HCV

genotype) from the included studies. Different disease severities may respond to treatment differently and thus affect patient survival. Specifically, the importance of pretransplantation liver biopsy was demonstrated in a recent study (*21*). It is still interesting to investigate the impact of HCV genotype on long-term survival after kidney transplantation as had been demonstrated previously (*30*). Third, antiviral therapy in each individual included study was not clearly defined. Current treatments of HCV infection in patients without chronic kidney disease include administration of interferon-α (preferably pegylated interferon) in combination with ribavirin. If patients receive proper treatments for HCV and reach to sustainable virologic response before transplantation, the outcomes of kidney transplantation should be good. For HCV infection at the stage of dialysis, the 2008 Kidney Disease: Improving Global Outcomes guidelines recommended standard interferon monotherapy with adjustments of dosage (*31*). However, we have observed in our clinics that adding small doses of ribavirin to interferon may associate with good outcomes. There was insufficient data about the use of antiviral treatments that we could extract from the included studies.

In conclusion, although recipients with HCV infection are associated with an increased risk of mortality compared with recipients without this infection, the results of this current systemic review suggest that HCV-infected patients who remain on maintenance dialysis have a higher risk of death compared with those who receive a kidney transplant. The result from our study serves as strong evidence to demonstrate the long-term survival benefit of kidney transplantation in comparison with dialysis in HCV-infected ESRD patients.

MATERIALS AND METHODS

Locate Studies

We performed electronic searching using Medline, EMBASE, and Scopus databases since inception to June 2011. PubMed, Ovid, and Scopus search engines were respectively used for these databases. For PubMed, the search strategy included both truncated free texts and Medical Subject Heading (MeSH) terms with details as follow: ("hepatitis C" OR "HCV") AND ("kidney transplant" OR "renal transplant") AND ("waiting list" OR "candidates" OR "waitlisted" OR "patient listed" OR "dialysis") AND "Mortality" [MeSH term]. Search strategies for the other two databases have been described in Appendix 1. Reference lists from eligible studies were also reviewed to search for more relevant articles. The search was limited to adults with age 19 years or older and English publications.

Study Selection

We sought to include cohort studies that analyzed adult ESRD patients with HCV infection and compared death rates between waiting list and kidney transplantation. The HCV infection was defined according to the original included studies that were mostly by the presence of positive HCV antibodies or positive HCV RNA in serum. The primary outcome of interest was death from any cause.

We excluded studies if they included patients with other multiple organ transplantations (i.e., liver-kidney and liver-heart), patients who had co-infections with hepatitis B or human immune deficiency virus, or insufficient data of death for pooling.

Data Extraction

Data extraction was performed independently by two investigators (A.T. and N.K.). Any disagreement was resolved by discussion and consensus. We extracted each study's characteristics (i.e., author, year published, country, setting, and follow-up time), diagnosis of HCV infection, and patient's characteristics (i.e., age and sex). In addition, we extracted the total number of deaths per group at the end of each study. Where numbers of deaths were not reported, death rates at 5 years between groups from the survival curves or HR of death along with its 95% CI were extracted.

Statistical Analysis

The crude RR of death along with its 95% CI was estimated for each study. Variation of treatment effect or heterogeneity across studies was evaluated using Cochran's Q test and a degree of heterogeneity was quantified using I^2 statistics. Heterogeneity was present if the Q test was significant or the I^2 was 25% or higher. A pooled RR was estimated using a random-effect model by Der-Simonian and Laird if the heterogeneity was present; otherwise, the fixed effect was applied. Metaregression was used to explore the source of heterogeneity by fitting covariates (i.e., age and sex) in a metaregression model. When the source of heterogeneity was detected, subgroup analysis was performed accordingly. Publication bias was checked using the Egger test and a contour enhanced funnel (*32, 33*) plot if required. $P<0.05$ was considered statistically significant, except for the heterogeneity test where $P<0.10$ was used. All data were analyzed by using Stata version 12.0 (StataCorp LP, College Station, TX).

ACKNOWLEDGMENT

The authors thank Dr. Sasivimol Rattanasiri (Section for Clinical Epidemiology and Biostatistics, Faculty of Medicine, Ramathibodi Hospital) for assistance with statistical analysis.

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Appendix 1. Search strategies

A. Search strategies: Medline (PubMed) (39)
("hepatitis C"[All Fields] OR "HCV"[All Fields]) AND ("kidney transplant"[All Fields] OR "renal transplant"[All Fields]) AND ("waiting list"[All Fields] OR "candidates"[All Fields] OR "waitlisted"[All Fields] OR (("patients"[MeSH Terms] OR "patients"[All Fields] OR "patient"[All Fields]) AND listed[All Fields]) OR "dialysis"[All Fields]) AND ("mortality"[Subheading] OR "mortality"[All Fields] OR "Mortality"[All Fields] OR "Mortality"[MeSH Terms])

B. Search strategies: EMBASE (8)
1. Hepatitis C virus
2. HCV.mp.
3. 1 or 2
4. kidney transplant.mp.
5. renal transplant.mp.
6. 4 or 5
7. waiting list.mp.
8. waiting listed.mp.
9. Candidates.mp.
10. patient listed.mp.
11. 7 or 8 or 9 or 10
12. Mortality.mp.
13. death/ or Death.mp.
14. 10 or 11
15. 3 and 6 and 11 and 14

C. Search strategies: Scopus (353)
(hepatitis c virus) OR (HCV)) AND (renal transplant) OR (kidney transplant) AND (mortality) AND ('waiting list') OR (candidates) OR (waitlisted) OR ('patient listed') AND (LIMIT-TO(DOCTYPE, "ar") AND (LIMIT-TO (SUBJAREA, "MEDI") OR LIMIT-TO(SUBJAREA, "MULT")) AND (LIMIT-TO(LANGUAGE, "English") AND (LIMIT-TO(SRCTYPE, "j")