Liver transplantation (LT) is a life-saving modality for treating well-selected patients with acute liver failure, end-stage liver disease, certain metabolic disorders and early hepatocellular carcinoma. The current practice of LT is limited by the significant disparity between organ availability and the number of patients awaiting transplantation. Donation after cardiac death (DCD) has become a significant source of transplantable organs in an attempt to expand the donor pool and increase organ supply (1-4). While DCD allografts are used as a source of transplantable organs in an attempt to expand the donor pool and increase organ supply (1-4), the use of DCD organs in recipients with hepatitis C is associated with higher rates of graft failure and biliary complications compared with donation after brain death (DBD) allografts (5,6). Previous studies have suggested that HCV-positive recipients have the potential to help address the disparity between organ availability and the number of patients awaiting LT, their use has been associated with higher rates of graft failure and biliary complication, particularly ischemic cholangiopathy, compared with donation after brain death (DBD) allografts (5,6).

Hepatitis C virus (HCV) infection is currently a leading indication for LT, constituting approximately 30% to 50% of all transplants (7-10). Previous studies have suggested that HCV-positive recipients have a higher risk of biliary complications compared with HCV-negative recipients (11-13). However, the impact of DCD transplantation on the outcomes of recipients with HCV infection remains unclear. The current practice of LT is limited by the significant disparity between organ availability and the number of patients awaiting transplantation, and the use of DCD organs in recipients with hepatitis C is associated with higher rates of graft failure and biliary complications compared with DBD allografts (5,6).

The objective of this study was to evaluate the clinical outcomes of DCD versus DBD LT in patients with HCV infection. The authors performed a systematic review and meta-analysis of studies comparing DCD versus DBD LT in HCV-positive patients undergoing LT. The search identified 58 citations, including three studies, with 324 patients meeting eligibility criteria. The use of DCD livers was associated with a significantly higher risk of primary nonfunction (RR 5.49 [95% CI 1.53 to 19.64]; P=0.009; I²=0%), while not associated with a significantly different patient survival (RR 0.89 [95% CI 0.37 to 2.11]; P=0.79; I²=51%), graft survival (RR 0.40 [95% CI 0.14 to 1.11]; P=0.08; I²=34%), rate of recurrence of severe HCV infection (RR 2.74 [95% CI 0.36 to 20.92]; P=0.33; I²=84%), retransplantation or liver disease-related death (RR 1.79 [95% CI 0.66 to 4.84]; P=0.25; I²=44%), and biliary complications.

CONCLUSIONS: While the literature and quality of studies assessing DCD versus DBD grafts are limited, there was significantly more primary nonfunction and a trend toward decreased graft survival, but no significant difference in biliary complications or recipient mortality rates between DCD and DBD LT in patients with HCV infection. There is insufficient literature on the topic to draw any definitive conclusions.

Key Words: Biliary complications; Donation after cardiac death; Hepatitis C; Liver transplantation; Outcomes

Comparing outcomes of donation after cardiac death versus donation after brain death in liver transplant recipients with hepatitis C: A systematic review and meta-analysis

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BACKGROUND: Liver transplantation (LT) using organs donated after cardiac death (DCD) is increasing due, in large part, to a shortage of organs. The use of DCD organs in recipients with hepatitis C virus (HCV) infection remains unclear due to the limited experience and number of publications addressing this issue.

OBJECTIVE: To evaluate the clinical outcomes of DCD versus donation after brain death (DBD) in HCV-positive patients undergoing LT.

METHODS: Studies comparing DCD versus DBD LT in HCV-positive patients were identified based on systematic searches of seven electronic databases and multiple sources of gray literature.

RESULTS: The search identified 58 citations, including three studies, with 324 patients meeting eligibility criteria. The use of DCD livers was associated with a significantly higher risk of primary nonfunction (RR 5.49 [95% CI 1.53 to 19.64]; P=0.009; I²=0%), while not associated with a significantly different patient survival (RR 0.89 [95% CI 0.37 to 2.11]; P=0.79; I²=51%), graft survival (RR 0.40 [95% CI 0.14 to 1.11]; P=0.08; I²=34%), rate of recurrence of severe HCV infection (RR 2.74 [95% CI 0.36 to 20.92]; P=0.33; I²=84%), retransplantation or liver disease-related death (RR 1.79 [95% CI 0.66 to 4.84]; P=0.25; I²=44%), and biliary complications.

CONCLUSIONS: While the literature and quality of studies assessing DCD versus DBD grafts are limited, there was significantly more primary nonfunction and a trend toward decreased graft survival, but no significant difference in biliary complications or recipient mortality rates between DCD and DBD LT in patients with HCV infection. There is insufficient literature on the topic to draw any definitive conclusions.

Key Words: Biliary complications; Donation after cardiac death; Hepatitis C; Liver transplantation; Outcomes

Liver transplantation (LT) is a life-saving modality for treating well-selected patients with acute liver failure, end-stage liver disease, certain metabolic disorders and early hepatocellular carcinoma. The current practice of LT is limited by the significant disparity between organ availability and the number of patients awaiting transplantation. Donation after cardiac death (DCD) has become a significant source of transplantable organs in an attempt to expand the donor pool and increase organ supply (1-4). While DCD allografts have the potential to help address the disparity between organ availability and the number of patients awaiting LT, their use has been associated with higher rates of graft failure and biliary complication, particularly ischemic cholangiopathy, compared with donation after brain death (DBD) allografts (5,6).
of DBD LT have worse outcomes than HCV-negative recipients, largely due to a more rapid and severe manner of recurrence of their HCV-related liver disease (9,11). Recurrence of HCV after LT is universal, with 20% to 40% of patients progressing to cirrhosis within five years of LT (12). Previous studies have shown that liver allografts from extended-criteria donors, such as those with advanced age, are at an increased risk of earlier and more severe HCV recurrence; this has deleterious impact on both patient and graft outcomes (13-16). It has also been suggested that organ cold/warm ischemia is a risk factor for increased severity of recurrence of HCV after LT. DCD organs experience warm ischemic injury not characteristic of DBD donors because of hypoperfusion and hypoxia during the agonal period of time of withdrawal of life support (11). It has, therefore, been theorized that HCV patients receiving DCD allografts may be at an increased risk for graft injury and accelerated HCV recurrence. Despite this theoretical risk, the literature investigating the outcomes of HCV-positive patients receiving DCD allografts is scant and conflicting reports have been published.

Tao et al (17) performed a retrospective matched control trial of 111 HCV-positive patients (37 receiving DCD LT and 74 matched controls receiving DBD LT). Although the two groups had similar donor and recipient characteristics, immunosuppression regimens, rates of acute cellular rejection and HCV profiles, the patients receiving DCD LT had a higher incidence of primary nonfunction (19% versus 3%; P=0.006) and significantly higher peak aspartate aminotransferase levels compared with DBD subjects. Although the survival rates were not significantly different, DCD LT recipients had lower one- and five-year survival rates (83% and 69% versus 84% and 78%, respectively; P=0.075) and graft survival rates (70% and 61% versus 82% and 74%, respectively; P=0.24). A total of 314 liver biopsies were performed; mixed modelling analysis showed that fibrosis progression rates were similar for the two groups (0.6 fibrosis units/year according to the Ishak modified staging system). The rates of severe HCV recurrence (retransplantation or death due to recurrent HCV and/or the development of stage 4/6 fibrosis or worse within two years) were not significantly different (three [8%] DCD patients versus 11 [15%] DBD patients; P=0.38). Cytomegalovirus infection (HR 7.9 [95% CI 2.1 to 28.9]; P=0.002) and acute cellular rejection (HR 6.2 [95% CI 2.0 to 19.7]; P=0.002) were the only independent risk factors for severe recurrence.

Taner et al (18) performed a retrospective analysis of 77 HCV-positive patients who received DCD liver grafts and 77 matched HCV-positive patients who received DBD liver grafts. There were no differences in one-, three- and five-year patient or graft survival rates among the groups. Multivariable analysis showed that the Model for End-Stage Liver Disease score (HR 1.037 [95% CI 1.006 to 1.069]; P=0.003) were significant factors for graft failure.

The objective of the present study was to perform a systematic review and meta-analysis of studies comparing clinical outcomes of DCD versus DBD orthotopic LT in patients with HCV. The primary outcomes of interest were patient survival rates, graft survival rates, recurrence of severe HCV, primary nonfunction, acute cellular rejection, biliary strictures (diffuse or localized, anastomotic or nonanastomotic), biliary leaks and vascular complications (hepatic artery stenosis, hepatic artery thrombosis, portal vein thrombosis).

METHODS

Primary objectives

To compare one-year patient and graft survival rates in recipients transplanted for HCV with DCD versus DBD grafts; and to compare one-year patient and graft survival rates in recipients with versus without HCV undergoing DCD versus DBD LT.

Secondary objectives

To determine whether DCD LT compared with DBD LT in HCV-positive patients increases rates of primary nonfunction, acute cellular rejection, biliary strictures (diffuse or localized, anastomotic or nonanastomotic), biliary leaks or vascular complications (hepatic artery stenosis, hepatic artery thrombosis portal vein thrombosis).

Eligibility criteria

Inclusion criteria were studies that compared DCD versus DBD LT in patients with HCV, as well as DCD LT in patients with and without HCV; and studies that evaluated adult recipients (age ≥18 years) who underwent primary LT. To be included, studies had to include at least one of the prespecified outcomes. There was no limitation on randomized control trials and no restrictions on language. Results duplicated in multiple articles were included only once.

Information sources

A clinical librarian experienced in conducting systematic reviews in the health care field assisted with the literature search. The following electronic databases were searched to March 29, 2012: MEDLINE, Cochrane Database of Systematic Reviews (Cochrane Reviews); Database of Abstracts of Reviews of Effects (Other Reviews); Cochrane Central Register of Controlled Trials (Clinical Trials); Cochrane Methodology Register (Methods Studies); Health Technology Assessment Database (Technology Assessments); and the NHS Economic Evaluation Database (Economic Evaluations). Relevant articles from incompletely and nonpublished literature were identified by consulting with experts in the field. Searches were supplemented by reviewing the reference lists of all citations that met inclusion criteria by screening the first 50 citations in the ‘See related articles’ function on PubMed of the included studies, and by searching www.clinicaltrials.gov for relevant trials. Corresponding authors were e-mailed when additional information was needed.

Study selection

Two investigators (MW and NC) independently screened the title and abstract of the citations. If either investigator believed that a citation was relevant, it was marked for full-text retrieval. Two investigators independently evaluated the retrieved full-text articles for eligibility. Cohen’s kappa statistic was used to quantify agreement between the investigators. Disagreements were resolved by discussion, and a third investigator (KC) was consulted in case of impasse.

Data collection

Two reviewers independently abstracted the data from included trials using a data collection form. Any disagreement in the abstracted data between the two reviewers was resolved by consensus. A third investigator resolved outstanding disagreements. In cases in which the data were incomplete or unclear, the study authors were contacted.
Data items

The following items were abstracted from the articles: demographic data of the study population and comparison group including age and sex; DCD versus DBD liver donations; features of the study design including allocation concealment, blinding, intention-to-treat analysis, number of patients lost to follow-up, rate of premature termination and funding source; the outcome measures of patient survival rate and graft survival rate; rates of primary nonfunction, acute cellular rejection, biliary strictures (diffuse or localized, anastomotic or nonanastomotic), biliary leaks, ischemic cholangiography, vascular complications (hepatic artery stenosis, hepatic artery thrombosis, portal vein thrombosis), HCV recurrence and retransplantation/liver-related death.

Risk of bias

The risk of bias on a study level was assessed by determining the adequacy of the method of randomization, allocation concealment, blinding of the trial participants, care providers and outcome assessors. Also assessed were whether the trial was terminated prematurely, whether the analysis was an intention-to-treat and the funding source.

The Grading of Recommendations, Assessment, Development and Evaluation approach (20) was used to characterize the risk of bias for each of the outcomes that had available data.

Statistical analysis

The meta-analysis was performed using the Cochrane Collaboration and the Quality of Reporting of Meta-analyses (QUORUM) guidelines. Statistical analyses were performed using Review Manager 5 (www.cochrane.org). The RR was used as a summary measure of efficacy for dichotomous data and the mean difference for continuous outcomes. Statistical heterogeneity was evaluated using the I² statistic. An I² value of 0% to 25%, 25% to 50% and >50% were considered to be indicative of low, moderate and high heterogeneity, respectively.

Risk of publication bias

Funnel plots were used to assess the risk of publication bias across trials for all outcome measures.

RESULTS

Study selection

Eighty-eight citations were screened, of which 15 were selected for full-text retrieval. Of these, three articles (17-19) fulfilled eligibility criteria and were, thus, selected (Figure 1).

There was no disagreement regarding eligibility of full-text articles (Cohen’s kappa = 1.00), and consensus was reached among all authors on inclusion and exclusion of all articles.

Twelve of the retrieved articles were excluded due to the absence of a comparison of DCD versus DBD liver donation in patients with HCV (n=10) (8,21-29) or the article was an editorial (n=1) (30).

Study characteristics

A total of 324 study participants in three trials comparing DCD versus DBD liver transplantation in HCV-positive patients. Study characteristics are included in Table 1.

Risk of bias within trials

The included trials had a high risk of bias. All three trials were retrospective analyses performed at single centres. There was no blinding and concealment.

Risk of bias across trials

The funnel plots of the RR for all outcomes did not show evidence of publication bias.

Recipient survival

Compared with DBD, orthotopic LT with a DCD liver was not associated with a significantly decreased patient survival (three studies; risk ratio 0.89 [95% CI 0.37 to 2.11]; P=0.79; I²=51%) (Figure 2). Heterogeneity was potentially explained by differences in length of follow-up. The overall quality of evidence was low (20).

Graft survival

DCD LT trended toward, but was not significantly associated with, a decrease in graft survival (n=2; RR 0.40 [95% CI 0.14 to 1.11]; P=0.08; I²=34%) (Figure 3). Heterogeneity was potentially explained by differences in length of follow-up. The overall quality of evidence was low (20).

Biliary complications

The risk of biliary leaks was not statistically significantly higher (n=2; risk ratio 2.22 [95% CI 0.42 to 11.88]; P=0.35; I²=35%) (Figure 4) in patients receiving a DCD versus a DBD LT. The level of heterogeneity was explained by length of follow-up, differences in the definition of biliary leak, and differences in postoperative imaging or investigations for leak. The overall quality of evidence was low (20).

Biliary strictures were not statistically different (n=2; RR 1.15 [95% CI 0.59 to 2.26]; P=0.68; I²=0%) (Figure 4) in patients receiving a DCD versus a DBD LT. The quality of evidence was low (20).

Patients receiving LT from a DCD versus a DBD did not have a significantly increased risk of ischemic cholangiopathy (n=3; RR 6.67 [95% CI 0.84 to 52.66]; P=0.07; I²=35%) (Figure 4). The quality of evidence was low (20).

Recurrence of HCV infection

Recurrence of HCV was not significantly different in patients receiving DCD versus DBD LT when patients from two studies were pooled, with a risk ratio of 2.74 (95% CI 0.36 to 20.92; P=0.33; I²=84%) (Figure 5). The overall quality of evidence was low (20).
Compared with DBD, LT with a DCD liver was associated with significantly increased primary liver nonfunction (three studies; risk ratio 5.49 [95% CI 1.53 to 19.64]; P=0.009; I²=0%) (Figure 6). The overall quality of evidence was low (20).

Retransplantation
DCD LT was not significantly associated with an increased risk of retransplantation (two studies; RR 1.79 [95% CI 0.66 to 4.84]; P=0.25; I²=44%) (Figure 7). The overall quality of evidence was low (20).

Transplant liver primary nonfunction
Compared with DBD, LT with a DCD liver was associated with significantly increased primary liver nonfunction (three studies; risk ratio 5.49 [95% CI 1.53 to 19.64]; P=0.009; I²=0%) (Figure 6). The overall quality of evidence was low (20).

**TABLE 1**

Characteristics of included studies

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<td>28/6/6/2</td>
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</table>

Recipient characteristics

| Age, years, mean ± SD | 54.2±5 | 54.5±9 | 53.4±5 | 53.4±5 | 53.4±5 | 53.4±5 |
| Sex, male:female, n | 15:2 | 22:5 | 58:42 | 39:61 | 31:6 | 58:16 |
| Race (Caucasian/African American/other), n | 77/6 | 77/6 | 77/6 | 77/6 | 77/6 | 77/6 |
| Body mass index, kg²/m² | N/A | N/A | 28.6 | 28.6 | 28.6 | 28.6 |
| MELD, mean ± SD | 17.8±5.1 | 19.7±5.3 | 19.9±5.7 | 19.8±5.7 | 19.6±5.7 | 19.6±5.7 |
| Hepatocellular carcinoma, n (%) | N/A | N/A | 24 (31.2) | 20 (26.0) | N/A | N/A |
| Hepatitis C genotype 1, n (%) | 12 (70.6) | 30 (71.4) | N/A | N/A | N/A | N/A |

**Figure 2** Forest plot of recipient survival. DBD Donation after brain death; DCD Donation after cardiac death; HCV Hepatitis C virus

**Figure 3** Forest plot of graft survival. DBD Donation after brain death; DCD Donation after cardiac death; HCV Hepatitis C virus

**Figure 4** Forest plot of biliary complications. DBD Donation after brain death; DCD Donation after cardiac death; HCV Hepatitis C virus

**Figure 5** Forest plot of recurrence of hepatitis C virus (HCV) infection. DBD Donation after brain death; DCD Donation after cardiac death

**Figure 6** Forest plot of primary nonfunction. DBD Donation after brain death; DCD Donation after cardiac death; HCV Hepatitis C virus

**Figure 7** Forest plot of retransplantation. DBD Donation after brain death; DCD Donation after cardiac death; HCV Hepatitis C virus

**DISCUSSION AND CONCLUSIONS**

Summary of evidence
Three trials evaluated DCD versus DBD LT in recipients with HCV infection. The use of DCD livers in HCV-positive recipients was associated with a significant increase in primary nonfunction, but no significant difference in biliary complications, graft survival rates and recipient mortality rates (Table 1).

Limitations
The conclusions that can be drawn from the present systematic review were limited by the small numbers of patients and the retrospective nature of the trials included. Length of follow-up varied substantially among the studies. Techniques and experience also vary among institutions. In addition, there was a lack of histopathological correlation and generalizability of results, in addition to potential selection biases. There were significant differences in rates of HCV recurrence that could, at least partially, be explained by differences in rates of antiviral treatment within the first year post-LT.
Despite these limitations, there is still value in the current meta-analysis because it is the first study of its kind and contributes to the knowledge base. Published experiences will likely never be prospective or randomized given the nature of transplantation, the complexities of organ allocation and important issues involving medical ethics. Therefore, high-grade evidence for this topic may never emerge.

Implications for clinical practice
Although significant for limitations, our meta-analysis indicates there is a substantial increase in primary nonfunction and a trend toward a decrease in graft survival, but no significant difference in other important clinical outcomes between DCD and DBD allografts in HCV-positive LT recipients.

Controversy remains in the use of DCD LT in HCV-positive patients. Individually, DCD LT and the presence of HCV have negative impact on patient and graft survival (11). It remains unclear whether the combination of DCD LT and HCV synergistically confers a worse outcome. The two studies that demonstrated no significant difference in patient outcomes with use of DCD LT in HCV-positive patients (17,18) included younger patients than the study that found a significant decrease in graft survival in HCV-positive patients undergoing DCD versus DBD LT (19).

DCD grafts are not contraindicated in well-selected HCV recipients and this is potentially an underutilized method to expand the donor pool. Over the past 10 years, approximately 700 to 800 patients have died awaiting LT (www.unos.org); DCD LT may be one of many solutions requiring further investigation.

Implications for research
DCD allografts have become a significant source of transplantable organs in an attempt to bridge the gap between supply and demand in LT. Our meta-analysis indicates an increased number of adverse events (namely primary nonfunction) with DCD allografts in HCV-positive patients and a trend toward decreased graft survival, but no significant decrease in patient survival.

Ideally, DBD allografts appear to be better suited to HCV-positive patients; however, organ availability necessitates the use of DCD allografts. The quality of evidence in the three included articles was low; a randomized control trial with protocolized liver biopsies would be ideal. However, this is not feasible because recipients could not be randomized because the process of listing recipients is complex and not amenable to a randomized control trial. In the absence of a trial, more observational, prospective and multicentre data are needed.

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AUTHOR CONTRIBUTIONS: All authors contributed to the concept and design, and provided intellectual content of critical importance to this work. Dr Wells, Ms Janik and Dr Chandok performed the electronic literature search and manual search for potential articles. Dr Wells and Dr Chandok retrieved citations, reviewed full text papers and abstracted the data. All authors participated in the analysis and interpretation. All authors approved the final version of this article.

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