Outcomes of Controlled Donation After Cardiac Death Compared With Donation After Brain Death in Liver Transplantation: A Systematic Review and Meta-analysis

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ABSTRACT

Background. Controlled donation after cardiac death (CDCD) is increasingly common for liver transplantation due to donor shortage. However, the outcomes, in terms of grafts and recipients, remain unclear. The current study is a systematic review and meta-analysis that compared CDCD with donation after brain death (DBD).

Methods. We conducted an electronic search of MEDLINE, EMBASE, and the Cochrane Database (from January 2007 to May 2017). Studies reporting Maastricht category III or IV CDCD liver transplantation were screened for inclusion. We appraised studies using the Newcastle-Ottawa scale and meta-analyzed using a fixed or random effects model.

Results. A total of 21 studies, with 12,035 patients, were included in data analysis. CDCD did not differ from DBD in patient survival (hazard ration: 1.20; 95% confidence interval [CI]: 0.98 to 1.47; $P = .07$), graft survival (hazard ratio: 1.24; 95% CI: 0.99 to 1.56; $P = .06$), primary nonfunction (odds ratio [OR]: 1.74; 95% CI: 1.00 to 3.03; $P = .05$), hepatic artery thrombosis (OR: 1.17; 95% CI: 0.78 to 1.74; $P = .45$). However, CDCD was associated with biliary complications (OR: 2.48; 95% CI: 2.05 to 3.00), retransplantation (OR: 2.54; 95% CI: 1.99 to 3.26), and peak alanine aminotransferase (weighted mean difference: 330.88; 95% CI: 259.88 to 401.87). A subgroup analysis that included only hepatitis C virus (HCV)–positive recipients showed no significant difference between CDCD and DBD in biliary complications ($P = .16$), retransplantion ($P = .15$), HCV recurrence ($P = .20$), and peak alanine aminotransferase ($P = .06$).

Conclusions. CDCD transplantation is the most viable alternative to DBD transplantation in the current critical shortage of liver organs. HCV infection may not be the inferior factor of postoperative outcomes and survival.

LIVER transplantation (LT) is a successful, life-saving modality for treating end-stage liver disease [1]. Unfortunately, organ scarcity remains a major problem worldwide in the field of LT. The contradiction between supply and demand has resulted in significant morbidity and mortality for patients awaiting LT and has turn to seek for alternatives to offer LT to more patients.

The critical shortage of liver organs has prompted a significant increase in the use of controlled donation after cardiac death (CDCD) donors in LT [2]. The irreversible cessation of circulatory and respiratory functions was the

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cornerstone for the definition of the four categories of CDCD proposed at the First International Workshop on CDCD held in Maastricht, The Netherlands, in 1995 [3]. Postoperative outcomes of CDCD donors were encouraging, and some studies reported that there were no significant differences in patient and graft survival rates between CDCD and DBD donors after LT [4–7]. Moreover, hepatitis C virus (HCV) infection is currently the most common indication for LT [8]. However, some studies have suggested that ischemia or reperfusion injury may predict poor outcomes in HCV recipients [9], whereas others have reported that biliary complications after LT are associated with worse HCV recurrence [10]. Therefore, the postoperative outcomes in HCV recipients receiving CDCD grafts have not yet been well described.

The purpose of this systematic review and meta-analysis was to describe postoperative outcomes, patient survival, and graft survival in LT using CDCD grafts and compare these with DBD grafts. Importantly, we used hazard ratio (HR) as a relevant measure for the effects of patient survival and graft survival.

MATERIALS AND METHODS

In this study, we followed the methods for conducting a systematic review according to the Institute of Medicine's Standards for Systematic Reviews [11] with small modifications. Besides, we reported our study results according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses [12] and Meta-Analysis of Observational Studies in Epidemiology [13].

Data Sources and Search Methods

An electronic search was performed and relevant publications were identified using electronic databases of PubMed, Embase, and the Cochrane Library from January 2007 to May 2017. The search terms included the following: DCD or CDCD or NHBD or donation after cardiac death or donor after cardiac death or donors after cardiac death or non–heart-beating donors or non–heart-beating donation, and liver transplant*. In addition, the related articles function was also used to broaden the search, and the computer search was supplemented with manual searches of the reference lists of all retrieved studies.

Inclusion and Exclusion Criteria

The included studies had to meet the following criteria: 1) must be retrospective comparative studies (cohort or match case-control studies); 2) must compare CDCD and donation after brain death (DBD); 3) must include comparing outcomes in recipients transplanted for HCV with CDCD versus DBD grafts; and 4) must include adult recipients (age $\geq$18 years) who underwent primary LT.

The exclusive studies had to meet the following criteria: 1) must be noncomparative studies or irrelevant to the subject; 2) must be lacking a comparison group of DBD liver transplant recipients; 3) must include Maastricht categories I, II, and the Maastricht categories of DBD grafts had to be uncontrolled or unclear; 4) must include editorials, meeting abstracts, letters to the editor, review articles, case reports, and animal experimental studies; and 5) literature must have had no extractable date.

DATA EXTRACTION

Studies that met all the inclusion criteria were retrieved as full-text articles. The data from the included studies were extracted and summarized independently by two authors (Tang and Fan); any disagreement was resolved by the determining senior author (Jiang). The primary outcomes were primary nonfunction, biliary complications, ischemic cholangiopathy, hepatic artery thrombosis, portal vein thrombosis, HCV recurrence, patient survival, and graft survival. The secondary outcomes were length of hospital stay, retransplantation, rejection episodes, and peak aminotransferase levels.

QUALITY ASSESSMENT AND STATISTICAL ANALYSIS

In this literature, we assessed the methodological quality of retrospective studies by the modified Newcastle-Ottawa scale [14], which consists of three elements: patient selection, comparability of the study groups, and assessment of outcome. A score of 0 to 9 (allocated as stars) was allocated to all included studies (Supplementary Table 1). Observational studies achieving 6 or more stars were considered to be of high quality [15].

All included studies were rated for the level of evidence according to criteria provided by the Centre for Evidence-Based Medicine in Oxford, United Kingdom. In addition, the meta-analyses were performed using Review Manager 5.0 (Cochrane Collaboration, Oxford, United Kingdom) and Stata 12.0 (StataCorp, College Station, Texas, United States). We determined the HR with 95% confidence intervals (CIs) from the publications as a relevant measure for the effects of patient survival and graft survival and estimated the HR from log-rank χ^2 statistics [16,17]. Studies that presented continuous data as means and range values were used to calculate the standard deviations using the technique described by Liberati et al [18]. Results were reported with 95% CIs.

Statistical heterogeneity between the included studies was appraised using the Q measure for statistical significance and the I^2 measure for the quantification of heterogeneity, with $P < .1$ being statistically significant and $I^2 > 50\%$ indicating substantial heterogeneity. A fixed-effects model based on the Mantel-Haenszel estimator was used when there was no significant heterogeneity between studies, otherwise, a random-effects model based on the DerSimonian-Laird estimator was used [19]. Subgroup analyses were preformed to assess outcomes comparing HCV-positive and HCV-negative recipients after LT. Sensitivity analysis was performed for high-quality studies. Funnel plots were used to screen for potential publication bias.

RESULTS

The initial search revealed 1973 studies. With the titles and abstracts of these studies screened, 156 studies were considered potentially useful for inclusion. Those were retrieved and their full text was reviewed; 132 of these 153