Vascular and Biliary Complications Following Deceased Donor Liver Transplantation: A Meta-analysis

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ABSTRACT

Objective. To assess biliary and vascular complications after liver transplantations (LTs) sourced from deceased donors.

Methods. This study reviewed potentially relevant English-language articles gathered from PubMed and Medline published from 2012 to 2017. One additional study was carried out using our institution's database for articles published from 2013 to 2017. Biliary and vascular complications from adult patients receiving their first deceased-donor LT were included. This meta-analysis was performed using Review Manager version 5.2 (Cochrane Collaboration, Copenhagen, Denmark) and the study quality was evaluated using the Newcastle-Ottawa Scale.

Results. Ten studies met our inclusion criteria. Heterogeneity in donation after cardiac death (DCD) and donation after brain death (DBD) recipients was observed and minimized after pooling a subgroup analysis. This latter analysis focused on biliary stricture, biliary leaks and stones, and vascular thrombosis and stenosis. Meta-analyses showed that patients receiving DCD organs have a greatly increased risk of biliary complications compared to those receiving DBD organs, particularly the following: biliary leaks and stones (odds ratio [OR] = 1.69, 95% confidence interval [CI] 1.22–2.34); and biliary stricture (OR = 1.58, 95% CI 1.21–2.06). DCD grafts tended to be but were not significantly associated with DBD regarding vascular thrombosis (OR = 1.62, 95% CI 1.05–2.50), and the risk of vascular stenosis in DCD grafts was not statistically significant (OR = 1.25, 95% CI, .70–2.25).

Conclusion. DCD was associated with an increased risk of biliary complications after LT, tended to indicate an increased risk of vascular thrombosis versus, and was not associated with an increased risk of vascular stenosis compared to DBD. There was no significant difference between the grafts.

LIVER transplantation (LT) is nowadays a standard treatment for patients with end-stage liver disease, and there have been many improvements in postoperative complication management [1]. In the late 1980s, interest in donation after cardiac death (DCDs) grew and the number of solid organ transplants has since increased in parallel with the growing demand for organs and because of medical advances and improvement of surgical techniques, behavioral research, and development of imaging technology for exploring postoperative complications after LT [2,3]. Early diagnosis leads to better outcomes after treatment [4]. The searcher hypothesis states that the donor, recipient, and technical variables may affect complications differently,

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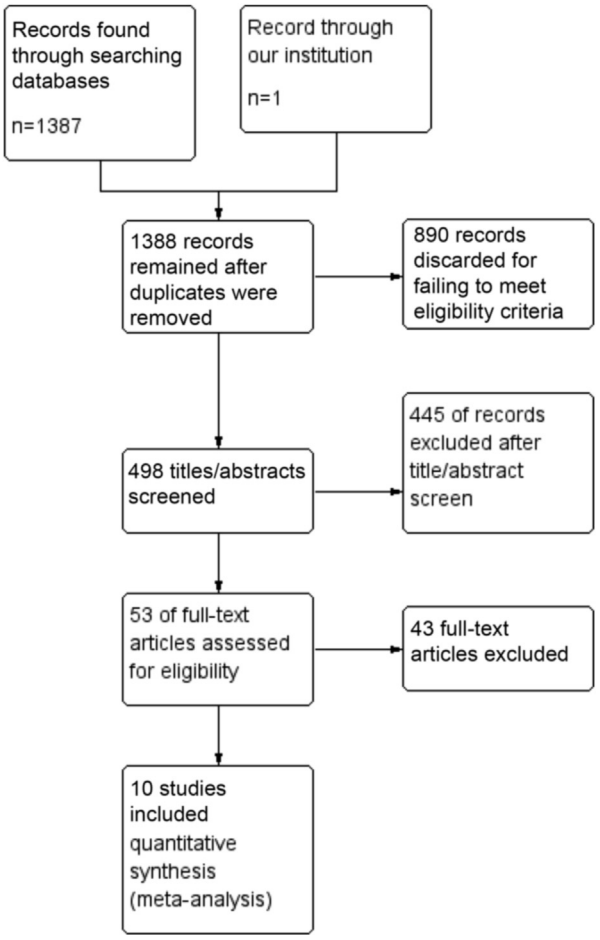

Fig 1. Schematic summary of study search and selection.

whereas histidine tryptophan ketoglutarate or University of Wisconsin solution was used to protect the appearance of complications, but this difference was not quite significant. The ideal strategy to resolve the onset of complications is to avoid them if possible rather than treat them. Good organ preservation offered the best opportunity for patients post-transplant and extended the organ utilization. It also reduced hospital stays following LTs [5,6].

Regarding vascular complications, vascular thrombosis, which includes hepatic artery thrombosis (HAT) and portal vein thrombosis (PVT), was a major complication that frequently occurred in graft failure, so retransplantation was usually necessary. Most mortalities occurring after LTs were the result of the complete occlusion of portal vein thrombosis, which affected overall survival; however, if the occlusion was not complete, it influenced the severity of illness and post-transplant outcomes [7–9]. It is the main cause of serious post-LT complications in most patients with HAT who resort to retransplantation [3,10,11]. A higher risk of HAT was caused by DCD livers, which are considered inferior grafts [12]. In other centers, PVT was not affected or not associated with worse post-LT complications and had similar outcomes [13].

Biliary complications are a frequent cause of morbidity graft loss and death after orthotropic LT [14]. Biliary leaks, strictures, and stone disease are the most common complications [15,16]. DCD LT had a higher incidence of biliary complications compared to donation after brain death (DBD) LT [17,18]. Gastaca [19] also confirmed that biliary strictures and leaks are the most common complications in deceased donor LTs. Hepatic artery complications are a risk factor for such biliary complications. Donation after cardiac death was found to be a likely a risk factor in decreasing the survival graft rate due to increased biliary complications [19].

LT recipients are at significant risk for developing different complications after LT. Therefore, more research is needed in this area in order to identify and understand the mechanism of these complications. Only in this way can more specific preventive and therapeutic strategies be developed that may further improve patient and graft survival after LTs. In this study we want to highlight the most common vascular and biliary complications following LTs using deceased donors based on the different reported articles and determine whether the type of donor increases the risk.

Table 1. Characteristics of the Studies Included in the Meta-analysis With Incidence of Complications

	Incidence (%) (DCD)					Incidence (%) (DBD)				
Authors (Year)	DCD No.	Biliary Leaks and Stones	Biliary Stricture	Vascular Thrombosis	Vascular Stenosis	DBD No.	Biliary Leaks and Stones	Biliary Stricture	Vascular Thrombosis	Vascular Stenosis
Taner et al [59] (2012)	200	-	-	3	-	1828	-	-	2	-
Meurisse et al [63] (2012)	30	6	46	-	-	385	6	-	-	-
Laing et al [62] (2016)	234	3	11	3	2	739	0.6	-	3	0.2
Croome et al [17] (2012)	36	-	19	-	-	327	-	8	-	-
Croome et al [65] (2017)	300	11	11	2	4	300	6	12	2	5
Doyle et al [61] (2015)	49	14	20	-	-	98	6	16	-	-
Firl et al [60] (2015)	92	1	15	2	-	92	2	18	3	-
Vannatta et al [66] (2013)	38	10	18	-	10	76	1	9	-	6
Marit et al [64] (2017)	115	18	-	6	-	326	18	-	3	-
Vivalda et al* (2018)	225	0.8	1.3	1.7	1.7	25	-	4	4	-

Abbreviations: DBD, donation after brain death; DCD, donation after cardiac death.
*Retrospective study between 2013 and 2017 data from institute of hepatobiliary disease in Zhongnan Hospital (unpublished data).

Table 2. Summary of Included Studies

Authors	Study Type	Comparison No. of Patients	Inclusion Criteria	Outcomes
Croome et al [17]	Retrospective study from the data prospectively entered into transplant database	DCD: 36 DBD: 327	All patients who underwent DCD LT and DBD LT between January 2006 and September 2011	Biliary complications and their subsequent endoscopic management
Meurisse et al [63]	Retrospective	DCD: 30 DBD: 385	Medical records between January 2003 and December 2010 of donor and recipients after DCD versus DBD-OLT were reviewed. Recipients $<$18 years old combined transplantations and patients who received a split liver graft were excluded	To analyze biliary complications, retransplantation rates, and patient graft survival
Croome et al [65]	Outside medical records and prospective study	DCD: 300 DBD: 300	All patients undergoing LT at Mayo Clinic Florida between the dates of February 28, 1998 and April 30, 2015 were identified	The primary outcome measures were graft and patient survival, post-LT biliary and vascular complications, and QOL scores.
Doyle et al [61]	Retrospective that used the prospective transplant database	DCD: 49 DBD: 98	Adult LT who received grafts from DCD donors and DBD donors from January 2005 to august 2014	All cases were studies for recipient and donor demographics, cause of liver disease, MELD score, operative details, immediate and later postoperative complications, and short-term as well as long-term overall and graft survival.
Firl et al [60]	Retrospective study retrieved from prospective transplant database	DCD: 92 DBD: 92	92 LT patients receiving a DCD graft and 92 recipients who received a DBD graft at Cleveland Clinic from January 2005 to June 2014. Recipients who received retransplantation or partial grafts were excluded from this study.	Post-operative characteristics by donor age and graft type, surgical complications.
Marit et al [64]	Retrospective	DCD: 115 DBD: 326	All consecutive patients who underwent deceased donor LT with age $\geq$18 years in our center from start of the DCD program were included. Exclusion criteria were retransplantation, split-liver LT, combined liver-kidney transplantation, and transplant for acute hepatic failure.	Postoperative complication after LT.

Table 2. (continued)

Authors	Study Type	Comparison No. of Patients	Inclusion Criteria	Outcomes
Laing et al [62]	The hospital transplant database is maintained prospectively and contains information on the donor, the recipient, the retrieval process, the perioperative period, complications, and follow-up.	DCD: 234 DBD: 739	Adult patients (aged >16 years) who underwent primary orthotopic LT between July 2004 and July 2014 were initially included. Pediatric transplants and recipients of grafts from living donors, split livers, machine-perfused grafts, domino grafts or multiple organs were excluded, as were patients with a primary etiology of acute liver failure (they would be less likely to receive a DCD graft).	Primary end points were overall graft and patient survival. Secondary end points included postoperative, biliary and vascular complications.
Taner et al [59]	Retrospective	DCD: 200 DBD: 1828	The study was performed via chart reviews of all LT cases with DCD or DBD organs during the same time period between December 1998 and February 2010 at Mayo Clinic Florida (Jacksonville, FL).	The outcomes included the patient and graft survival rates for recipients of liver grafts from DCD or DBD donors, the retransplantation rates, and the incidence of PNF, HAT, and IC in recipients of DCD grafts.
Vanatta et al [66]	Retrospective	DCD: 38 DBD: 76	adult LT recipients at the University of Tennessee/Methodist University Hospital Transplant Institute, Memphis, Tennessee	A comprehensive approach controlling for careful donor and recipient matching, surgical technique, and preservation solution was used to address the dynamics of WIT, cold preservation, and reperfusion injury that contribute to the biliary complications and graft failure in DCD donors.
Vivalda et al*	Retrospective view of all adult patients who underwent their first LT from 2013 to 2017 in our institution	DCD: 225 DBD: 25	All adult patients >17 years old who underwent LT from January 2013 to December 2017 were reviewed. Multiple organ transplant, retransplantation, age <17 years were excluded.	Biliary and vascular complications post LT

Abbreviations: DBD, donation after brain death; DCD, donation after cardiac death; HAT, hepatic artery thrombosis; IC, ischemic cholangiopathy; LT, liver transplantation; MELD, Model for End-Stage Liver Disease; OLT, orthotopic liver transplantation; PNF, primary non-function; QOL, quality of life; WIT, warm ischemia time.
*Retrospective study between 2013 and 2017 data from Institute of Hepatobiliary Disease in Zhongnan Hospital.

METHODS

Eligibility Criteria

All articles must be based on a cohort study and include postoperative complications after LTs using grafts from deceased donors, with a focus on biliary and vascular complications. Articles must be full-text articles published in English from 2012 to 2017: published and unpublished data were gathered. All adult patients who had undergone a first orthotropic LT with a deceased donor organ were considered. Multiple organ transplants, split-liver LTs, live donor transplants, and retransplantations were excluded.

The studies comparing the postoperative complications of LTs of both recipient categories (DCD vs DBD) were analyzed. The comparison outcomes focused on biliary and vascular complications, each category divided into two groups: biliary complications were divided into biliary leaks and stones and biliary stricture, while vascular complications were divided into vascular thrombosis and stenosis.

A primary outcome measure was the proportion of biliary complications that can be defined as biliary stricture, and biliary leaks and stones after LTs in patients who received DCD vs DBD. A secondary outcome was the proportion of vascular complications following LTs, such as vascular thrombosis and stenosis. The outcome measure was the proportion for those complications in those grafts.

Information Sources and Study Selection

Studies were identified by searching electronic databases provided on PubMed, as well as other Internet sources that potentially included references of relevant articles and unpublished data. The following terms were used to search the electronic databases: liver transplantation, liver transplantation complications, deceased donor, DCD (donation after cardiac death), or DBD (donation after brain death). The language limitation applied was English, and the relevant date restriction applied ranged from January 2012 to December 2017. The last search was run on February 6, 2018. We captured data from the database in our institution between January 2013 and December 2017.

The studies were selected in a concise manner according to the eligibility criteria. After title and abstract selection, full-text articles were assessed to enhance the study selection and to investigate the outcomes. Article selection or rejection required a full-text review. All reports showed that study characteristics may differ from report to report, including the description of the design, number of patients analyzed, and outcomes.

Data Items

Information was extracted from the research comparing DCD to DBD grafts in the post-LT complications of adult patients who had undergone their first deceased donor LT. Multiple organ transplants, split-liver LTs, living donor transplants, and retransplantations were excluded. The analysis focused on the details of the following vascular and biliary complications after LTs: biliary stricture, leaks, and stones; HAT and hepatic artery stenosis (HAS); portal vein stenosis (PVS) and PVT; and inferior vein cave thrombosis (IVCT) and stenosis (IVCS).

Quality Assessment

The quality of included studies was assessed using the Newcastle-Ottawa Scale, which is based on 3 principal parameters: selection, comparability, and outcome/exposure. Each parameter includes its own points: selection (4), comparability (1), and exposure (3), and these quality choices were identified with stars. A maximum of 1 star was given for each item within the selection and exposure/outcome categories, and a maximum of 2 stars was given for comparability.

Summary of Measurements

The meta-analyses were performed by quantitative analyses using Review Manager version 5.2 software in agreement with the recommendations of the Cochrane Collaboration. A multivariable analysis was conducted on the complication rate in DCD and DBD grafts after LTs by combining evidence effects in odds ratio (OR) and 95% confidence intervals (CI) for each side effect with all side effects calculated. The results of individual studies were then combined into a single effect size. The χ^2 tests (I^2 tests) were used to measure a degree of heterogeneity between studies and to describe the percentage of variance within each study rather than supply error. The subgroup analysis was established to investigate that heterogeneity. The outcomes measured the rates of biliary and vascular complications following LTs DBD and DCD recipients, as well as the difference of those complications for each donor type. Subgroup analyses were performed on biliary subgroups and vascular subgroups: biliary structure and biliary leaks and stones formed the 2 biliary subgroups, while vascular thrombosis and vascular stenosis formed the 2 vascular subgroups. If significant heterogeneity was found, the results were analyzed as limited information revealing differences in studies.

RESULTS

Study Selection

The searches provided a total of 1387 citations. After adjusting for duplicate records and adding 1 record from our institution's database, the search total was 1388. Of these, 890 were removed because they did not meet the primary eligibility criteria (human species, publication dates). Title and abstract reviews were performed for the remaining 498 studies, 445 of which were discarded. The full texts of the remaining 53 citations were examined in more detail. Forty-three studies [14–16,19–58] did not meet the inclusion criteria as described because they lacked DBD and DCD comparisons or included living donors, pediatric transplantation, multiple transplanted organs, or retransplantation. Nine studies [17,59–66] and one study through our institution met the inclusion criteria and were included in the meta-analysis (see Fig 1). These 10 cohort studies [17,59–66] and the one from our institution were subjected to the meta-analysis. The sample included only those studies that focused on the number of patients receiving organs from DCD and DBD donors who had biliary (stricture, leaks and stones) and vascular (PVT, PVS, HAT, HAS, IVCS, IVCT) post-LT complications. These studies involved a total of 5515 participants: 1319 transplanted patients received DCD donor organs and 4196 received DBD organs, which were the main inclusion criteria detailed earlier. All of the studies were multicenter and were conducted in the United States, Europe, and China. The included studies are summarized in Table 1 and a narrative summary describing the tabular data is presented in Table 2.

The estimated effect and confidence intervals for each study and percentage weights are presented as forest plots (see Figs 2, 3).

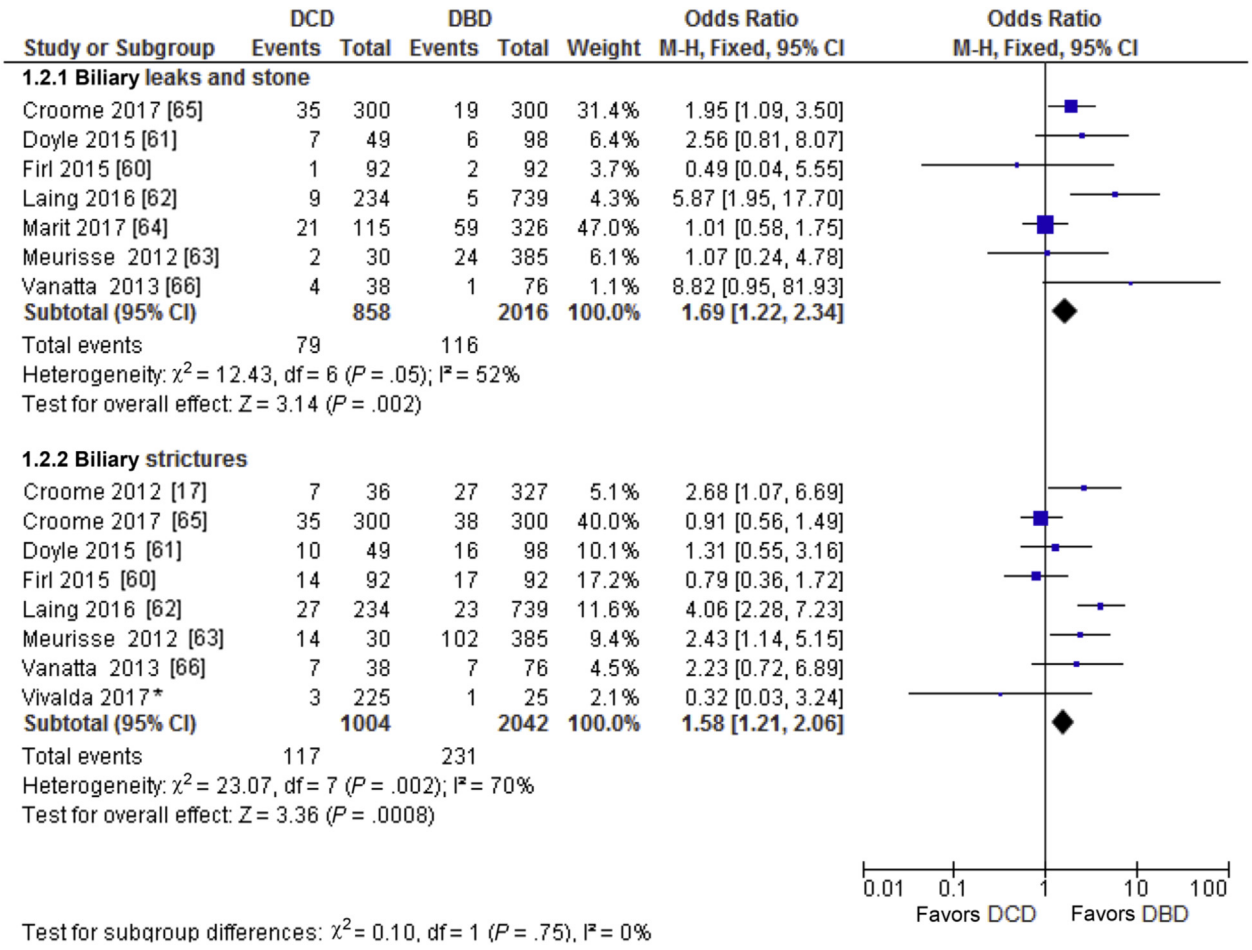

Fig 2. Incidence of biliary complications associated with DCD grafts compared to DBD grafts, including biliary stricture, leaks, and stones. *Retrospective study between 2013 and 2017 data from Institute of Hepatobiliary Disease in Zhongnan Hospital.

Syntheses of Results

Nine studies [17,60–66] and the one from our institution reported biliary complications in 3487 LT recipients (1119 DCDs and 2368 DBDs). Of these, 7 studies [60–66] reported rates on bile leaks and stones affecting 2874 participants. LTs with DCD donors was associated with a significant increase in complications, as mentioned above, when compared to DBDs with combined incidence (OR: 1.69 [95% CI = 1.22 to 2.34] $P = .002$; $I^2 = 52\%$) and the risk of bile stricture with 3046 participants increased significantly following DCD grafts, as reported in 8 studies [17,60–63,65,66] and the one from our institution with a pooled incidence (OR: 1.58 [95% CI = 1.21–2.06] $P = .0008$; $I^2 = 70\%$) (see Fig 2).

Vascular complications such as HAT, HAS, PVT, PVS, IVCS, and IVCT following LT were reported in 7 studies [59,60,62,64–66] and the one from our institution on a total of 4590 LTs: 1204 patients received DCDs and 3386 received DBDs. In our research, 7 studies [59,60,62,64–66] and one throughout from our institution reported vascular thrombosis affected 4590 participants; these studies found that DCD LTs tended to be but were not significantly different from DBD with pooled incidence (OR: 1.62 [95% CI = 1.05, 2.50] $P = .03$; $I^2 = 42\%$). Rates of vascular stenosis were reported in 3 studies [62,65,66] with a combined incidence (OR: 1.25 [95% CI = .70, 2.25] $P = .45$; $I^2 = 68\%$) where the risk of difference in DCD vs DBD was also not statistically significant. These results are presented in Fig 3.

We detected an important heterogeneity within those comparisons: Retrospective exploration of this heterogeneity revealed that the percentage of variation across studies was explained by differences in the study conditions, effects of the interventions, study populations, and study design.

Quality Assessment

From 10 included studies [17,59–66] and the one from our institution, 2 papers [62,65] were prospective studies and another 8 [17,59–61,63,64,66] and one from our institution… were retrospective studies within 2 case control

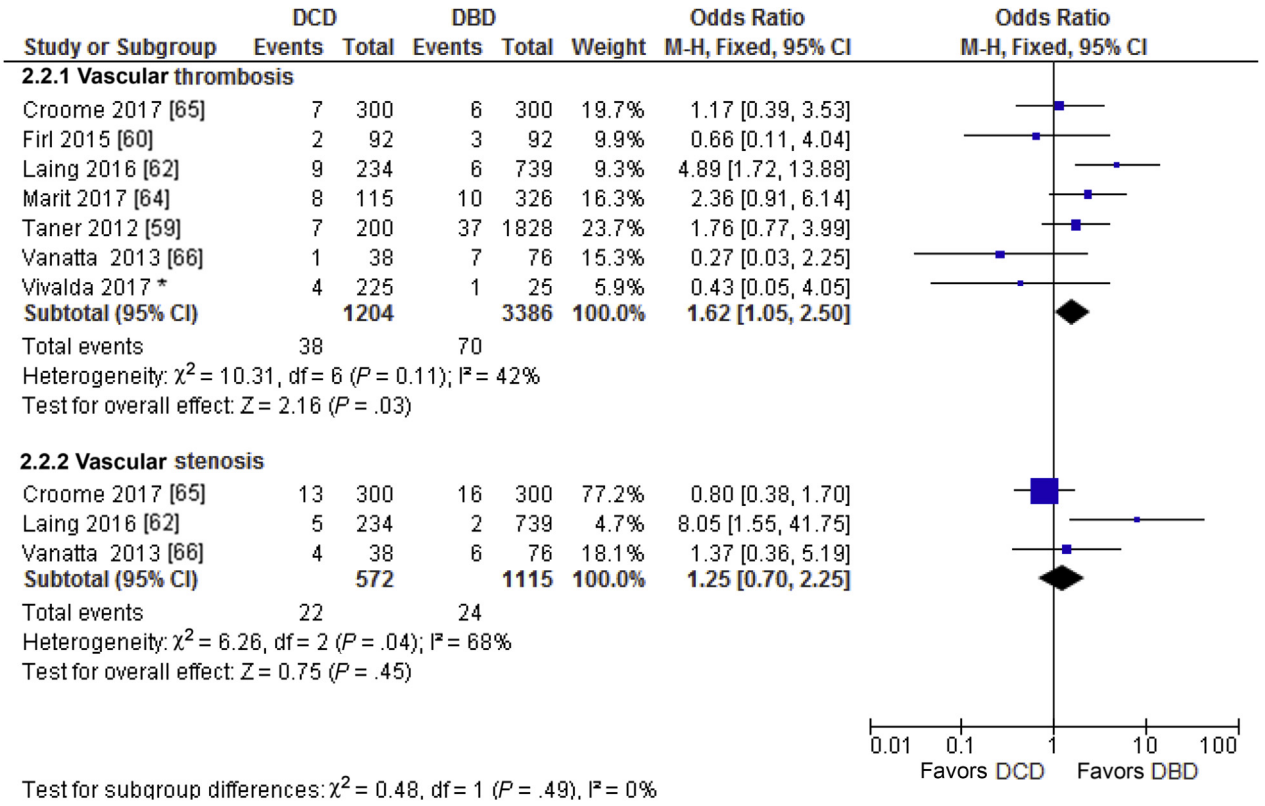

Fig 3. Incidence of vascular complications associated with DCD grafts compared to DBD grafts, including vascular stenosis and thrombosis. *Retrospective study between 2013 and 2017 data from institute of hepatobiliary disease in Zhongnan Hospital.

studies [60,66]. The meta-analysis with non-randomized studies was assessed according Newcastle-Ottawa Scale on moderate or high methodological quality which was at least 6 stars, as summarized in Table 3.

DISCUSSION

Summary of Evidence

Only 10 studies [17,59–66] and one from our institution… compared DCD and DBD grafts, which allowed for a substantial crossover of biliary (strictures, leaks and stone) and vascular (thrombosis and stenosis) complications following LT. Overall, the evidence indicated that the use of DCD livers in transplantation as opposed to DBD was associated with a significantly increased risk of biliary complications. This association, however, was not seen in vascular complications; although transplantations using DCD livers produced a slight increase in cases of vascular thrombosis, the increase was not statistically significant.

LIMITATIONS

A limitation that can be drawn from the meta-analysis is the heterogeneity of the studies. This might be due to the large numbers of DCD and DBD recipients in the sources assessed. Most sample populations of patients who received DCD organs reviewed in the included articles were fewer than 300 (5 studies [59,62,64,65] and one from our institution… featured patient samples of 100–300 individuals, and 5 studies [17,60,61,63,66] featured patient samples of 30–90 individuals). This was not the case with the DBD organ recipients; most samples of these patients were over 300 individuals [17,59,62,65], and only 4 studies, one sourced by our institution and 3 from published data [60,61,66] had sample populations of 25–98 patients. In this meta-analysis only 2 studies [60,65] had an equal number of patients receiving

Table 3. Newcastle-Ottawa Scale Scores for Non-randomized Studies

Authors	Selection	Comparability	Outcome/Exposure
Croome et al [17]	★★★	★	★★
Meurisse et al [63]	★★★★	★	★★★
Croome et al [65]	★★★★	★	★★★
Doyle et al [61]	★★★★	★	★★★
Firl et al [60]	★★★	★	★★★
Marit et al [64]	★★★★	★	★★★
Laing et al [62]	★★★★	★	★★★
Taner et al [59]	★★★★	★	★★★
Vanatta et al [66]	★★★	★★	★★★
Vivalda et al*	★★★★	★	★★★

*Retrospective study between 2013 and 2017 data from Institute of Hepatobiliary Disease in Zhongnan Hospital.

DCDs and DBDs. Croome et al [65] found that DCD donation was associated with an increased risk of biliary leaks and stones but that this was not significantly different from DBD donors. The result was the same in our study, in which there was no significant difference between the two types of liver grafts. Firl et al [60] found that the risk of biliary stricture, leaks, and stones increased with DCD grafts but that this increase was not significantly different from DBD grafts or vascular complications. These 2 studies showed that with the same number of patient grafts, the result was the same as in our study, which indicates that the heterogeneity seen could be due to other reasons or is retrospective in nature. In our study, DBD grafts were used in almost all of the studies reviewed, except in one study from our institution which focused on DCD donors. However, the results of that study indicated that there was no significant difference in complications caused by DCD and DBD grafts (biliary stricture and vascular thrombosis). In our center, DCD is not an inferior graft. When used in treatment with machine perfusion or chirurgical efforts, DCD grafts perform very well. In their study Ye et al emphasized the importance of surgical techniques to vascular drainage [67]. Donor type is not a sufficient reason underlying the risk of biliary and vascular complications, but it is associated with organ procurement, surgical technique, and patient care. Chatzizacharias et al found that hepatic graft blood acts a big role in LT [10]. In the last 10 years, DCD grafts have produced satisfactory survival rates, indicating that they are not inferior to DBD grafts [62]. However, after analyzing the combined incidences reported in all the included articles, the results of this study indicate that the use of DCD is slightly different from that of DBD, although this was first associated with an increased incidence of biliary complications.

Foreseeing the difficulties present in assessing the outcome of our analyses, we used multiple strategies and sensitive analysis techniques to minimize heterogeneity. Despite our efforts, heterogeneity persisted though the subgroup comparison analysis, although it was reduced. We hypothesize that the effect may differ according to the methodology of the studies and different outcome assessors. In spite of the limitations, our meta-analysis indicated that DCD grafts were a significant source of increased biliary complications and tended to be associated with vascular thrombosis, although there was no significant difference when compared to DBD grafts. More research should be done on postoperative complications after LTs because of the increased use of DCD donors. We would like to stress that researchers should deeply analyze the mechanisms of those complications in order to predict and minimize them, improving both patient care and graft survival.

CONCLUSIONS

In summary, our meta-analysis showed that post-LT complications resulting from DCD grafts were not significantly different from those associated with DBDs, even though there were higher associated incidences of biliary complications (stricture, leaks and stones) and vascular thrombosis. Both types of LT grafts were similar in terms of outcomes. The DCD liver graft is actually an innovation, and the results of our study confirm that clinicians to use them and advance organ donation.

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