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Review Article

Outcome of pancreas transplantation from donation after circulatory death compared to donation after brain death

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ABSTRACT

Introduction: To overcome the gap of organ shortage grafts from donation after circulatory death (DCD) can be used. This review evaluates the outcomes after DCD pancreas donation compared to donation after brain death (DBD).

Materials and methods: A literature search was performed using Medline, Embase, and PubMed databases. All comparative cohort studies reporting the outcome after DCD and DBD pancreas transplantation were included. All data were assessed according to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines. To evaluate the event rates, pooled odds ratios (ORs) as well as the 95% confidence intervals (CI) were calculated. Since the number of studies is small we used the random-effects model only to overcome heterogeneity.

Results: There is no difference in 1-year pancreas graft survival (OR 1.092, CI 95% 0.649–1.837, P = 0.741) or patient survival (OR 0.699, CI 95% 0.246–1.985, P = 0.502). Simultaneous pancreas-kidney (SPK) transplantation showed significantly higher graft survival rates compared to pancreas transplantation alone (87.2% vs. 76.6%, P < 0.001 in DBD and 86.5% vs. 74.9%, P < 0.001 in DCD). DCD SPK grafts show a higher delayed kidney graft function rate compared to DBD SPK-grafts (OR 0.209, CI 95% 0.104–0.421, P < 0.001). There is significantly less pancreas graft thrombosis after DBD-donation (OR 0.567, CI 95% 0.340–0.946, P = 0.030). We found no difference in the HbA1c level at 1-year follow-up with a median of 5.4% in both groups and a mean of 5.63% (DCD) vs 5.43% (DBD).

Discussion: DCD pancreas transplantation has comparable patient and 1-year graft survival rates and should be considered a safe alternative for DBD pancreas transplantation.

1. Introduction

Organ transplantation is an effective treatment for patients with end-stage organ failure to improve their quality of life and increase their life expectancy. Initially, most kidney transplant programmes used donors after circulatory death (DCD). Subsequently, with the wide acceptance and criteria for brain death, together with better outcomes of organs used from brain death donors (DBD), DCD programmes were mostly replaced by DBD programmes. However, from the 1990's many countries have reintroduced DCD programmes due to a growing organ shortage [1–3].

DCD kidney donation is widely used and long-term outcomes are comparable to DBD kidney donation, although there is a higher rate of delayed graft function [4–9]. DCD liver transplantation has also been reintroduced, although with a higher risk of primary graft failure and biliary complications compared to DBD liver transplantation [9–13]. DCD lung transplantation shows promising results as well with at least comparable outcomes to DBD lung transplantation [14–16]. There is much less experience with DCD pancreas transplantation mostly due to concerns about post-operative dysfunction and pancreatitis. There are relatively few published series that describe the outcomes of DCD pancreas transplantation. The aim of this study is to give a comprehensive systematic review of the current literature on the outcomes of DCD pancreas transplantation and provide a meta-analysis of the available data.

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2. Material and methods

2.1. Literature search

Studies describing the outcome after pancreas transplantation were identified from PubMed, the Medline electronic database and Embase from 1966 until July 2014. The following MeSH terms were used: 'pancreas transplantation', 'cause of death', 'death, sudden, cardiac', 'brain death', 'host vs graft reaction' and 'treatment outcome'. We also searched with text words: 'cardiac death', 'brain death', 'circulatory death', 'heart-beating', 'non-heart-beating', 'outcome', and 'survival'. The studies were limited to be at least a comparative cohort study, relating human research and written in English. Cross-referencing was used to identify additional articles. Studies were included for analysis if they met all of the following inclusion criteria: 1) the study was at least a cohort study, 2) all reported patients had received a pancreas alone or a combined pancreas-kidney transplantation, and 3) data on treatment outcome were available. All studies were evaluated by two independent investigators (EL and RP). Agreement concerning potential relevance was reached by consensus and full text copies of relevant papers were obtained. If more than one study was published describing the same cohort, the most recent study was included to avoid overlapping results. A sensitivity analysis was performed on these separate studies. However, the previous publication was assessed for additional information. Fig. 1 shows the process of identification of papers for inclusion.

2.2. Quality assessment

All data were assessed according to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines [17]. A modification of the Newcastle-Ottawa Scale (NOS) was used as an assessment tool for selection, comparability and outcome assessment [18]. The NOS ranges between zero (worst) and nine stars (best). Studies with a score of seven stars or greater were considered to be of high quality.

2.3. Outcome measures

The primary endpoint was pancreas graft survival at 1-year follow-up, which was defined as removal of the graft or loss of endocrine functioning requiring return to insulin therapy or oral hypoglycaemic medication. Secondary outcomes were patient survival, graft thrombosis (defined as venous thrombosis, requiring graft pancreatectomy), endocrine pancreas function in terms of HbA1c and delayed graft function of the kidney for simultaneous pancreas kidney (SPK) transplantation (defined as the need for dialysis treatment during the first week after transplantation, except when required for hyperkalemia in the first 24 h).

2.4. Statistical methods

A meta-analysis was performed for each endpoint if at least two studies could be combined. To evaluate the event rates, pooled odds ratios (ORs), as well as the 95% confidence intervals (CI), were calculated. Statistical significance between the two groups was defined as $P < 0.05$. Heterogeneity was tested in all of the included studies. Since the number of studies is small and to overcome heterogeneity, we used the random-effects model only [19,20]. Not every included study describes all outcomes measures, so results are shown in Forrest plots when more than one study was found describing the same outcome measure, with relative weights added according to sample sizes. All statistical analyses were done with Comprehensive Meta-analysis, standard edition (Biostat inc.

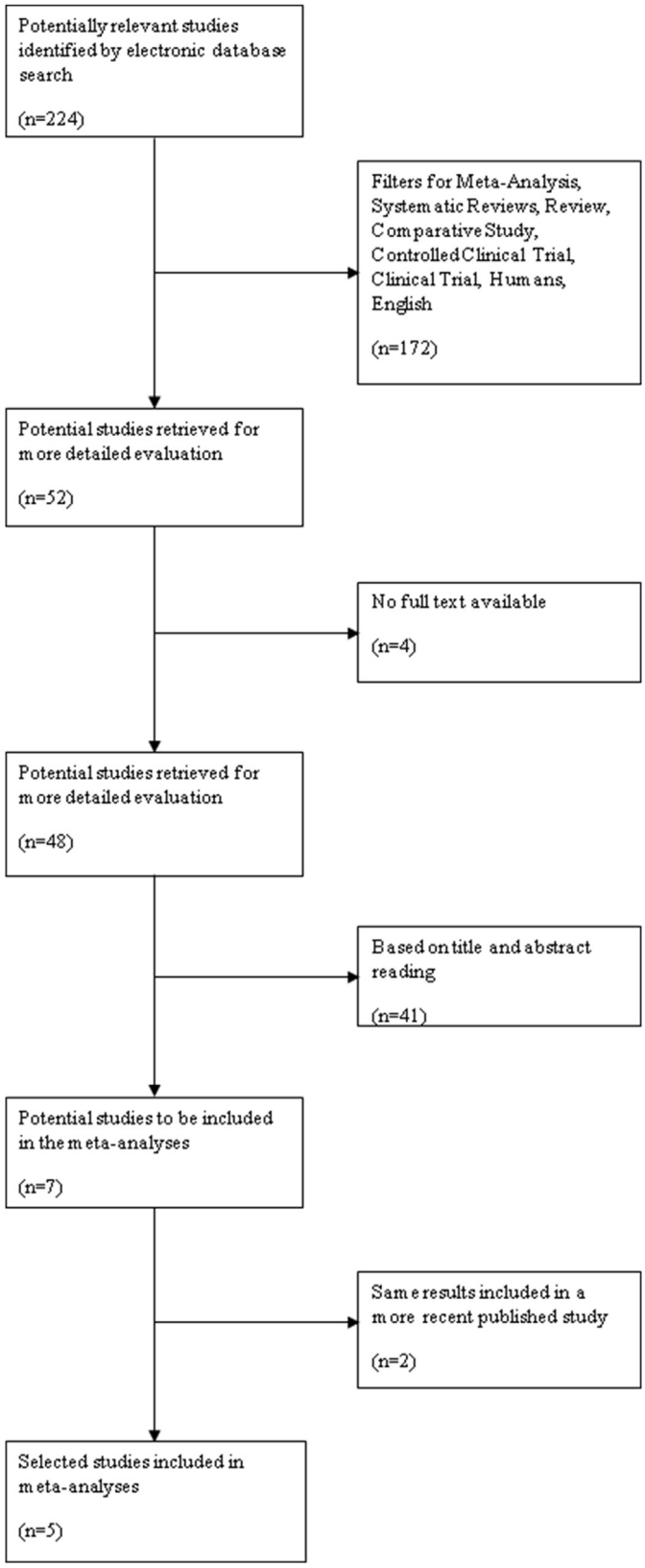

Fig. 1. Flowchart of studies included in meta-analyses.

Englewood, NJ, USA). To identify statistical differences between two groups in terms of graft survival χ^2 was used in 'R' version 3.1.1.

3. Results

3.1. Methodological quality of included studies

Our primary search resulted in 224 studies. Of those 172 did not meet the inclusion criteria based on following exclusion criteria; type of study, humans and English language. Fifty-two studies were retrieved for a more detailed evaluation which resulted in seven studies that met the inclusion criteria. Because of the retrospective design of the selected studies no papers were excluded based solely on the NOS. The large cohort analysis by Siskind et al. reported different outcome measures compared to the other studies and could therefore not be included in the meta-analysis for a pooled analysis but was used in the general review for support. One additional study was excluded because of data overlapping with a more recent publication which resulted in 5 studies being suitable for meta-analysis (Table 1). The studies by Salvalaggio and Siskind both analysed the United Network for Organ Sharing (UNOS) database, while the study by Bellingham and Fernandez both describe the single center experience of the University of Wisconsin. Although these studies show partially overlapping results, all studies were included, however for the meta-analyses only the results of one of those studies was included.

3.2. Donor characteristics

In the study by Muthusamy et al. DCD donors were significantly younger than DBD donors, 28 vs. 37 years ($P < 0.0001$) and had a lower BMI (23 vs. 24, $P = 0.04$) [21]. In the remaining studies there were no differences in donor age [22–26], nor in BMI [22,23,26]. There were significantly more donors after cerebrovascular accidents in the DBD-group compared to the DCD-group [21,23,24].

3.3. Technical aspects of organ procurement

Both studies by Muthusamy and Qureshi were performed in the UK where premortem cannulation is not allowed. After a 5 min no-touch period, followed by declaration of death, cannulation of the common iliac vessels or aorta was performed through a midline laparotomy and perfusion with University of Wisconsin (UW) solution was carried out [21,23]. In the studies from the University of Wisconsin by Fernandez and Bellingham, with family consent, premortem dissection or cannulation of the femoral vessels was performed with administration of heparin and phentolamine prior to the cessation of support. Perfusion with UW solution took place after a no-touch period of 5 min after declaration of death [24,25].

Because of different definitions of warm ischemic time (WIT) no overall median WIT could be calculated. In the study by Muthusamy median first WIT (defined as withdrawal of support to asystole) was 13 min (range 0–30) and median second WIT (from asystole to initiation of in situ cold perfusion) was 12 min (range 8–17). In the study by Bellingham the mean WIT (defined as time from withdrawal of support to initiation of cold perfusion) was 17.5 min (range 6–48). The study by Bellingham used the same definition and described a mean WIT of 20.8 min (±10.9). The study by Qureshi described a median WIT (time of cardiorespiratory arrest to initiation of cold perfusion) of 24 min (range 16–110).

In the study by Qureshi et al. there was a difference in cold ischemic time in pancreas grafts between DCD and DBD donors: median 8.2 h (5.9–10.5) vs. 9.5 h (3.8–12.5), $P = 0.004$ [23]. In the remaining studies there were no differences in pancreatic cold ischemic time between DCD and DBD donors [21,22,24,25]. The studies by Salvalaggio and Fernandez both described a significantly higher use of vasopressors for haemodynamic support in the DBD donors compared to DCD donors [22,24].

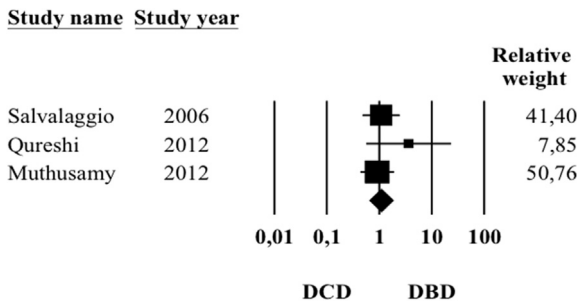

Fig. 2. Overall analysis of cohort studies comparing the 1 year pancreas graft survival after simultaneous pancreas kidney transplantation. Overall result: OR 1.092, CI 95% 0.649–1.837, n = 3313, P = 0.741, weighted mean of 87.2% in the DBD group vs. 86.5% in the DCD group (heterogeneity, P = 0.400).

3.4. Graft survival

Three studies reported 1-year pancreas graft survival for SPK transplantation in DBD and DCD donors [21–23]. In the overall analysis there is no difference in pancreas graft survival (OR 1.092, CI 95% 0.649–1.837, P = 0.741), with a weighted mean of 87.2% in the DBD-group vs. 86.5% in the DCD group (Fig. 2). In order to reduce the likelihood of overlap between studies a sensitivity analyses was performed with studies from the US and UK cohorts which yielded the same results (OR 0.986, CI 95% 0.573–1.695, P = 0.959), with a weighted mean of 86.6% in the DBD group vs. 86.7% in the DCD-group [21,22].

Two studies evaluated the 1-year pancreas graft survival for pancreas alone (PA) transplantation in DCD and DBD donors [22,23]. In the overall analysis there is no difference in pancreas graft survival (OR 1.059, CI 95% 0.531–2.113, P = 0.871), with a weighted mean of 76.6% in the DBD-group vs. 74.9% in the DCD group (Fig. 3).

When comparing pancreas graft survival after SPK transplantation with PA transplantation, SPK showed significantly

Table 1
Studies included in meta-analysis.

Author (year of publication)	Study period	Data/place	DCD		DBD	
			SPK	PA	SPK	PA
Fernandez et al. (2005) [24]	Jan 1993–Dec 2003	University of Wisconsin	37		539	
Salvalaggio et al. (2006) [22]	Jan 1993–Dec 2003	OPTN/UNOS	47	10	2431	1607
Bellingham et al. (2011) [25]	1980–2009	University of Wisconsin	68	4	744	159
Qureshi et al. (2012) [23]	Aug 2008–Jan 2011	University of Cambridge	20		40	
Muthusamy et al. (2012) [21]	2006–2011	United Kingdom	79	55	724	151

DCD, donation after circulatory death; DBD, donation after brain death; SPK, simultaneous pancreas-kidney transplantation; PA, pancreas alone transplantation; OPTN/UNOS, Organ Procurement and Transplantation Network/United Network for Organ Sharing.

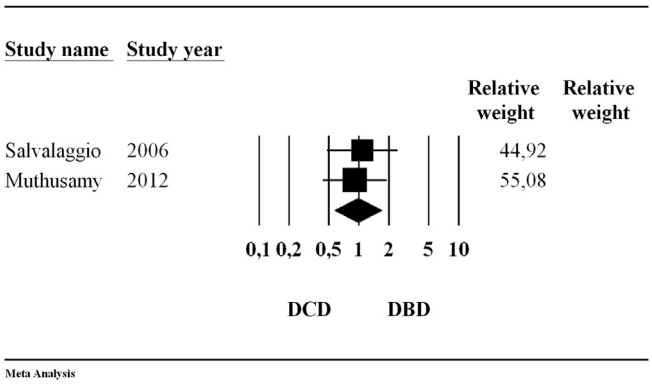

Fig. 3. Overall analysis of cohort studies comparing the 1 year pancreas graft survival after pancreas alone transplantation. Overal result: OR 1.059, CI 95% 0.531–2.113, n = 1810, P = 0.871, weighted mean of 76.6% in the DBD group vs. 74.9% in the DCD group (heterogeneity, P = 0.419).

higher graft survival rates after both DBD donation (87.2% vs. 76.6%, P < 0.001) as well as DCD-donation (86.5% vs. 74.9%, P < 0.001).

Two studies reported the 1-, 3- and 10-year pancreas graft survival irrespective of the type of transplantation (PA, SPK or PAK) in DCD and DBD donors. Bellingham et al. described their single-center results in pancreas transplantations performed from 1993 until 2008 [24]. The study by Siskind et al. describes the results of pancreas transplantation registered in the UNOS database from 1996 until 2012, partially overlapping the data of Bellingham et al. Overall 1-, 3- and 10 years pancreas graft survival was similar between studies, respectively 82.8%, 73.6% and 48.7% in the DBD groups vs. 83.0%, 75.5% and 55.2% in the DCD group [26].

3.5. Patient survival

Two studies evaluated the 1-year patient survival after DCD and DBD SPK transplantation [21,22]. In the overall analysis there was no difference in patient survival (OR 0.699, CI 95% 0.246–1.985, P = 0.502), with a weighted mean of 95.3% in the DBD group vs. 96.5% in the DCD group (Fig. 4). The overall analysis of the 1-year patient survival after DCD and DBD PA transplantation was also similar (OR 8.895, CI 95% 0.010–7750.299, P = 0.527) with a weighted mean of 96.9% in the DBD-group vs. 96.6% in the DCD group (Fig. 5).

Siskind et al. showed comparible 1-year patient survival results irrespective of type of transplantation, with 95.1% in the DBD group and 94.7% in the DCD group [26].

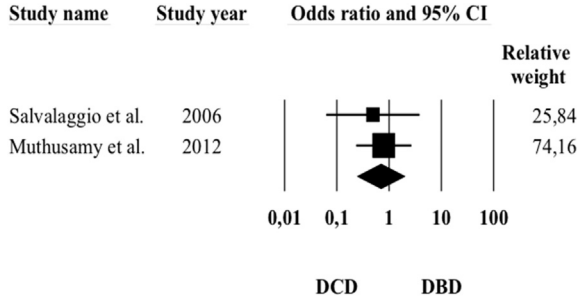

Fig. 4. Overall analysis of cohort studies comparing the 1 year patient survival after simultaneous pancreas kidney transplantation. Overall result: OR 0.699, CI 95% 0.246–1.985, n = 3253, P = 0.502, weighted mean of 95.3% in the DBD group vs. 96.5% in the DCD group (heterogeneity, P = 0.693).

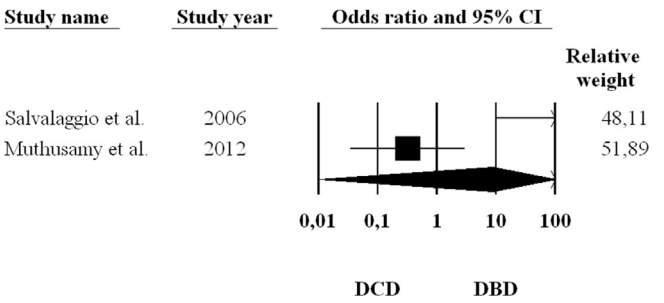

Fig. 5. Overall analysis of cohort studies comparing the 1 year patient survival after pancreas alone transplantation. Overall result: OR 8.895, CI 95% 0.010–7750.299, n = 1775, P = 0.527, weighted mean of 96.9% in the DBD group vs. 96.6% in the DCD group (heterogeneity, P = 0.001).

3.6. Graft thrombosis

Three studies evaluated the risk of graft thrombosis after pancreas transplantation in DCD and DBD donors [21,23,25]. In the overall analysis more graft thrombosis occurred after DCD donation (OR 0.567, CI 95% 0.340–0.946, P = 0.03), with a weighted mean of 5.2% in the DBD group vs. 9.0% in the DCD group (Fig. 6). In order to reduce the likelihood of overlap between studies a sensitivity analyses was performed with studies from the US and UK cohorts which yielded the same results (OR 0.552, CI 95% 0.327–0.932, P = 0.026), with a weighted mean of 5.3% in the DBD group vs. 9.2% in the DCD group [23,25].

3.7. HbA1c

There is no difference in the HbA1c level 1-year after pancreas transplantation, with a mean of 5.43% in the DBD group and 5.63% in the DCD group and a median of 5.4% in both groups [23,25]. Due to the lack of comparative data no meta-analysis could be performed.

3.8. Delayed graft function of kidney in SPK transplantation

Two studies reported DGF of the kidney in SPK grafts in DCD and DBD donors [22,23]. In the overall analysis DCD grafts show a higher delayed graft function rate compared to DBD-grafts (OR 0.209, CI 95% 0.104–0.421, P < 0.001), with a weighted mean of 8.2% in the DBD group vs. 27.6% in the DCD group (Fig. 7).

4. Discussion

This is the first systematic review and meta-analysis comparing the outcome of pancreas transplantation after DCD and DBD

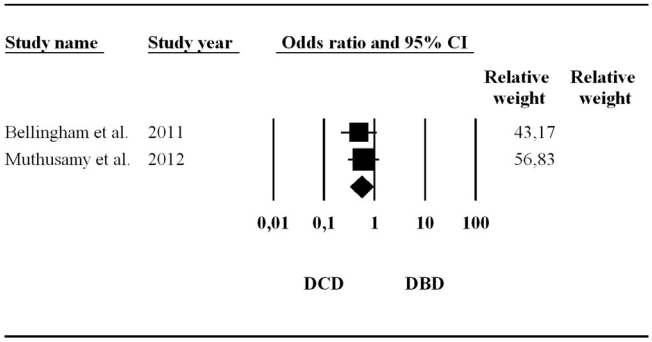

Fig. 6. Overall analysis of cohort studies comparing the 1 year graft thrombosis after pancreas transplantation. Overal result: OR 0.567, CI 95% 0.340–0.946, n = 2044, P = 0.030), weighted mean of 5.2% in the DBD group vs. 9.0% in the DCD group (heterogeneity, P = 0.832).

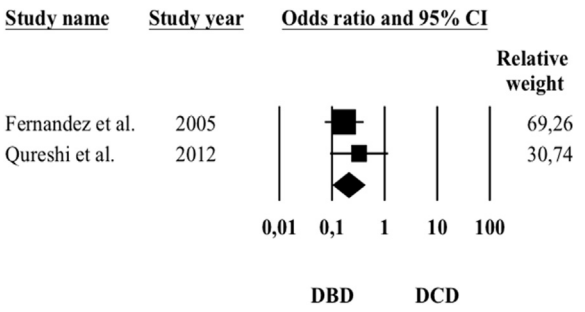

Fig. 7. Overall analysis of cohort studies comparing delayed graft function after simultaneous pancreas-kidney transplantation. Overall result: OR 0.209, CI 95% 0.104–0.421, n = 636, P < 0.001, weighted mean of 8.2% in the DBD group vs. 27.6% in the DCD group (heterogeneity, P = 0.401).

donation. According to our analysis DCD pancreas transplantation should be considered a feasible source to expand the donor pool.

Pooled 1-year pancreas graft survival and patient survival rates are similar after DCD and DBD pancreas transplantation. Data on long-term outcome are still limited to case-series and a few cohort studies and therefore could not be included in this meta-analysis.

This study shows that after DCD pancreas transplantation there is a higher risk of graft thrombosis resulting in a higher reoperation rate [23]. Remarkably this does not lead to a lower overall graft or patient survival which is encouraging for DCD pancreas programs.

Our pooled analysis showed a significantly higher rate of DGF of the kidney in DCD SPK grafts compared to DBD SPK grafts, an outcome which corresponds with the known literature on DCD kidney transplantation. When DGF occurs it does not result in a decreased graft survival of DCD grafts although patients with DGF of the kidney do require oral hypoglycemic agents more often during the first year [27–30].

Currently there is no consensus regarding the presence and definition of DGF after pancreas transplantation. For this reason we were unable to add this as an outcome measure. A common definition of DGF is the need for exogenous insulin to control hyperglycemia within the first week after transplantation. Alternative definitions reported in the literature add the total cumulative insulin requirement in which 19 IU or greater fits the diagnosis DGF [30]. But despite the controversy the incidence is estimated to be as high as 35% (ranging from 18.6 to 60%) and it is associated with a greater risk of overall pancreas graft failure and death-censored graft failure [31].

When looking for opportunities to expand the donor pool utilizing extended criteria donors (ECD) may be an option. These donors are generally considered to be of high age (beyond the currently applicable criteria), have a high body mass index (>30 kg/m^2) or are hemodynamically unstable prior to or during the procurement [32–35]. The study by Tomimaru et al. described 148 pancreas transplantations, of which 108 donors were considered ECD, including two DCD donors. They found a comparible overall patient survival rate after transplantation even though pancreas graft survival seemed to be slightly lower after ECD pancreas transplantation, although this did not reach statistical significance [33]. However, using donors of patients over 45 years of age does seem to result in a worse long-term outcome [36–38]. Nevertheless, SPK donation from these older donors still resulted in a lower mortality rate compared to remaining on the waiting list, though this survival benefit was only found in patients with waiting times >605 days [37]. Overall current literature shows proof that the donor criteria for pancreas transplantation could possibly be extended. However, data on long-term follow-up are still very limited and although cautiously embraced they must be critically assessed. The pancreas donor risk index (PDRI) remains a valuable tool to systematically assess the quality of the graft and potentially improve the utilization of higher risk organs [39].

The main benefit of pancreas transplantation is maintaining or even improving health-related quality of life [40]. But because of the uncertain survival gain conservative donor selection criteria are used for pancreas transplantation. The high mortality on the waiting list however does justify further research into the efficacy of extended criteria grafts [41]. The OPTN annual data report of the last two years showed a steady but high waiting list mortality of 6% with an increase with age (>50 years) of >8 per 100 waiting list years [42,43]. When comparing survival between transplanted patients and patients on the waiting list, the relative risk of dying within the first year is 2.67 (95% CI:0.81–3.51) to the detriment of waiting list patients. After 1 year this even increases to 5.89 (95% CI: 1.70–3.20) [44]. These data further support the belief that the surgical risk does not outweigh the risk of death on the waiting list and transplanting patients as quickly as possible is literally of vital importance.

This study has a few limitations that need to be addressed. First, no randomized controlled trial comparing DCD and DBD were available. This leads to a meta-analysis with only retrospective cohort studies and thus lower quality data. Secondly, the studies can be divided into two groups: 1. US-studies, using the OPTN/UNOS or University of Wisconsin data [22,24–26] and 2. UK-studies, using the UK Transplant Registry or the University of Cambridge data [21,23]. Because of partially overlapping results in these studies, we performed a sensitivity analysis using the largest published study of each group. For a few outcome parameters this results in a meta-analyses of only two studies (one US and one UK-study), further contributing to the weakness of the data quality. Thirdly, we performed our meta-analysis using the published data instead of the source data. Although this is considered a validated method it created the possibility of bias. Fourthly, graft thrombosis was one of the secondary outcome measures in our analysis. However, we acknowledge that there are several other factors which may affect the occurrence such as donor type, a hypercoagulable state, platelet dysfunction in uremic patients and differences in prophylactic therapies. Unfortunately, this information was not available for a more detailed analysis.

In conclusion, to overcome the gap of organ shortage ECD can be used. Even though there is a natural reluctance to use these donors for pancreas transplantation, DCD pancreas donation appears safe with comparable 1-year graft survival rates. However, larger prospective data with longer follow-up is required to definitely answer this question.

Conflict of interest

non declared.

Funding sources

non declared.

Authorship page

Ellen S. van Loo, MD: Conceived the study and its design, acquired the data and was involved in data analysis, interpretation and writing the manuscript. Approved the final version of the manuscript.

C. Krikke, MD: Was involved in data analysis and interpretation and contributed to the final adjustments to the manuscript after critically revising it for intellectual content. Approved the final version of the manuscript.

H.S. Hofker, MD: Was involved in data analysis and interpretation and contributed to the final adjustments to the manuscript after critically revising it for intellectual content. Approved the final version of the manuscript.

Stefan P. Berger, MD, PhD: Was involved in data analysis and interpretation and contributed to the final adjustments to the manuscript after critically revising it for intellectual content. Approved the final version of the manuscript.

H.G.D. Leuvenink, Msc PhD: Was involved in data analysis and interpretation and contributed to the final adjustments to the manuscript after critically revising it for intellectual content. Approved the final version of the manuscript.

R.A.Pol, MD, PhD: Conceived the study and its design and was involved in data analysis, interpretation and writing the manuscript. Contributed to the interpretation of results and to the final adjustments to the manuscript. Approved the final version of the manuscript.

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