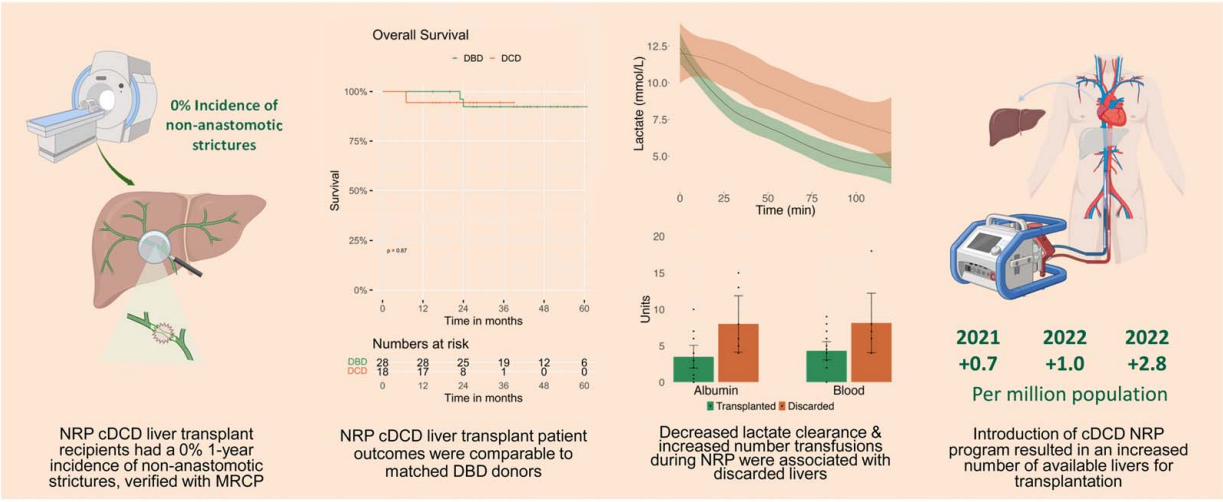
Normothermic regional perfusion in controlled DCD liver procurement: Outcomes of the Swedish national implementation protocol

VISUAL ABSTRACT

Implementation and outcomes of a national a-NRP liver transplantation program



NRP cDCD liver transplant recipients had a 0% 1-year incidence of non-anastomotic strictures, verified with MRCP

NRP cDCD liver transplant patient outcomes were comparable to matched DBD donors

Decreased lactate clearance & increased number transfusions during NRP were associated with discarded livers

Introduction of cDCD NRP program resulted in an increased number of available livers for transplantation

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ORIGINAL ARTICLE

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Normothermic regional perfusion in controlled DCD liver procurement: Outcomes of the Swedish national implementation protocol

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Abstract

Liver transplantation (LTX) using donors after controlled circulatory death (cDCD) is associated with poorer graft survival and increased incidence of nonanastomotic biliary strictures (NASs) compared to livers procured from brain-dead donors (DBD). The use of normothermic regional perfusion (NRP) during cDCD procurement may improve posttransplant outcomes and reduce the incidence of NAS. In Sweden, cDCD LTX was introduced through a national pilot protocol with mandatory NRP. This study aims to evaluate the outcome of cDCD LTX during the pilot period. Donor and recipient data were collected on all cDCD liver transplants during the pilot period between January 2020 to December 2022. Outcome on NAS, patient and graft survival, early allograft dysfunction, acute kidney injury, and comprehensive complication index was compared to a matched cohort of 28 patients transplanted with a DBD liver between 2018 and 2022. Eighteen patients were transplanted with a liver from a cDCD donor after using NRP. The mean functional warm ischemia time was 29 ± 6 minutes. The mean lactate reduction during NRP was 8.7 ± 2.4 mmol/L, and the end NRP perfusate alanine aminotransferase was 1.4 ± 1 μkat/L. When comparing recipients of

Abbreviations: AKI, acute kidney injury; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CCI, comprehensive complication index; cDCD, controlled donation after circulatory death; DBD, donation after brain death; DCD, donation after circulatory death; EAD, early allograft dysfunction; ERCP, endoscopic retrograde cholangiopancreatography; ICU, intensive care unit; LTX, liver transplantation; MRCP, magnetic resonance cholangiopancreatography; NAS, nonanastomotic biliary stricture; NRP, normothermic regional perfusion; PMP, per million population; WIT, warm ischemic time.

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cDCD liver transplant to DBD, no significant differences were observed in the incidence of NAS, patient and graft survival, comprehensive complication index, early allograft dysfunction, or acute kidney injury. Study protocol magnetic resonance cholangiopancreatography in cDCD patients showed no signs of subclinical biliary strictures. Evaluation of the Swedish national pilot of cDCD LTX with mandatory NRP shows comparable outcomes to a matched DBD cohort with 94.4% 1-year patient and graft survival and no incidence of NAS within the first year.

BACKGROUND

Liver transplantation (LTX) is a lifesaving procedure in patients with chronic and/or acute liver failure.[1] As the discrepancy between the availability and demand of livers for transplantation widens, extended criteria donors are increasingly used. Livers procured from controlled donation after circulatory death (cDCD) are increasingly used but are considered extended criteria grafts.[2]

LTX using grafts from cDCD donors have poorer outcomes compared to livers from brain-dead donors (DBD).[2,3] cDCD LTX is associated with lower graft survival, higher incidence of nonanastomotic biliary strictures (NASs), and a higher rate of postoperative complications.[3] cDCD procurement innately adds a period of warm ischemia compared to DBD donation. The damage caused to the biliary tree during the warm ischemic period is considered the main contributing factor to the inferior results after cDCD LTX.[4] Both in situ and ex situ machine perfusion have been shown to reduce ischemia-reperfusion injury and improve outcomes in cDCD LTX.[5,6] In normothermic regional perfusion (NRP), in situ perfusion of the organs intended for transplantation is performed following the circulatory arrest and declaration of death in cDCD donors. NRP has been shown to be safe and beneficial in cDCD procurement and to reduce incidences of NAS.[7]

From 2018 to 2019, cDCD donation of kidneys and lungs was evaluated through a Swedish national pilot.[8] Since 2020, cDCD donation has been considered clinical routine in Sweden and has since been implemented in intensive care units (ICUs). From 2020 to 2022, cDCD LTX was introduced in Sweden according to a national pilot protocol with mandatory use of NRP. LTX is considered highly specialized health care by the National Board of Health and Welfare and is centralized at Karolinska University Hospital, Stockholm, and Sahlgrenska University Hospital, Gothenburg. Sweden has a population of 10.5 million inhabitants, and both centers perform 160–200 liver transplants per year together.[9]

Here, we aim to describe the introduction and evaluation of a national cDCD LTX pilot protocol with a mandatory NRP program in Sweden. cDCD LTX outcome is compared to a matched DBD cohort during the same time period in terms of NAS, patient survival, graft loss, early allograft dysfunction (EAD), acute kidney injury, and overall complications.

METHODS

The introduction period of liver donation from cDCD donors using NRP ranged from 2020 to 2022. Donor and recipient selection criteria during the pilot protocol are shown in Table 1.

Organ utilization

In Sweden, there are 3 organ procurement organizations divided by geographical localization, each covering a population of 2–4.5 million. All hospitals within

TABLE 1 Swedish national pilot protocol: Donor and recipient criteria for donation and transplantation with a liver graft from cDCD donor using NRP

Donor	Recipient
Age ≤65 y	Age >18 y
BMI ≤28	MELD score ≤20
Agonal period ≤60 min	No preoperative ventilator support
fWIT time ≤30 min	No preoperative hemodialysis
Cold ischemia time ≤8 h	No portal thrombosis
No macroscopic steatosis	No previous large abdominal surgery
	Not in need of split or reduced graft

Note: Agonal period is defined as the time from withdrawal of life-sustaining treatment until asystole. Functional warm ischemic time (fWIT) is defined as the time from systolic blood pressure <50 mm Hg until the start of NRP. Cold ischemic time is defined as the time from cold perfusion in the donor until portal reperfusion in the recipient.

Abbreviations: BMI, body mass index; cDCD, controlled donation after circulatory death; MELD, Model for End-Stage Liver Disease; NRP, normothermic regional perfusion.

each region have received training and information on how and when to contact the respective organ procurement organizations. Instructions for cDCD donation specify that all patients where an independent decision to withdraw life-sustaining treatment has been made should be referred to the respective organ procurement organization without any prior assumptions based on medical measurements or history. All registered entries of possible cDCD donors registered in Sweden during 2020–2022 were retrospectively retrieved and analyzed from the digital web application used by all organ procurement organizations in Scandinavia (YASWA). Reasons for exclusion as potential, eligible, actual, and utilized donors for any type of solid organ were identified and listed. The same exclusion was also done for cDCD liver donation specifically. Definitions for donor categories followed published definitions by Dominguez-Gil et al.[10] The liver donor conversion rate was defined as the number of utilized liver donors divided by the number of potential cDCD liver donors. The liver utilization rate was defined as the ratio of successfully transplanted livers from cDCD liver donors to the number of actual cDCD liver donors.[7]

NRP procedure

During the pilot period, all current and newly listed patients on the LTX waiting list fulfilling the selection criteria were offered to receive a cDCD liver graft. Both written and oral information regarding NRP and cDCD donation was provided. Donor relatives received information on the cDCD procedure. However, no additional consent for the NRP procedures was obtained from the donor relative.

Cardiohelp (Getinge, Sweden), with a closed tubing circuit without a reservoir (Getinge, Sweden) (Supplemental Digital Information S1, http://links.lww.com/LVT/A619), was used. The system was primed with Plasmalyte, antibiotics, and heparin (Supplemental Digital Information S2, http://links.lww.com/LVT/A619). Depending on availability, the NRP circuit was managed by either a licensed extracorporeal membrane oxygenation (ECMO) nurse or a surgeon from the Department of Transplantation Surgery. All personnel had received prior hands-on training on running an NRP circuit.

NRP procurement was undertaken without premortem interventions, for example, vascular catheter insertion or heparinization. Withdrawal of life-sustaining care was done in the ICU. Functional warm ischemic time (WIT) was defined as the time from systolic blood pressure <50 mm Hg in the donor until the start of NRP perfusion in the donor. Agonal time was defined as the time from withdrawal of life-sustaining treatment until confirmed ceased circulation in the donor. After asystole, a 5-minute no-touch period was observed before the declaration of death. After the declaration of death, the donor was transported to the operating room. Following laparotomy and sternotomy, cannulas were placed in the infrarenal aorta and inferior vena cava. The descending aorta was cross-clamped in the thoracic compartment, and lack of cerebral blood flow was ascertained by arterial cannula in the aortic arch vented to atmospheric pressure.

During NRP, we strived to maintain a flow of 2–3 L/min, a venous saturation of 70%–80% with a venous paO_2 of >5 kPa, and pH between 7.35 and 7.45. The temperature was kept between 35.5 and 37.5. Calcium levels were corrected, and volume was replenished as needed with albumin and packed red blood cells depending on venous blood gases and hemodynamic data, maintaining a hematocrit of $>20\%$. An additional 150 U/kg body weight (BW) of heparin was given at 90 minutes. The liver was deemed transplantable if at least 60 minutes of perfusion had been completed with a reduction of lactate, alanine aminotransferase (ALT) <3 μkat/L, stable glucose levels, and a positive trend of pH and bicarbonate. Cold perfusion commenced immediately after NRP was terminated. NRP failure could be classified into 3 different categories: failure to cannulate, failure to establish or maintain NRP for 30 minutes, or lastly, failure to continue perfusion during the planned time.

NRP biochemistry

Data on all cDCD donors with NRP during 2020–2022 were collected. Venous blood gas analysis was drawn at 0, 15, 30, 45, 60, 90, and 120 minutes (lactate, glucose, pH, base excess, HCO_3, pO_2, pCO_2, Ca2+, and hemoglobin). Blood chemistry was drawn at 0, 30, 60, 90, and 120 minutes (creatinine, ALT, aspartate aminotransferase [AST], c-peptide, and pancreas-amylase). Blood cultures were taken at the start and end of NRP perfusion. Blood chemistry was compared between cases of successful NRP and nonsuccessful NRP where the liver was not used for LTX.

We also assessed any impact of packed red blood cell transfusion on lactate levels during NRP. For every NRP cDCD donor, each time interval between 2 time point measurements was assessed for delta lactate, and the number of units of packed red blood cells was provided. This was displayed as the mean change in lactate per number of units transfused.

Comparison of cDCD with DBD

The outcome of all LTX using cDCD livers was compared to a matched cohort of DBD liver transplants during 2018–2022. The DBD control group was matched using only the recipient criteria (Supplemental

Digital Information S4, http://links.lww.com/LVT/A619; n = 104) as well as both donor and recipient criteria for cDCD (Table 1; n = 28). Information on DBD outcomes was retrospectively extracted from the Nordic Liver Transplant Registry and digital medical records. Data collected included donor demographic information (sex, age, length, weight, blood group, and cause of death); donor laboratory values (ALT, AST, and creatinine); recipient information (sex, age, height, weight, blood group, and indication for transplantation); recipient preoperative and postoperative biochemistry (ALT, AST, bilirubin, creatinine, hemoglobin, and international normalized ratio [INR]) at day 0, 1, 7, 30, 90, 180, and 365 days; patient and graft survival status; any radiology depicting the liver or biliary tree including endoscopic retrograde cholangiopancreatography (ERCP); postoperative hospital stay; all complications recorded during the first 3 months; ischemia times; rejections; biopsies; and readmissions. For cDCD recipients, UK DCD risk score was calculated.[11]

We thereafter compared the cDCD group to the DBD group in terms of the following outcomes.

Outcomes

Symptomatic biliary complications within the first year were assessed. Complications were classified as either anastomotic biliary stricture diagnosed through magnetic resonance cholangiopancreatography (MRCP) or ERCP with a symptomatic stricture or narrowing present at the level of biliary anastomosis or as a NAS, diagnosed through MRCP or ERCP with a symptomatic stricture or narrowing at any level in the biliary tree except at the biliary anastomosis. Symptomatic was defined as jaundice and/or cholangitis or elevated cholestatic biochemistry in the presence of a patent hepatic artery. In addition, to assess the presence of any nonsymptomatic biliary strictures, a follow-up MRCP was offered to all patients transplanted with a cDCD liver at 6 months following LTX with additional informed consent.

One-year graft and patient survival was compared between the groups. Early allograft dysfunction was defined according to Olthoff criteria.[12] Postoperative acute kidney injury was defined according to the International Club of Ascites: increase in serum creatinine $\geq$0.3 mg/dL within 48 hours or an increase in serum creatinine $\geq$1.5 baseline within 7 days.[13] Delta estimated glomerular filtration rate at 365 days postoperative was calculated using the revised Lund Malmö formula.[14] Post-reperfusion syndrome was defined as either of the following criteria occurring within 5 minutes after portal perfusion: heart rate $<$30 and/or systolic arterial pressure $<$75 mm Hg and/or mean arterial pressure $<$65 mm Hg sustained for at least 1 minute and/or significant cardiac arrhythmia. Overall complications at 90 days were evaluated using the comprehensive complication index (CCI) score. All complications within the first 3 months after transplantation were classified according to Clavien Dindo criteria, and each patient received a composite CCI score.[15]

We also compared liver steatosis and ischemia grade from donated livers. At the end of LTX surgery, a routine post-reperfusion biopsy was taken from the lateral segment and was independently evaluated by 2 pathologists providing a measure of steatosis and ischemia. Macrovesicular steatosis was measured through direct histological visualization of the number of cells with intracellular fat vacuoles. Ischemic damage was expressed as a composite grading from 0 (none) to 5 (severe), including the neutrophilic infiltrate, apoptosis, and hepatocyte dropout similar to previously published protocols.[16]

Statistics

Descriptive statistics were used, and data were represented with mean $\pm$ SD if normally distributed and compared using *t* test. If not normally distributed, median with IQR was used and comparisons were made using the Mann-Whitney *U* test. Categorical variables were described using frequencies and percentages and analyzed using the chi-square test. The dynamics of NRP biochemistry were compared between transplanted and discarded livers using mean value at time point 0–120 minutes using paired *t* test. End-of-perfusion values were compared at 120 minutes between transplanted and discarded livers using *t* test. Patient and graft survival were assessed with Kaplan-Meier curves and compared using log-rank test. R studio version 2021.09.02 was used for all statistics.

Ethics

All research was conducted in accordance with both the Declarations of Helsinki and Istanbul. This study was authorized by the Swedish Ethical Committee 2022-03240-01.

RESULTS

During the pilot period between 2020 and 2022, there were 140 registered entries for possible cDCD donors in Sweden, of which 132 were deemed to be potential cDCD donors (exclusion included expected prolonged WIT [n = 6], missing information [n = 2]). Of 132 potential cDCD donors, 90 met the criteria to be eligible cDCD donors for any solid organ donation; the reasons for exclusion were classified as stand down (n = 8),

medically not suitable (n = 20), and lack of permission (n = 14). Of the 90 eligible cDCD donors, 75 were eligible for cDCD liver donation specifically; exclusion included stand down (n = 4), medically unsuitable (n = 10), and no permission (n = 1). In total, 5 were excluded as actual cDCD liver donors due to logistical problems (n = 1) and lack of suitable recipients (n = 4). Of the 70 actual cDCD liver donors, 18 became utilized cDCD liver donors in which NRP procurement of the liver was performed. The exclusion was due to missed opportunities where NRP was never planned or initiated (n = 45) owing to the criteria for the pilot project (high age [n = 19], occurring in hospitals not initially included in the pilot project [n = 14], lack of perfusionist [n = 7], and high body mass index [n = 5]). In addition, 7 cases where NRP was initiated were also excluded due to unfavorable biochemistry (n = 3), liver cirrhosis (n = 2), and NRP failure (n = 2). Both instances of NRP failure occurred after 30 minutes of perfusion in which no adequate perfusion flow could be obtained; in one of the cases, a thrombus was observed on the cannula. Unfavorable biochemistry included one case with increasing lactate and two cases with ALT above 3× reference value (increasing trend) with lactate slowly reducing during NRP, however, pH never stabilized. In total, 18 livers were procured from cDCD donors and successfully transplanted and included in the study, yielding a donor conversion rate of 13.6% and a liver utilization rate of 25.7%. In addition to the livers from the 25 actual cDCD donors where NRP was initiated, 53 kidneys and 1 pancreas were procured along with 3 pairs of lungs through simultaneous thoracic rapid cold perfusion (Figure 1).

DCD process

In the 25 cases in which NRP was initiated, the mean agonal time was 17 ± 11 minutes and the functional warm ischemic time was 28 ± 6.1 minutes. The average time for transport and draping was 4.9 ± 1.3 minutes, the time from knife to skin to NRP initiation was 13 ± 6.2 minutes and NRP perfusion time was on average 121.3 ± 27.7 minutes (Figure 2).

Biochemistry and blood gas analysis during NRP

The mean overall lactate reduction from 0 to 120 minutes was 6.9 ± 3.6 mmol/L. Donors in which the liver was utilized had a significantly higher lactate clearance compared to nonutilized donors (−7.9 mmol/L vs. −3.6 mmol/L, $p = < 0.001$). Utilized liver donors showed significantly lower end perfusion (120 minutes) concentrations of lactate (4.3 ± 2.0 vs. 6.6 ± 2.1 mmol/L [$p = 0.04$]), ALT (1.3 ± 1 vs. 3.2 ± 1.6 μkat/L [$p = 0.03$]), and AST (2 ± 1.4 vs. 3.4 ± 1 μkat/L [$p = 0.02$]). No differences in end-of-perfusion values for creatinine, pH, saturation, or hemoglobin were seen (Figure 3).

Median erythrocyte concentrate and albumin transfusions were significantly higher during NRP in the donors in whom the liver was discarded. Median volumes of erythrocytes transfused were 4 IQR = 4 versus 7 IQR = 2 units (250 ml per unit), and for albumin 3.5 IQR = 5.4 versus 6 IQR = 7 units (200 ml per unit) (Figure 4).

Delta lactate after transfusion ranged from −1.3 mmol/L (0 units transfused) to −0.8 mmol/L (5 units transfused). No number of units transfused resulted in a positive delta lactate (Supplemental Digital Information S3, http://links.lww.com/LVT/A619).

None of the blood cultures taken at the start and end of NRP perfusion showed bacterial or fungal growth.

Patients

In total, 18 patients underwent LTX with a cDCD liver during the study period. Two livers were used outside of the pilot protocol criteria for 2 patients in need of an urgent retransplantation. Both patients are included in the analysis and results. In the historical control group, 28 patients met the recipient and donor criteria (Table 1) and were included in the study.

There were no significant differences between cDCD and DBD recipients with regard to the recipient or donor age, sex, or body mass index. Indication for LTX did not significantly vary between cDCD and DBD recipients, with the major indication in both groups being chronic liver disease 61.1% versus 50.0% (Table 2). cDCD donors spent a significantly longer time in the ICU (4.0 [IQR = 3.0] vs. 2.0 [IQR = 2.3] d, $p = 0.005$) cold ischemic time, which was significantly lower in the cDCD group (336 [±70.8] vs. 389 [±43.7] min, $p = 0.01$). Model for End-Stage Liver Disease score was lower in the DBD group (12.5 [IQR = 3.8] vs. 11.5 [IQR = 5.3] units, $p = 0.03$) (Table 2).

Biliary complications

There was no statistical difference in the overall biliary strictures within 1 year (5.6% [n = 1] in the cDCD group and 17.8% [n = 5] in the DBD group). Among the DCD recipients, 1 patient presented with cholestatic symptoms, increased transaminases, and bilirubin. MRCP showed an anastomotic stricture, which was also confirmed and treated with ERCP. In the DBD group, 10.7% (n = 3) patients had an anastomotic stricture, and 7.1% (n = 2) were diagnosed and treated for NAS (Table 3).

To investigate any potential asymptomatic strictures, MRCP was performed according to protocol. Of the 18

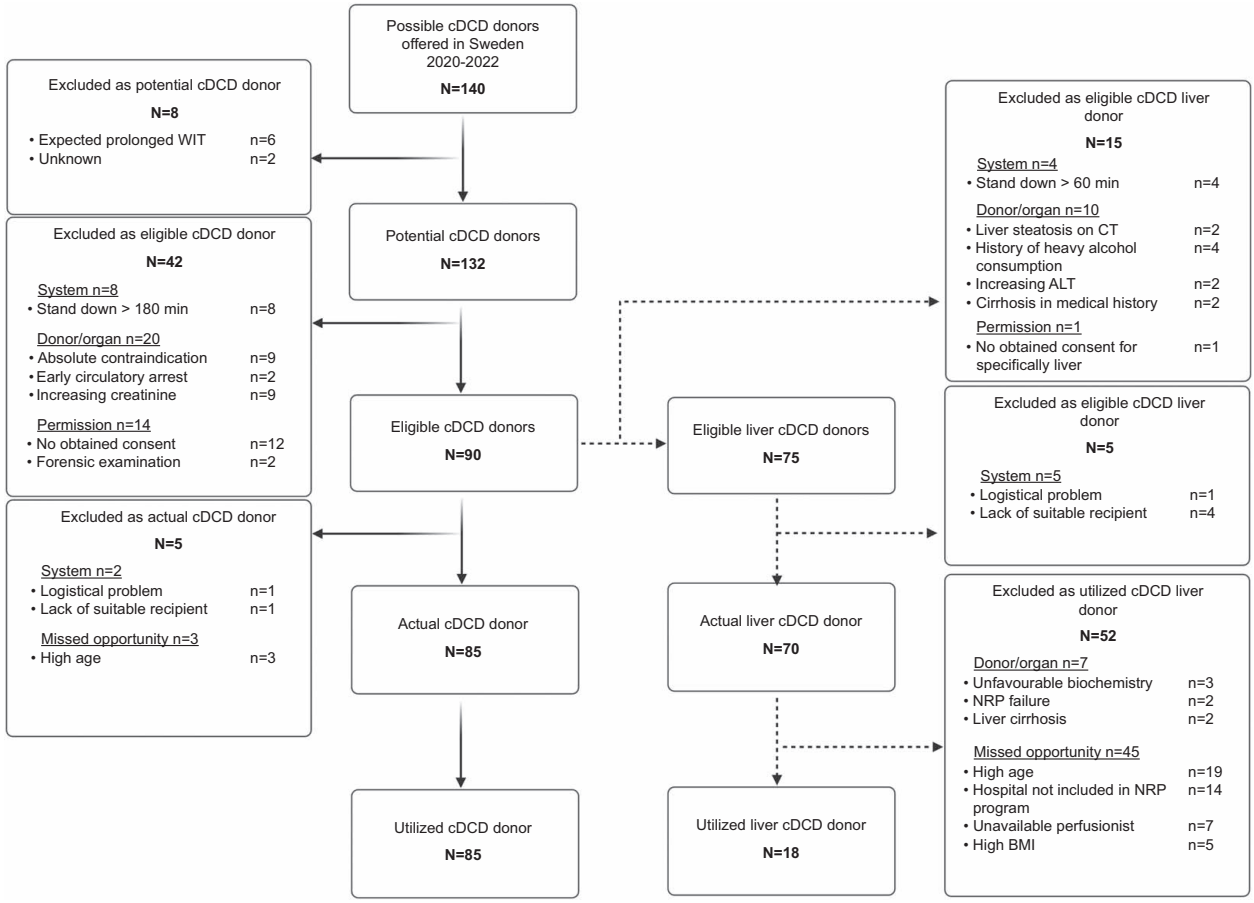

FIGURE 1 Inclusion of cDCD liver donors in Sweden during 2020–2022. Abbreviation: cDCD, controlled donation after circulatory death.

cDCD patients, 3 underwent MRCP on clinical indication while 3 patients declined the test. In total, 15 patients underwent MRCP, of which 1 showed an anastomotic stricture, while the other 14 had no radiological signs of NAS or anastomotic strictures.

Patient and graft survival

There was no significant difference in 1-year patient and graft survival. In the DCD group, patient and graft survival was 94%. One patient died due to metastatic angiosarcoma 7 months after LTX. In the DBD group, the 1-year patient survival was 100%, and the graft survival rate was 96.4% due to primary nonfunction in 1 patient who was successfully retransplanted (Figure 5).

Clinical outcomes

No DCD nor DBD recipient was diagnosed with hepatic artery thrombosis during the study period. There was no significant difference between cDCD and DBD liver recipients in the clinical outcomes measured with comparable CCI scores, incidence of post-reperfusion syndrome, and EAD as shown in Table 3. The kidney function immediately after LTX and at 12 months was comparable between the cDCD and DBD groups, with an incidence of acute kidney injury of 33.3% (n = 6) in cDCD and 32.1% (n = 9) in the DBD group. No differences were observed in the number of patients with a biopsy-proven acute rejection within the first year, 11% (n = 2) vs. 28.6% (n = 8). Comparative analysis of post-reperfusion biopsies showed no significant differences in the level of ischemia-reperfusion injury (2.1 [± 1.2] vs. 2.1 [± 1.3]) or macrovesicular steatosis (5 [IQR: 8.5] vs. 2.5 [IQR: 10]%).

DISCUSSION

This study evaluates the introduction of cDCD LTX in Sweden using a mandatory NRP protocol as well as defined donor and recipient selection criteria. During the evaluation period, 18 patients have been transplanted with a cDCD liver. Posttransplant outcomes in terms of biliary complication and patient and graft survival were not significantly different when compared to a matched group of patients undergoing LTX receiving a liver from a DBD donor.

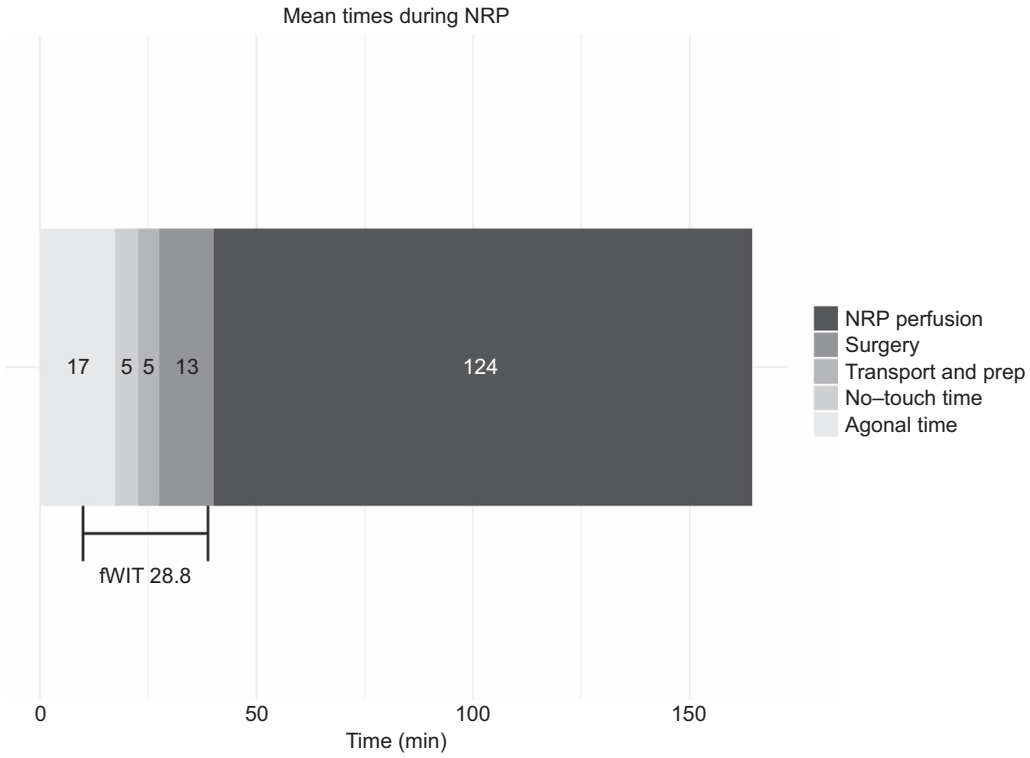

FIGURE 2 Mean times of all 25 cDCD donors included in the study. fWIT is defined as the time from systolic blood pressure <50 mm Hg in the donor until the start of NRP perfusion. Agonal time is defined as the time from withdrawal of life-sustaining treatment in the donor until confirmed ceased circulation. Transport and preparation include transport of donor to operation room as well as sterilizing and draping of the donor. Surgery time is defined as the time from donor incision until the start of NRP perfusion. Abbreviations: cDCD, controlled donation after circulatory death; fWIT, functional warm ischemic time; NRP, normothermic regional perfusion.

NRP was initiated in 25 cDCD donors of which 7 livers were declined, and 18 livers were utilized, with a utilization rate of 25.7%. Discarded livers showed a significantly lower lactate clearance, which is not surprising as lactate clearance was one of the selection criteria based on previous literature.[17] In addition, there was a significant difference in the volume of fluids required during NRP perfusion when comparing procured and discarded livers. Previous literature has suggested that an increased lactate level can be observed after transfusions of old packed red blood cells.[18] In our study although we could see a significant difference in transfusion levels between procured and discarded livers, no trend in increased lactate following large transfusions could be seen. It is, therefore, unlikely that the high number of transfusion resulted in falsely increased levels of lactate, resulting in the erroneous discarding of the liver. Initially, during the study period, the procuring surgeon would clamp the inferior vena cava above the diaphragm. We noticed that leaving the cava open allowed for increased volume return from the thoracic cavity, thereby requiring fewer transfusions but this reduced the lactate clearance making the interpretation of bold results potentially more challenging. In addition to the 18 livers, 53 kidneys, 1 pancreas, and 3 pairs of lungs were utilized, suggesting that NRP is both safe and does not interfere with other organs procurement.

Outcomes after LTX with a cDCD liver were compared to a historical cohort of 28 DBD liver recipients. The groups were matched on the donor and recipient criteria for the cDCD LTX protocol. After matching, a significant difference in donor ALT, creatinine, Model for End-Stage Liver Disease score, and cold ischemia time remained. The majority of NRP procedures were undertaken in the same hospital as the transplantation procedures, resulting in shorter transportation and, thereby, shorter cold ischemia times. No difference between the groups was observed in terms of biliary complications, patient and graft survival, CCI, or acute kidney injury. No difference in levels of ischemia-reperfusion injury was observed on post-reperfusion biopsies. Our results indicate that NRP improves the quality of the livers from cDCD donors, resulting in excellent results comparable to those with livers procured from DBD donors, confirming what has been described previously.[7]

The incidence of NAS was 0% in the cDCD group compared to 7.1% in the DBD group. The unusually high NAS incidence (2/28) is most likely caused by the low sample size of the DBD control group, fulfilling both donor and recipient selection criteria. When comparing to the larger DBD control group (Supplemental Digital

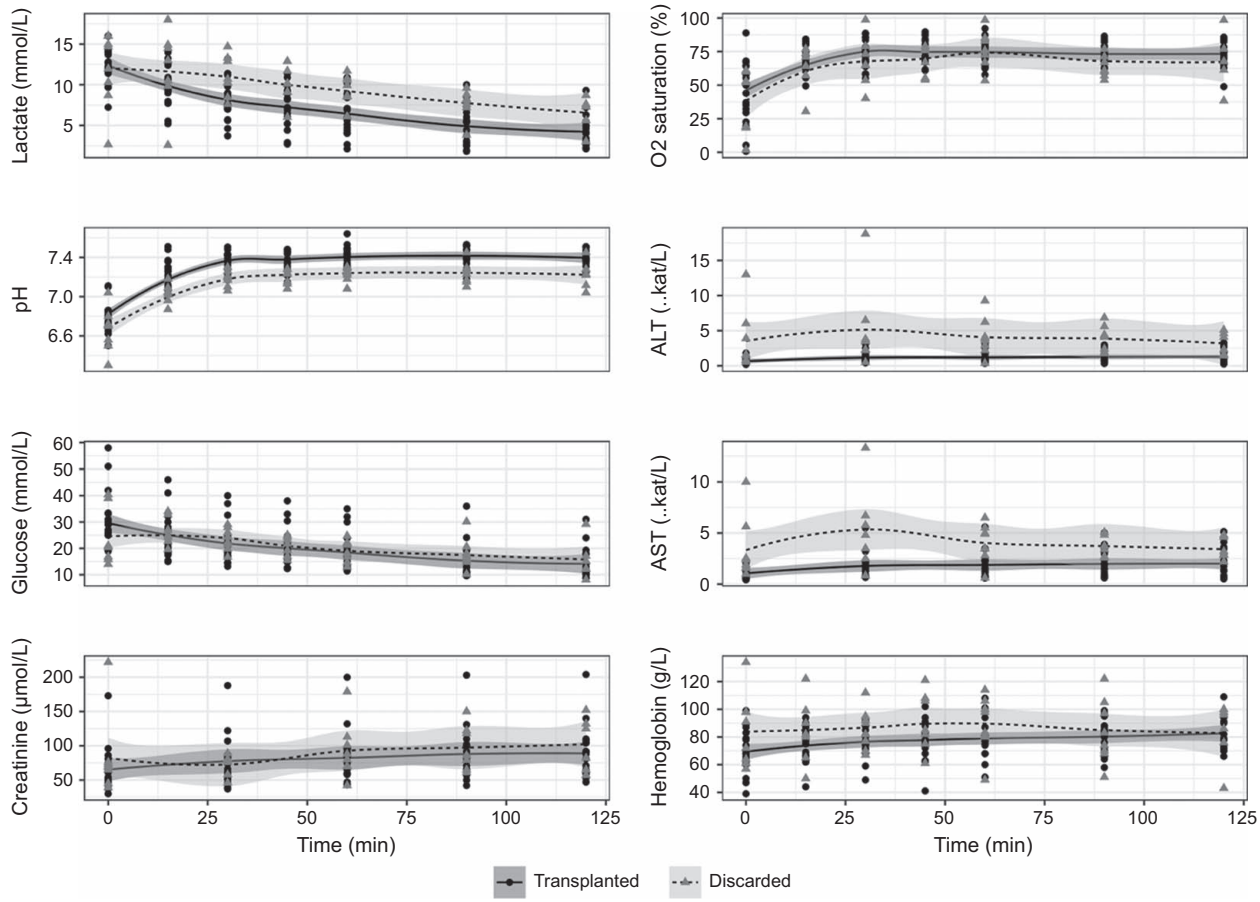

FIGURE 3 Evolution of blood biochemistry and blood gas analyses during normothermic regional perfusion (dark gray dots indicate utilized livers, and light gray triangles indicate discarded livers). The line at the mean and error envelope shows 95% CI.

Information S4, http://links.lww.com/LVT/A619) (n = 104) only fulfilling recipient selection criteria, a NAS incidence of 2.9% was observed. Furthermore, the very low NAS frequency in NRP cDCD LTX is well in line with a multicenter outcome analysis to define global benchmarks for DCD LTX. Although all cDCD LTX are outside of the benchmark cohort criteria due to asystolic warm ischemia time above 15 minutes, NRP leads to similarly low rates of NAS as in the benchmark population.[19]

Prior studies suggest that livers transplanted from cDCD donors without in situ or ex situ machine perfusion have an increased risk of NAS of 7%–16% compared to an incidence of NAS of 2% in LTX using DBD donors.[20,21] In contrast to previous publications, our study included a protocol MRCP to objectively determine the presence of NASs. Among the 18 recipients of cDCD LTX, no instances of NAS were observed, which was confirmed with MRCP imaging. Consequently, the results suggest that using NRP in cDCD donors seems to counteract the ischemic damage to the biliary tree and/or help identify donors with biochemistry during NRP indicative of a non-damaged biliary tree.

Other strategies for reducing the occurrence of NAS in LTX from cDCD donors include the use of *ex situ* perfusion, at both hypothermic and normothermic temperatures. van Rijn et al showed in a randomized trial that using ex situ dual hypothermic oxygenated perfusion reduced the incidence of clinically significant NAS from 18% in the control group to 6% in the machine-perfused DCD livers.[5] Moreover, ex situ hypothermic machine perfusion reduced the incidence of EAD from 40% in the control group to 24% in the treatment group. The advantage of hypothermic ex situ perfusion is that it requires fewer resources, is simpler to use and manage, and has static cold storage as a fallback option. However, the drawback is that there is no method to reliably assess liver viability during hypothermic perfusion. Moreover, NRP allows the perfusion of multiple organs simultaneously, thus potentially reducing the need for individual ex situ organ perfusion devices. Although currently there is limited evidence to quantify the benefit of NRP for kidneys and pancreas transplantation, studies have reported better 1-year function, decreased graft loss, and decreased delayed graft function for kidneys transplanted after abdominal NRP.[7,22,23]

An Italian study proposed a combined protocol in cDCD, where NRP was followed by ex situ hypothermic

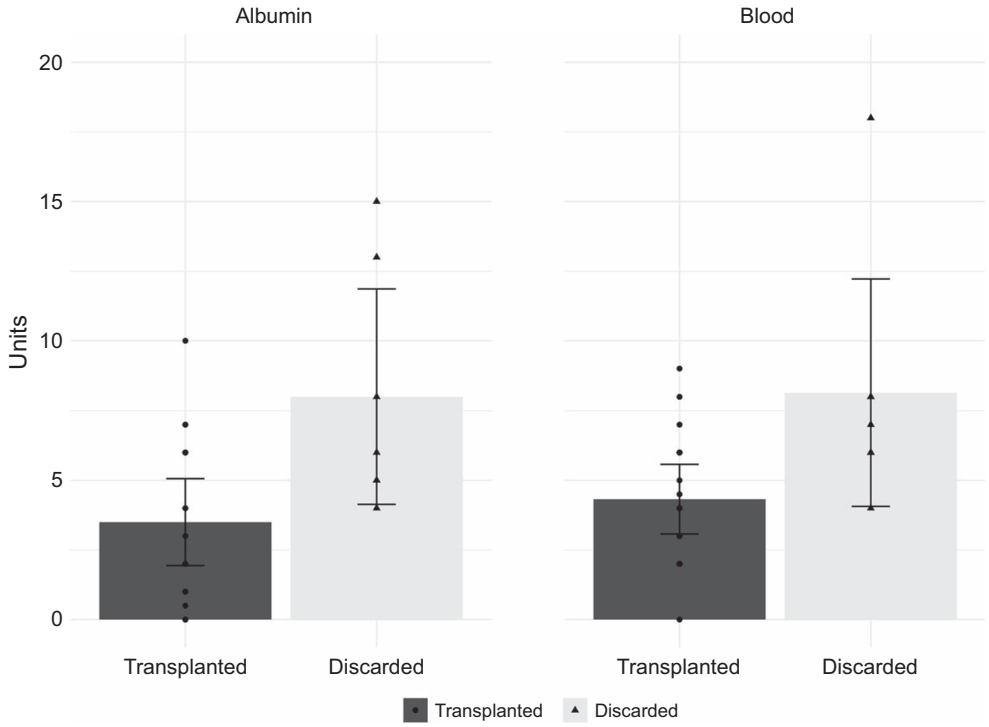

FIGURE 4 Transfusion volume during NRP. Bars showing mean and whiskers indicating 95% CI. Abbreviation: NRP, normothermic regional perfusion.

oxygenated machine perfusion, and compared this group to a propensity-matched DBD cohort.[24] The cDCD outcomes were similar to our experience, with comparable rates of NAS and 1-year graft survival of 90% in the DCD group and 95% in the DBD group. Much like the Italian setting, Swedish legislation prohibits premortem cannulation, which increases WIT; however, the Italian legislation also requires 20 minutes of no-touch period, further extending WIT. Despite prolonged WIT, EAD was lower in the Italian study by 5% compared to 22% in our series. Perhaps combining the technologies could be an approach to further expanding donor criteria, although further prospective studies are needed to define the potential benefits of a combined protocol.

A French study compared the use of normothermic ex situ liver perfusion (normothermic machine perfusion) to NRP in cDCD LTX.[25] The study showed improved patient and graft survival in both groups when compared to historical data on static cold storage and low levels of NAS (3% and 9%, respectively), similar to rates found in our study. Moreover, the authors argue that normothermic machine perfusion has the potential benefit of improving organ utilization rate compared to static cold storage.

Similarly, Oniscu et al[23] have shown that the use of abdominal NRP increases organ utilization rate compared to static cold storage. In Sweden, the use of NRP is mandatory when procuring livers from cDCD donors; hence, we cannot compare organ utilization rates or outcomes to standard cold storage cDCD. In our study, the organ utilization rate was 25.7%, although it is important to recognize that during the pilot period, cDCD donors were selected, with 45 cases classified as a missed opportunity. The major reasons for missed opportunities were high age, logistical issues with a lack of perfusionist, and hospitals not included in the program, as well as patients with high body mass index. It is likely that if these donors had progressed to actual donors where NRP was planned, the utilization rate would be higher (Table 1). Schurink et al[26] demonstrated that the use of NRP can rescue cDCD livers previously declined due to old age or deemed to have poor organ function. Moreover, in this study, agonal time cutoff was <120 minutes and a functional warm ischemic time of <60 minutes, compared to 60 and 30 minutes, respectively, in our study. As NRP allows for evaluation of the liver during perfusion, where potential damage can be assessed, it seems reasonable to argue for an expansion of donor criteria to further increase the number of utilized cDCD liver donors. As a result of this evaluation, cDCD LTX is considered routine health care and has been implemented into national guidelines and selection criteria for both donor and recipient have been widened.

Overall, introducing cDCD donation of liver with NRP has increased the availability of livers for transplantation in Sweden. In 2021, cDCD livers increased the donation rate in Sweden from 15.5 to 16.2 liver donors per million population (PMP), in 2022, from 14.8 to 15.8 liver donors

TABLE 2 Donor and recipient characteristics for DBD and DCD liver recipients

	DBD (N = 28)	DCD (N = 18)	*p*
Donor sex, n (%)			
Female	9 (32.1)	8 (44.4)	0.60
Male	19 (67.9)	10 (55.6)	
Donor age (y)			
Median [IQR]	48.5 [21.3]	53.5 [12.5]	0.20
Donor body mass index			
Mean (SD)	24.4 (2.2)	24.9 (4.2)	0.62
Donor time in ICU			
Median [IQR]	2.0 [2.3]	4.0 [3.0]	0.005
Donor creatinine, μmol/L			
Median [IQR]	81.5 [116]	61.0 [43.0]	0.02
Donor ALT, μkat/L			
Median [IQR]	1.3 [1.7]	0.7 [0.5]	0.02
Recipient sex, n (%)			
Female	10 (35.7)	6 (33.3)	1
Male	18 (64.3)	12 (66.7)	
Diagnose category, n (%)			
Chronic	14 (50.0)	11 (61.1)	0.19
Malignancy	54 (42.9)	4 (22.2)	
Other	7 (7.1)	1 (5.6)	
Retransplantation	0 (0)	2 (11.1)	
Recipient age (y)			
Median [IQR]	55.1 [19.8]	57.0 [17.5]	0.58
Recipient body mass index			
Mean (SD)	27.5 (4.7)	26.9 (4.5)	0.71
MELD (units)			
Median [IQR]	11.5 [5.3]	12.5 [3.8]	0.03
Cold ischemia time (min)			
Mean (SD)	389 (43.7)	336 (70.8)	0.01
UK DCD risk score			
Median [IQR]	—	7 [4.75]	NA

Abbreviations: ALT, alanine aminotransferase; DBD, donation after brain death; DCD, donation after circulatory death; ICU, intensive care unit; MELD, Model for End-Stage Liver Disease score; NA, not available.

TABLE 3 Outcome after transplantation for patients receiving a liver from a donor after circulatory death (DCD) or after brain death (DBD)

	DBD (N = 28)	DCD (N = 18)	*p*
Biliary complications, n (%)			
None	23 (82.1)	17 (94.4)	0.40
Anastomotic stricture	3 (10.7)	1 (5.6)	
Nonanastomotic stricture	2 (7.1)	0 (0)	
Rejection, n (%)			
No	20 (71.4)	16 (88.9)	0.30
Yes	8 (28.6)	2 (11.1)	
Post perfusion syndrome, n (%)			
No	24 (85.7)	15 (83.3)	1
Yes	4 (14.3)	3 (16.7)	
Early allograft dysfunction, n (%)			
No	20 (71.4)	14 (77.8)	0.89
Yes	8 (28.6)	4 (22.2)	
Acute kidney injury, n (%)			
No	19 (67.9)	12 (66.7)	1
Yes	9 (32.1)	6 (33.3)	
Delta eGFR at 12 months			
Mean (SD)	14.0 (13.0)	17.4 (18.4)	0.54
Hospital stay (d)			
Mean (SD)	12.8 (8.4)	10.8 (5.4)	0.33
Post-op intensive care stay (d)			
Mean (SD)	2.1 (4.9)	1.2 (1.6)	0.35
Readmissions			
Mean (SD)	1.0 (1.5)	0.8 (1.3)	0.66
Comprehensive complication index			
Mean (SD)	34.0 (16.5)	34.1 (14.1)	0.97
0-biopsy steatosis (%)			
Median [IQR]	2.5 [10.0]	5.0 [8.5]	0.66
0-biopsy ischemia score			
Mean (SD)	2.1(1.3)	2.1 (1.2)	0.93

Abbreviations: DBD, donation after brain death; DCD, donation after circulatory death; eGFR, estimated glomerular filtration rate.

PMP, and in 2023 (after expanding cDCD LTX criteria) from 15.9 To 18.8 PMP.[27–29] In addition to increasing available livers for transplantation, having a functional abdominal NRP program lays the foundation for future expansion into thoracoabdominal NRP, allowing for the procurement of hearts from cDCD donors.[30] Furthermore, the results of this pilot represent an important boost for the program, given that the number of cDCD donors in Sweden is rapidly increasing.

While NRP increases organs for transplantation, it is important to recognize the increased resources needed for a successful NRP program compared to standard DBD or cDCD retrieval. In addition to costs for disposables, an additional perfusionist, additional staff for laboratory analysis, and training for the procurement team are needed. Our experience was that manpower could be scaled down as the team gained more experience during the study period. Moreover, disposables could be spared from disuse due to standing down by priming the machine after asystole occurs in the donor.

Implementation of an NRP program in the Swedish context shares many similarities to what has been described elsewhere.[31] Adaptability and portability have previously been highlighted as crucial aspects of implementing an NRP program.[32] Similarly, we opted for a transportable setup, allowing for NRP procurement within the whole country. In our protocol, we choose to utilize a heat exchanger to maintain normothermia. However, other centers have chosen to omit this to increase portability while still maintaining a temperature

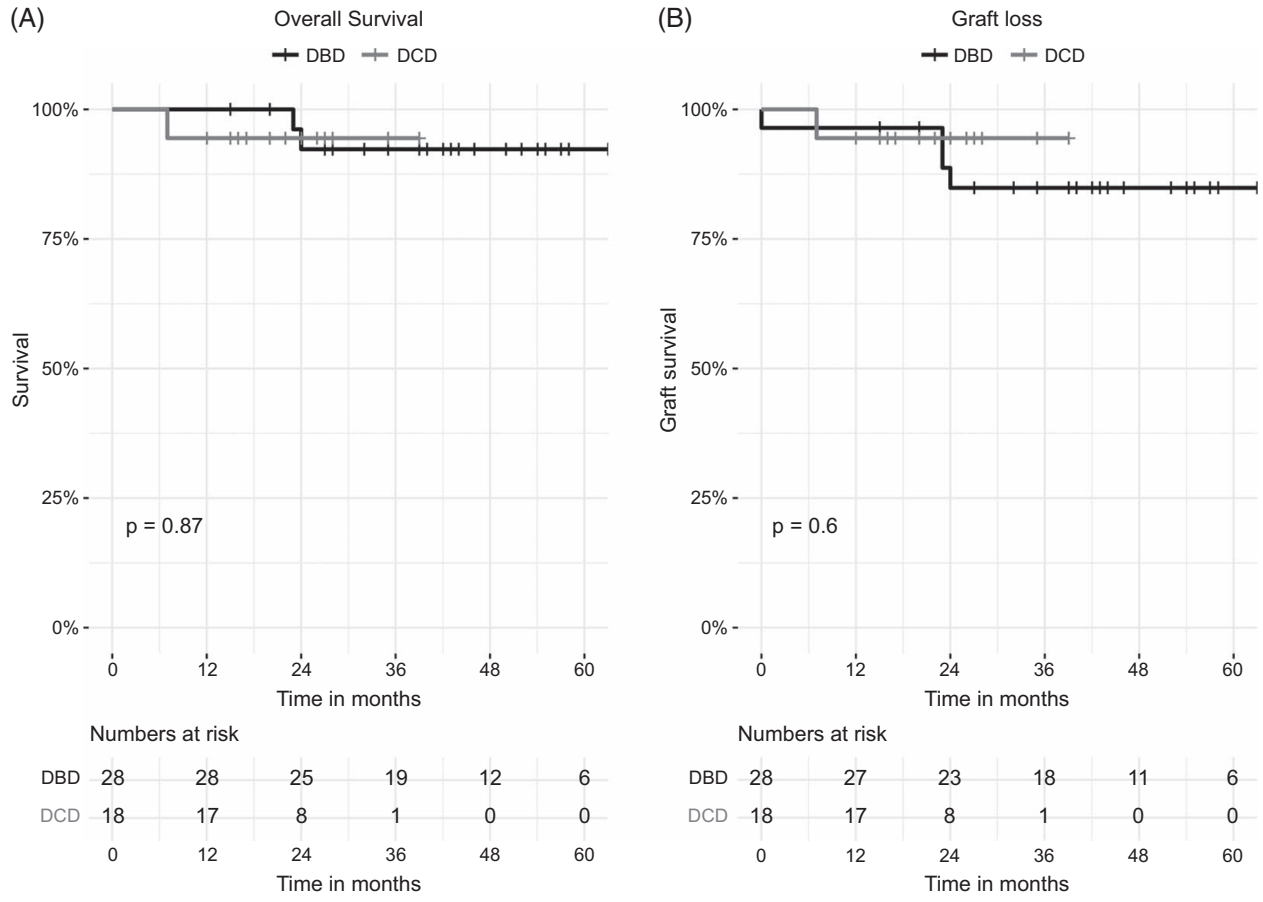

FIGURE 5 (A) Overall patient survival. (B) Graft survival. Light gray line indicates DCD patients, and dark gray line indicates DBD patients. Abbreviations: DBD, donation after brain death; DCD, donation after circulatory death.

of 34°C–35°C. Mild subnormothermia in the context of NRP should be further investigated as it may carry certain advantages.[32] As Croome et al[31] described in their experience, we aimed for a flow of 2–3 liters per minute, and following the establishment of perfusion, sufficient hemostasis, and cannulation of the bile duct, further dissection was kept to a minimum as mobilization tended to affect flow.

An important limitation of this study, besides those inherent to a retrospective study, was the differences observed in donor characteristics between the cDCD and DBD groups. Despite applying the same donor and recipient selection criteria utilized in the cDCD NRP pilot protocol, significant differences could be noted. The DBD control group showed shorter ICU stay, longer cold ischemia time, lower Model for End-Stage Liver Disease score, higher creatinine, and higher ALT. The differences observed may reflect a small sample size as well as a high degree of selection of the cDCD donors at the start of a new program. Despite this limitation, the DBD control group is important from a patient perspective as it reflects the alternative donors during the pilot period. However, patient outcomes after cDCD LTX were excellent with 0% NAS and 94% patient and graft survival. In addition, UK DCD risk score for the cDCD patients included in our study remained high, with a median of 7. Conversely, the study is strengthened by the inclusion of MRCP to evaluate NAS, as well as the comparison of CCI.

In conclusion, cDCD LTX has been successfully introduced in Sweden through a national pilot protocol. The pilot evaluation shows that NRP could be safely introduced with a high organ utilization rate and excellent posttransplant results.

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CONFLICTS OF INTEREST

Gabriel C. Oniscu received grants from Aferetica. The remaining authors have no conflicts to report.

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