# Long-term Outcomes After Controlled Oxygenated Rewarming of Human Livers Before Transplantation

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**Background.** Controlled oxygenated rewarming (COR) has been shown to be a feasible and safe method in clinical practice and to reduce peak serum transaminases after liver transplantation. This study aimed to demonstrate further clinical experience of this method of now 18 clinical liver transplantations utilizing COR and demonstrate the long-term results. **Methods.** In this extended series of 18 patients, cold-stored livers were subjected to machine-assisted slow COR for ≈120 minutes before transplantation. A cohort of 178 patients transplanted during the same period with similar clinical characteristics were used for comparison of key outcomes. **Results.** All livers were perfused in accordance to the COR protocol without incidences and transplanted successfully. Early allograft dysfunction was observed in 2 (11.1%) cases after COR. Liver elasticity measurements indicated normal healthy liver parenchyma at the last follow-up. Graft survival demonstrated excellent outcomes after COR. The 1-, 3-, and 5-year patient survival rates were 100%, 100%, and 93.8% compared with 84.5%, 82.0%, and 75.8% in the control group ($P = 0.12$). **Conclusions.** The present study demonstrates excellent clinical outcomes after COR before liver transplantation. Comparison with a control cohort shows superiority of graft survival. Further evidence is needed to assess this promising method to improve organ preservation, finally.

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Cold storage has been the method of choice for liver preservation for <50 years now. Hypothermia effectively protects the organ by reduced metabolism for distinct periods. However, the organ is exposed to hypoxic, hypoenergetic, and hyponutritional conditions. These are nonfunctional in the cold but unmasked upon reperfusion and trigger cellular signal pathways leading to hepatocellular injury and

compromised graft recovery.[1] Therefore, research in the last decades focused on methods of dynamic preservation, allowing for continuous supply of the allograft with oxygen and nutrients as well as removal of metabolic waste products. Machine perfusion of the liver can be performed under various conditions. The concept of controlled oxygenated rewarming (COR) is an end-ischemic allograft perfusion model, which utilizes the advantages of cold storage for transportation of the allograft and is meant to recondition the allograft in the accepting transplantation center before liver transplantation (LT). It is based on the observations that the abrupt temperature shift on warm reperfusion triggers mitochondrial dysfunction due to a progressive mitochondrial transition pore opening.[2-4] Preceding studies have shown that slowly increasing the temperature from the cold provides a transient phase of cold to mid-thermic perfusion, which allows for a gentle restitution of mitochondrial function at limited workload and demonstrates excellent restitution of hepatocellular function. This alleviated the trigger for mitochondrial dysfunction upon normothermic reperfusion. The first clinical application of COR before liver transplantation was performed in 6 extended criteria donor liver allografts and demonstrated convincing clinical results[5] during short-term follow-up of 6 months. Now, our experience of COR was extended to 18 clinical liver transplantations giving more precise insights into perfusion dynamics and biochemical parameters during rewarming of human livers from the cold to subnormothermic temperatures. Furthermore, long-term follow-up is now

available for assessment of development of potential late complications and general safety up to 5 years after transplantation. Aim of the present study is to display our extended experience of now 18 clinical liver transplantations utilizing COR and demonstrate the long-term results of the recipients.

## MATERIALS AND METHODS

### Patients

All data were collected prospectively. The first series of COR applications was performed between March 2014 and May 2014.[5] Between June 2014 and June 2016 COR was applied in 12 additional allografts allocated to our center by EUROTRANSPLANT.

Indications for COR were given in cases of marginal allograft quality. All allografts were allocated by the rescue allocation mechanism of EUROTRANSPLANT after multiple refusals by several centers, indicating severely limited allograft quality. Underlying reasons were heterogeneous. The decision to accept these allografts for transplantation was made independently of the applied machine perfusion and thereby acquired hemodynamic or biochemical perfusion parameters.

Recipients with worse clinical condition than depicted by their laboratory model for end-stage liver disease scores (LabMELD) and without exceptional MELD scores have few chances to receive a liver allograft in a reasonable time. Such candidates were informed about the transplantation of marginal allografts, allocated by the rescue allocation mechanism by EUROTRANSPLANT, routinely during listing for LT and written informed consent was obtained. For the application of COR, every recipient was informed at the time of listing for transplantation and once again, when admitted for transplantation, that an individual treatment of the allograft was performed before transplantation and written informed consent was obtained.

The control group was created from all other consecutive liver transplantations performed during the same era (2014–2016) with similar characteristics regarding donor acceptance policies, recipient population, immunosuppression, surgeons, etc at our center. To achieve similar characteristics in both cohorts, we excluded recipients younger than 18 years of age, retransplantations, combined transplantations, living-related liver donations, split transplantations, and recipients with portal vein thrombosis.

### Ethical Approval

The Ethics Committee of the University Hospital Essen approved the underlying study procedures (13-5409-BO).

### Machine Perfusion (COR)

All donor allografts underwent the standard procurement procedures of cold storage at distant hospitals were preserved in either the University of Wisconsin or histidine tryptophan ketoglutarate (Custodiol) solution and then sent to our clinic. Upon arrival, allografts were revisited by an experienced transplant surgeon for suitability of transplantation. COR was performed in a standardized fashion during induction of anesthesia and hepatectomy. Detailed description is given elsewhere.[6] The protocol of COR was designed with intention to avoid prolongation of overall cold ischemia time of the allograft. Back table preparation was performed as usual. Hepatic artery and portal vein were cannulated and

separately perfused. Pulsatile perfusion pressure was used for hepatic artery, while continuous perfusion pressure was used for the portal vein. Pressures were set at 25 mm Hg (60 bpm) and 2–4 mm Hg, respectively. For machine perfusion, 2 L of Custodiol-N (Dr Köhler Chemie, Bensheim, Germany) was utilized and the solution actively oxygenated with 100% oxygen. Perfusion was started at 10°C and gradually increased to 12°C, 16°C, and 20°C after 30, 45, and 60 minutes, respectively. At the end of the COR procedure, immediately before implantation into the recipient the temperature of the allograft was reduced to approximately 16°C by flush with 1 L of cold (4°C) Custodiol solution. This approach presumably reduces warm ischemic damage during implantation. The core temperature was not measured in this series of COR applications. Preclinical data (not shown) demonstrated reduction of the core temperature of liver grafts to approximately 14°C to 16°C. Perfusion flows of hepatic artery and portal vein were measured during perfusion and perfusate samples collected. Laboratory investigations included amongst others oxygen pressure, pH, and lactate, as well as analysis of aminotransferases.

### Surgery and Immunosuppression

Procurements were performed in standard fashion as defined by EUROTRANSPLANT.[7] Transplantation was performed with caval replacement and end-to-end-anastomoses of the hepatic artery, portal vein, and bile duct in all cases. Bypass techniques are not used at our center. The regimen of immunosuppression was standardized utilizing intravenous corticosteroids intraoperatively, followed by a standardized reduction scheme, calcineurin inhibitors (tacrolimus, trough level 6–8 ng/mL), and mycophenolate mofetil (0.5–1 g, twice daily). All patients were sent to intensive care unit (ICU) after transplantation and monitored closely. After discharge, all patients were followed by our outpatient clinic on a regular basis with ultrasound and fibroscan of the liver as routine procedures.

### Fibroscan

A representative area of liver parenchyma of the right lobe was identified by B-mode ultrasound. Hepatic elasticity was evaluated at this area by transient ultrasound elastography. Mean values of 10 measurements are reported.

### Definition of Early Allograft Dysfunction

The definition by Olthoff et al[8] from 2010 was utilized: early allograft dysfunction (EAD) was diagnosed if bilirubin was 10 mg/dL or greater on postoperative day 7 and international normalized ratio was 1.6 or greater on postoperative day 7 and aspartate aminotransferase or alanine aminotransferase >2000 IU/L within the first 7 days. Currently, EAD represents the best-validated and clinically relevant parameter for early liver allograft assessment after LT.

### Definition of Ischemic Type Biliary Lesion

Ischemic type biliary lesions (ITBLs) were defined as intrahepatic biliary strictures and dilatations on a cholangiogram, in the absence of hepatic artery thrombosis. Diagnosis of ITBL was predominantly based on endoscopic retrograde cholangiogram (ERC) findings in the present study. ERC was performed as clinically indicated in cases of suspected biliary complications after exclusion of graft rejections. Routine magnetic resonance cholangiopancreatographies are not performed at our center.

### Statistics

Data were shown as the mean and SEM, or the median and range, as appropriate. Graft and patient survival were analyzed using the Kaplan-Meier analysis and compared using the log-rank test. A $P < 0.05$ was considered statistically significant. We limited the comparison of the COR group with the control group to the most relevant endpoints (survival, EAD, ITBL, and length of stay) to avoid statistical issues due to multiple testing and underpowered comparisons. SPSS version 24 (IBM, Armonk, NY) was used for statistical analysis.

## RESULTS

### Donors and Recipients

Donor and recipient demographics are given in Table 1. Indications for transplantation were given for alcoholic liver cirrhosis in 10 (55.6%), hepatitis B induced liver cirrhosis in 2 (11.1%), hepatitis C induced liver cirrhosis in 1 (5.5%), and other reasons in 4 (22.2%) cases. An HCC was diagnosed in 3 (16.7%) cases. Allograft steatosis was determined by prospectively collected biopsies. Macrovesicular steatosis was <40% in all organs, concomitant to our local center acceptance policy. The median donor risk index (DRI) was 1.8 (1.03–2.5) in allografts undergoing machine perfusion. The median allograft weight was 1610 (1190–2570) grams. Reasons to select allografts for the machine perfusion protocol were as follows: extensive donor risk profiles in 5 cases with DRI >2, extensive long cold ischemia time (>12 h) in 6 cases, severe steatosis of the allograft diagnosed by biopsy in 5 cases, liver fibrosis in combination with poor macroscopic organ quality in 2 cases, and in 1 case additional brain malignancy (anaplastic astrocytoma) in combination with severe atherosclerosis of the abdominal arterial vessels leading to extended criteria donation.

### TABLE 1.

**Donor and recipient characteristics of COR treated patients**

| Parameter | Value |
| --- | --- |
| Recipient age (y) | 54.2 ± 2.3 |
| Recipient gender n (%) F; M | 6 (33.3); 12 (66.6) |
| Recipient BMI (kg/m²) | 25.6 ± 1.1 |
| LabMELD | 14 (9–23) |
| DRI | 1.8 (1.03–2.5) |
| Donor gender n (%) F; M | 5 (27.8); 13 (72.2) |
| Donor age (y) | 53.7 ± 4.5 |
| Donor BMI (kg/m²) | 26.4 (1.2) |
| Donor ICU stay (d) | 3 (1–9) |
| Donor COD (%) | |
|   Trauma | 2 (11.1) |
|   Anoxia | 5 (27.8) |
|   CVA | 8 (44.4) |
|   Other | 3 (16.7) |
| Steatosis total (%) | 25 (0–90) |
| Steatosis macro (%) | 5 (0–40) |
| Steatosis micro (%) | 20 (0–90) |
| Solution (UW/HTK) (%) | 2/16 (11.1/88.9) |
| CIT (min) | 549 (369–990) |
| WIT (min) | 27 (18–43) |
| Duration of surgery (min) | 246.5 (155–377) |

BMI, body mass index; CIT, cold ischemic time; COD, cause of death; COR, controlled oxygenated rewarming; CVA, cerebrovascular accident; DRI, donor risk index; F, female; HTK, Histidin-Tryptophane-Ketoglutarat; ICU, intensive care unit; LabMELD, laboratory model for end-stage liver disease; M, male; UW, University of Wisconsin; WIT, warm ischemic time.

### Machine Perfusion

All livers were perfused in accordance to the COR protocol without incidences and transplanted successfully. Arterial perfusion flows and portal vein perfusion flows are depicted in Figure 1. The temperature slope of rewarming was very similar in all allografts, independent from the allograft weight. After 30 minutes of cold perfusion mean arterial perfusion flow was 109 ± 15.1 mL/min rising to 169 ± 20.4 mL/min at 120 minutes of perfusion and 20°C. The portal vein flow increased from 118 ± 24 to 139 ± 45 mL/min at those time points. Lactate concentrations were 2.5 (0.9–4.9) mmol/L after 30 minutes of perfusion and 3.25 (1.1–6.7) mmol/L at the end of perfusion. Concentration of aminotransferase aspartate aminotransferase was 998 (131–3935) U/L 30 minutes after induction of perfusion and increased to 1645 (244–5328) U/L after 120 minutes of perfusion and elevation of the temperature to 20°C. Bile production was minimal during 120 minutes of perfusion and was, therefore, not quantified in detail.

### Postoperative Outcomes

An overview of outcome data after application of COR before LT is given in Table 2. Detailed postoperative laboratory courses are given in Figures 2 and 3. EAD was observed in 2 (11.1%) cases after COR and based on elevations of aminotransferases >2000 U/L within the first 7 days after LT. Primary nonfunction (PNF) was not observed. No patient required retransplantation. Length of the first stay (if readmission to ICU only the first stay was counted) in the ICU was median 5 days and hospital stay was median 21 days. An ITBL was observed in 1 patient (5.5%) after transplantation with preceding COR. The donor liver of this recipient was afflicted with an extensive cold ischemia time of >14 hours. This patient was treated by multiple ERCs and stenting of the biliary system in the further follow-up; however, he died due to progressive disease and recirrhosis. All other patients are well and alive. The according 1-, 3-, and 5-year patient survival rates are 100%, 100%, and 93.8%, respectively.

### Fibroscan

All patients underwent routine fibroscan investigations at routine visits at our outpatient clinic. Liver elasticity was median 4.65 (2.8–14.8) kPa at the last follow-up in patients without ITBL, indicating normal healthy liver parenchyma.

### Comparison With Control Cohort

For further classification of the presented results of COR before LT, we generated a control cohort based on similar clinical characteristics. Comparison with the COR group showed a significantly higher LabMELD score in the control group (Table 3) and, on the other hand, a significantly longer cold ischemic time (CIT) in the COR group. No baseline characteristics showed relevant differences between groups.

We limited the comparison of the COR group with the control group to the most relevant endpoints (EAD, ITBL, length of stay, and survival) to avoid statistical issues due to multiple testing and underpowered comparisons. Rate of EAD after LT was numerically lower in the COR group compared to the control group without statistical significance. Rate of PNF and retransplantation did not qualify for statistical comparisons, due to low number of events. Application of hemodialysis after LT was similar in both groups as well as length of ICU stay and hospital stay. ITBLs were observed in similar

**Perfusion Flow during COR**
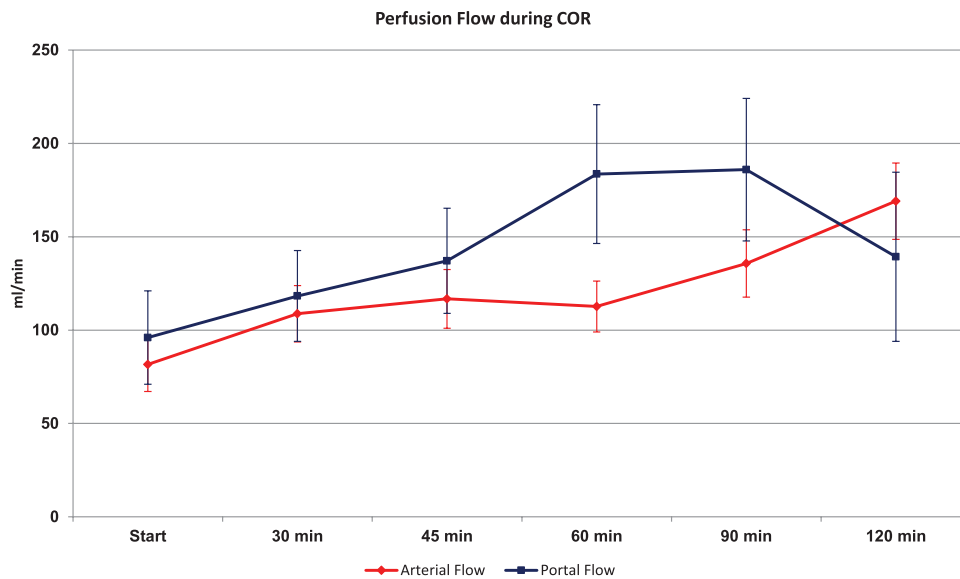


**FIGURE 1.** Arterial and portal perfusion flow during COR. COR, controlled oxygenated rewarming.

frequency in the COR group and control group. Comparison of graft survival demonstrated superior outcomes after COR without statistical significance ($P = 0.12$): The 1-, 3-, and 5-year patient survival rates for the COR and control groups are depicted in detail in Figure 4.

## DISCUSSION

This study displays our extended experience of application of COR as end-ischemic machine perfusion modality in 18 recipients before clinical liver transplantation. The presented results demonstrate first of all safety of this new technique in clinical liver transplantation for short- and long-term follow-up.

All donor organs which were selected for the COR procedure had extensive risk profiles, resembled by a median DRI of 1.8. Organs were allocated by the rescue allocation mechanism by EUROTRANSPLANT indicating that these were organs that nobody wanted. However, some organs had a low DRI but were afflicted with other risk factors like distinct steatosis, which is not reflected by the DRI. Perfusion characteristics were in line with our preclinical and clinical experience: portal and arterial perfusion flows increased in accordance to elevation of perfusion temperature. Lactate concentrations rose moderately during perfusion. Aminotransferase

release was highest in the first 30 minutes, thereafter increasing moderately in individual ranges for each allograft. Release of aminotransferases has been shown to correlate well with posttransplant hepatocellular injury[9] and might be a useful parameter to predict suitability of the allograft before transplantation. However, investigations in a larger number of patients are needed to prove this observation.

After transplantation, we detected only mild to moderate hepatocellular injury after COR treatment, displayed by aminotransferase release as usually seen in optimal allografts (Figure 2). Accordingly, liver function stabilized quickly represented by laboratory values of bilirubin and international normalized ratio, which nearly normalized in the first 7 days after transplantation in all recipients (Figure 3). PNF was not observed. These results clearly support our first experience of COR after cold storage before LT, which was published in 2016.[5] The clinically important end point of EAD[10] was observed in 2 out of 18 patients (11.1%) only after COR. Accordingly, the outcome in the first months after LT was excellent with survival rates after 1, 3, and 6 months of 100% (Figure 4).

During the further long-term follow-up 1 patient was diagnosed with ITBL and treated repeatedly by ERC, dilatation, and stent implantation.[11] This patient died due to biliary complications and recirrhosis nearly 3 years after LT. All other patients have no evidence of ITBL and are well and alive after a median follow-up of 1546 (749–1933) days, demonstrating excellent long-term outcomes in spite of the elevated risk afflicted with the utilized allografts. Such outcome data are far superior to the usual results in the EUROTRANSPLANT area with survival rates of ≈80% and 65% after 1 and 5 years, respectively.[12]

With the knowledge that survival after LT is multifactorial[13,14] it can be questioned whether recipient selection impacts the presented results: Recipient characteristics demonstrate that fair candidates were selected as recipients for this series of COR applications in terms of the LabMELD scores.

For further classification of our presented COR results, we created a control cohort with similar clinically relevant

<table>
<tr><td colspan="2">**TABLE 2.**</td></tr>
<tr><td colspan="2">**Clinical outcome after COR**</td></tr>
<tr><td>**Parameter**</td><td>**Value**</td></tr>
<tr><td>ICU stay (d)</td><td>5 (2–26)</td></tr>
<tr><td>Hospital stay (d)</td><td>21 (14–102)</td></tr>
<tr><td>EAD, n (%)</td><td>2 (11.1)</td></tr>
<tr><td>PNF, n (%)</td><td>0 (0)</td></tr>
<tr><td>ReTx, n (%)</td><td>0</td></tr>
<tr><td>Dialysis, n (%)</td><td>5 (27.8)</td></tr>
<tr><td>ITBL, n (%)</td><td>1 (5.5)</td></tr>
<tr><td>Fibroscan, kPa</td><td>4.7 (2.8–14.8)</td></tr>
</table>

COR, controlled oxygenated rewarming; EAD, early allograft dysfunction; ICU, intensive care unit; ITBL, ischemic type biliary lesion; PNF, primary nonfunction; ReTx, retransplantation.

## Hepatocellular injury after LT
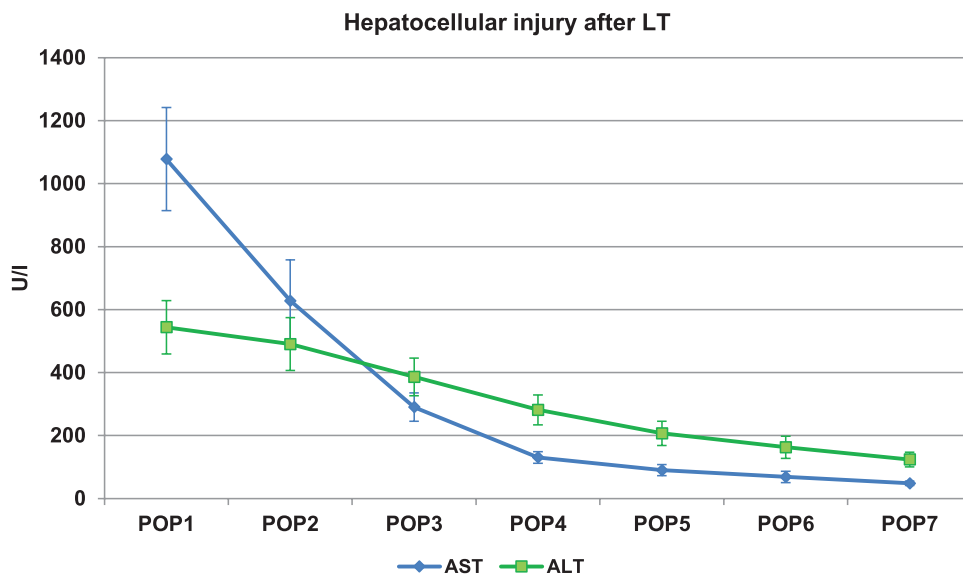


**FIGURE 2.** Hepatocellular injury after LT in COR treated patients. COR, controlled oxygenated rewarming; LT, liver transplantation.

## Liver function after LT
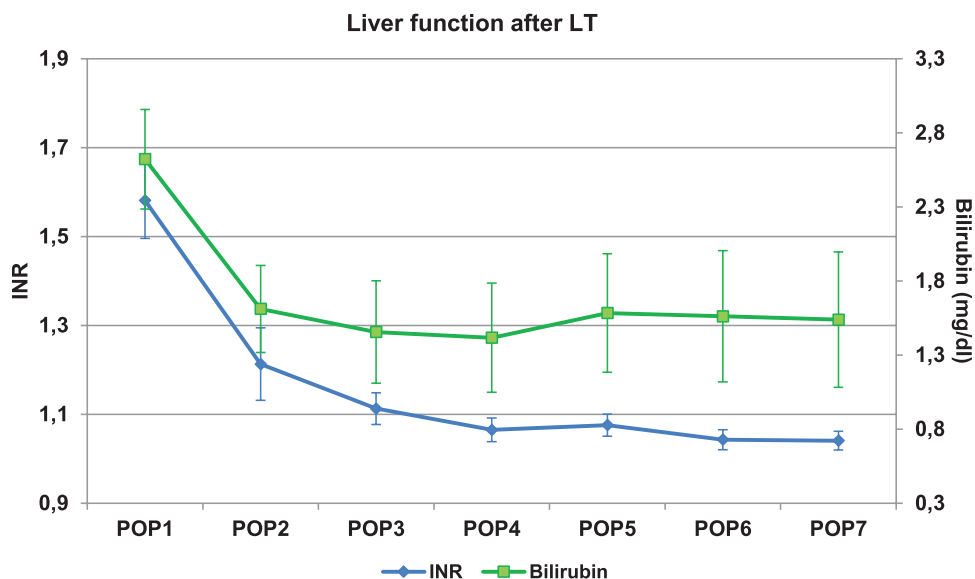


**FIGURE 3.** Liver function after LT in COR treated patients. COR, controlled oxygenated rewarming; INR, international normalized ratio; LT, liver transplantation.

parameters influencing postoperative results: all control patients were adults undergoing their first liver transplantation and we excluded combined transplantations, living-related liver donations, split transplantations, and recipients with portal vein thrombosis. We want to emphasize that the presented study procedures were not designed as a controlled study and no power analysis or sample size calculations were performed. In this context, we compared only the most important clinical endpoints after transplantation with intention to abstain from statistical issues of multiple testing. Comparisons of both groups showed a higher LabMELD score in the control group, which most likely demonstrates a selection bias of the COR patients. As the MELD score predicts posttransplant survival in some studies the reported results should be construed against this background and presumably limits the interpretation of the results in favor of COR. We cannot rule out that the difference in survival observed in this study is

(at least in part) due to the different MELD scores and not only associated with COR. On the other hand, the CIT was significantly longer in the COR group adding relevant risks to the profiles of these organs.[14,15] All other comparisons of the COR group with the control group demonstrated similarity in recipient, donor, and procedure characteristics (Table 3) as expected. Investigated outcome parameters did not show any statistical difference between groups (Table 3). The graft survival demonstrated clinically relevant superior results after COR (Figure 4), suggesting a protective effect of COR, however, not reaching statistical significance. Although nonsignificant, the numerical difference of EAD between groups might be a major reason for this result, especially as graft survival decreased in the early period after transplantation in the control group. Early graft failure is associated with suboptimal liver function after transplantation, leading frequently to infectious complications with deteriorating liver function and
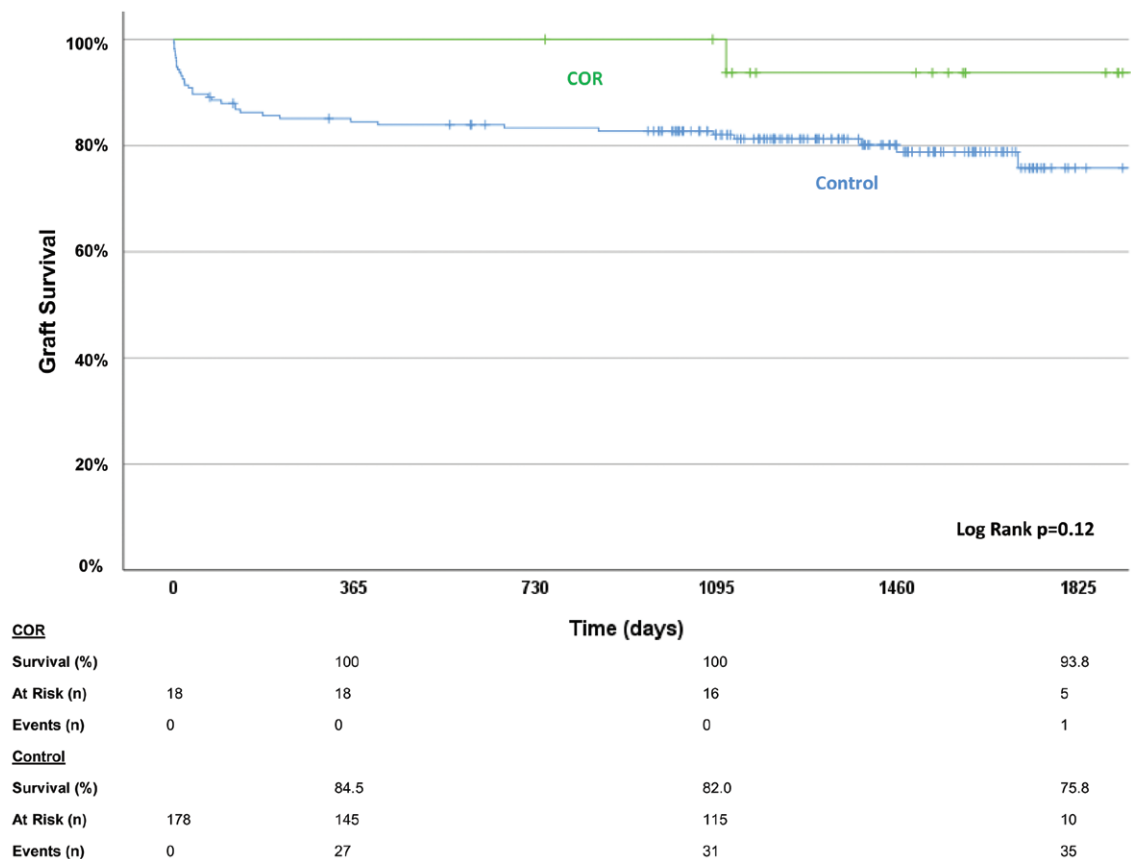
**Comparison of COR treated patients with controls**

| Parameter | COR (n=18) | Control (n=178) | P |
|---|---|---|---|
| Recipient age | 54.2 ± 2.3 | 53.2 ± 0.9 | 0.71 |
| Recipient gender F (%); M (%) | 6 (33.3); 12 (66.7) | 49 (27.5); 129 (72.5) | 0.6 |
| LabMELD | 14 (9–23) | 19.7 (7–40) | 0.005 |
| DRI | 1.8 (1.03–2.5) | 1.7 (1.02–2.64) | 0.23 |
| Solution (UW/HTK) | 2/16 (11.1/88.9) | 24/146 (14.1/85.9) | 0.97 |
| CIT | 549 (369–990) | 461.5 (0–1000) | 0.001 |
| WIT | 27 (18–43) | 31 (17–80) | 0.09 |
| Duration of surgery | 246.5 (155–377) | 232.5 (130–1044) | 0.82 |
| ICU stay (d) | 5 (2–26) | 4 (1–106) | 0.99 |
| Hospital stay (d) | 21 (14–102) | 18 (1–123) | 0.12 |
| EAD | 2 (11.1) | 45 (25.3) | 0.18 |
| PNF | 0 (0) | 13 (7.3) | NA |
| Retransplantation | 0 | 5 (2.8) | NA |
| Dialysis | 5 (27.8) | 25 (14.04) | 0.12 |
| ITBL, n (%) | 1 (5.5) | 10 (5.6) | 0.9 |

CIT, cold ischemic time; COR, controlled oxygenated rewarming; DRI, donor risk index; EAD, early allograft dysfunction; F, female; HTK, Histidin-Tryptophane-Ketoglutarat; ICU, intensive care unit; ITBL, ischemic type biliary lesion; LabMELD, laboratory model for end-stage liver disease; M, male; NA, not available; PNF, primary nonfunction; UW, University of Wisconsin; WIT, warm ischemic time.

graft failure.[10,16] Definite superiority of COR in comparison to other preservation strategies needs to be further investigated in a randomized controlled trial, which is already initiated and recruiting at our center (ISRCTN 94691167).

The rate of ITBL was similar in both groups with ≈5%. This complication is feared after LT and presumably based on suboptimal microperfusion of biliary capillaries, therefore, injury of peribiliary glands and vascular plexus resulting in suboptimal preservation of ischemia sensitive biliary epithelial cells.[17,18] Unfortunately, destruction of the biliary tree results leading to formation of biliary cast, cholestasis, cholangitis, and finally recirrhosis.[19] It is of major interest



Log Rank p=0.12

| COR | | | | | |
|---|---|---|---|---|---|
| Survival (%) | | 100 | | 100 | 93.8 |
| At Risk (n) | 18 | 18 | | 16 | 5 |
| Events (n) | 0 | 0 | | 0 | 1 |
| Control | | | | | |
| Survival (%) | | 84.5 | | 82.0 | 75.8 |
| At Risk (n) | 178 | 145 | | 115 | 10 |
| Events (n) | 0 | 27 | | 31 | 35 |

**Figure 4**
Graft survival after COR compared to historical controls.

**FIGURE 4.** Graft survival after COR compared to historical controls. COR, controlled oxygenated rewarming.

to reduce this complication and perfusion modalities are thought to improve the capillary flow and energy supply of the tissue, theoretically reducing the risk for ITBL. However, the results of the present study do show a case of ITBL in the COR group and, therefore, do not support this in the given very small sample size and, therefore, underpowered analysis. Other perfusion modalities like normothermic machine perfusion demonstrated a rate 7.5% of nonanastomotic strictures after machine perfusion compared to 5.4% after static cold storage in line with the incidence of the study at hand.[20] Future studies with sufficient numbers of patients to investigate this question are of high interest, however, difficult to accomplish due to the high number of patients needed for a sufficiently powered analysis. So far, data from clinical applications are the only source to give more insights on this very important topic.

The concept and physiology of COR have been investigated thoroughly in preclinical studies.[21] It was demonstrated that key for integrity of the parenchyma and function of the allograft is the slow elevation of the temperature and not only the simple increased mean temperature during perfusion.[21] Interestingly, the flush of the liver at the end of COR with cold preservation solution reduces the temperature to 14°C to 16°C only. Therefore, the washout of the machine perfusate has only little influence on the core temperature of the graft. A recent case report demonstrated that it might be feasible to waive this maneuver before implantation in clinical practice,[22] but this remains a matter of future investigations. In our understanding, the abrupt rewarming injury, which might be associated with such flush out maneuver, is most relevant after longer periods of hypothermia but rather undetected when starting from temperatures around 16°C.[23] So COR after cold storage restores energy homeostasis of the tissue at cold to subnormothermic conditions and optimally reconditions the allograft for the implantation warm ischemia, warm reperfusion with blood and the concomitant reperfusion injury. Experimental data suggest that this results in less oxidative injury, lower vascular resistance in the portal vein, and significant reduction of inflammation on reperfusion.[6]

The evolution of different perfusion modalities and adoption from laboratory to the clinic in the recent years, namely hypothermic machine perfusion,[24] hypothermic oxygenated machine perfusion,[25] and normothermic machine perfusion[20] resembles the most relevant progress in the field of organ preservation for decades. While all have demonstrated feasible and promising results in clinical application so far it remains unclear which perfusion modality is superior to others or whether different strategies are needed for different allografts in dependence of risk profiles (eg, long CIT, steatosis, DCD, etc). Future studies will hopefully gain insight of these exciting questions.

Limitations of the present study include the monocentric approach and nonrandomized design. Furthermore, selection of allografts for the COR protocol was based primarily on the rescue allocation mechanism of EUROTRANSPLANT, resembling a heterogeneous group of organs of limited quality and adoption of the results to a certain risk group of organs is not suitable so far. Moreover, the control group differs significantly in terms of MELD score, potentially influencing the patient survival after transplantation in this group. As far as this study is based on a nonrandomized design, the impact of the intervention should be interpreted with caution.

In conclusion, the present study demonstrates excellent clinical long-term outcomes after application of COR before LT in the largest clinical data set available so far. Comparison with a similar control cohort shows superiority of graft survival. A randomized controlled clinical trial has been initiated and is recruiting to give further evidence of this promising method to improve organ preservation.

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