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# Development And Validation Of A Novel Risk Prediction Model For Kidney Transplant Outcomes In A European Population

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## Background

Living donor kidney transplantation (LDKT) offers superior patient and graft survival outcomes compared to DDKT. Clinicians must often select between multiple potential (in)compatible donors and decide on the best match in kidney exchange programs. In these scenarios, validated tools to predict long-term outcomes are critical to ensure informed decision-making and equitable allocation. The (L)KDPI is the only validated risk calculator but is calibrated to the characteristics of the US DDKT population and does not adequately reflect the European population and transplant practices. We hypothesize that the development of novel prediction models will provide robust tools for accurately predicting kidney transplant outcomes and compare donors in a European context.

## Methods

All adult-to-adult LDKT and DDKT in the UK between 2007 and 2023 were included in this study. The EKTRA and LEKTRA (Living Donor European Kidney Transplant Risk Assessment) scores were developed using Cox proportional hazards models with donor variables. Donors and recipients without complete data were removed. LEKTRA, for living donors, uses coefficients from a multivariable Cox model, scaled relative to EKTRA (for deceased donors). Both scores were evaluated for AUC values from time-dependent ROC analysis at 1, 5, and 10 years.

## Results

A total of 14,508 LDKT and 24,432 DDKT were analyzed. The EKTRA score achieved an AUC of 0.657 at 10 years, demonstrating a clear improvement over KDPI. At 10-years, significant differences in graft survival were observed between all LEKTRA quartiles ( $p < 0.001$ ), indicating strong predictive value. The LEKTRA score showed excellent predictive performance, with a C-index of 0.67 and time-dependent AUC values of 0.67, and 0.70 at 5, and 10 years. Compared to the LKDPI score (C-index = 0.55), LEKTRA demonstrated improved discrimination across time points.

## Conclusions

This study introduces the EKTRA and LEKTRA scores, tailored for DDKT and LDKT in Europe. Both models demonstrated strong predictive performance,



with (L)EKTRA outperforming (L)KDPI in discrimination across all time points. This improvement is primarily attributed to differences in the European and American DDKT populations and the enhanced optimization of predictive variables in our models. These findings highlight the potential to improve clinical decision-making and optimize transplant outcomes.



02

# Short-Term Fasting In Living Kidney Donor Population: A Multicentre RCT

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## Background

Short-Term Fasting (STF) is a dietary approach that reduces calorie intake without causing undernutrition. It is aimed at enhancing resilience and resistance to acute stress, with benefits in lowering the risk of age-related diseases and extending lifespan. Caloric interventions like STF have shown preventive effects on genomic stress, ischemia-reperfusion injury, and aging. While STF's feasibility and safety have been proven in human trials, its full benefits for living kidney donors are unclear.

## Methods

We performed a multicentre randomised controlled trial in two academic centres, including living kidney donors and their recipients. Donors were randomly assigned to either control or a STF-diet before surgery. To mitigate potential bias, we incorporated two additional control cohorts: a historical and active control group. The primary endpoint was postoperative fatigue, 4 weeks after donation. Secondary endpoints included postoperative hospital admission time, feasibility of STF, and postoperative recovery of donor and recipient kidney function. Participants were sent RAND-36 questionnaires to assess subjective outcomes, and clinical data was extracted from the electronic health record.

## Results

In this study, which ran from August 2021 to August 2024, 180 participants were included out of 570 screened. Of the 361 eligible patients, 181 declined participation. Adherence to the intervention was high, with minimal side effects reported. The primary outcome was not met according to the intention-to-treat analysis; the physical component score (PCS) was 44.8 vs 43.8 ( $p = 0.467$ ). Secondary outcomes were comparable, but postoperative kidney function favoured the intervention and functional delayed graft function (fDGF) did occur significantly less in recipients of STF-Donors (11.6% vs 31.5%,  $p = 0.008$ ). Physical activity data indicated no significant differences pre- and post-surgery between groups, though there was a favourable trend in the intervention group.

## Conclusions

While STF did not significantly affect PCS, it demonstrated high feasibility of the STF-Diet, with logistic issues affecting adherence. Despite the diet not showing the anticipated clinical benefits to the same extent, both STF-Donors and their recipients displayed a trend towards improved outcomes and experienced less adverse outcomes like fDGF. Further investigation with larger and more diverse populations is needed to clarify its clinical impact.

03

# Cross-Over+ Simulation: The Potential To Double The Number Of Cross- Over Transplants

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## Background

The Dutch Transplant Foundation is currently implementing a new matching algorithm in the national kidney exchange program (KEP). This Cross-over+ algorithm prioritizes selected highly immunized (sHI) patients and allows for ABO-incompatible (ABOi) matching in long waiting (LW) patients. Additionally, Cross-over+ allows for limiting non-directed donor (NDD) KEP participation to matches with patients from the same transplant center.

## Methods

Monte Carlo simulations were performed on a database constructed in collaboration with the Dutch Transplant Foundation and all seven Dutch transplant centers. KEP couples, NDDs and the deceased donor waitlist between 2018-2023 were included. Patients were retrospectively labeled as sHI, LW, or regular. Real cross-over was compared with three scenarios, each tested with 10 simulations: simulated current cross-over, simulated Cross-over+, and simulated Cross-over+ with additional NDD participation.

## Results

In reality, 152 of 501 pairs (30%) were transplanted in cross-over between 2018-2023, which was in line with a simulated median of 163 pairs (33%). Cross-over+ simulation significantly increased transplant rate to median 234 pairs (48% versus 33%,  $p=0.002$ ).

In reality, 10% of sHI and 24% of LW pairs were transplanted in cross-over, which was 19% for sHI and 21% for LW pairs in simulated cross-over. Cross-over+ simulation significantly increased matches for these difficult-to-match patients as compared with simulated cross-over: median 37% versus 19% for sHI ( $p=0.002$ ) and 73% versus 21% for LW pairs ( $p=0.002$ ). In the simulated period of six years, median 67 LW and sHI patients were matched ABOi in Cross-over+.

Between 2018-2023, 143 NDDs donated outside KEP in their own center, while 21 (13%) participated in KEP. Simulating the option of local NDD KEP participation of 143 NDDs triggered additional domino chains for median 52 pairs (KEP transplant rate 59% versus 48%,  $p=0.002$ ). Hypothetical participation of all NDDs in national Cross-over+, not limited to their center, would lead to an increase of median 80 KEP transplants for pairs (63% versus 48%,  $p=0.002$ ).

## Conclusions

The new matching algorithm Cross-over+ will significantly improve transplant rates for difficult-to-match patients. Transplant centers should counsel all NDDs for local and national KEP participation, as the combination of ABOi-matching and additional NDD participation could double cross-over transplants for pairs.

# Graft Nephrectomy Versus Embolization In Kidney Transplant Recipients With A Non-Functioning Allograft: A Retrospective Cohort Study

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## Background

Graft nephrectomy is an invasive procedure associated with a high rate of complications. Our center adopted a less invasive procedure: percutaneous embolization of the renal artery of the allograft. In this study, we evaluate and compare both treatments.

## Methods

This is a retrospective single-center cohort study of patients who underwent either a graft nephrectomy or embolization between January 2018 and September 2024. Patients with gain of space as indication were excluded. Graft intolerance syndrome was defined as suspected allograft rejection with clinical signs such as pain, fever or hematuria. We reported post-embolization

syndrome (fever within five days post-embolization), blood transfusions up to one month, post-operative complications (Clavien-Dindo classification score  $\geq 3$ ), length of hospital stay upon procedure, readmissions up to three months and mortality within six months.

## Results

We included 46 patients: 33 underwent initial graft nephrectomy and thirteen patients underwent embolization. Mean age at treatment was 57.0 vs. 59.5 years, respectively. Main treatment indication was graft intolerance syndrome (21/33 versus 12/13,  $p=0.07$ ). Other indications were infection (7/33 versus 1/13), thrombosis, (3/33) and neoplasia (2/33).

Mean length of stay was longer after graft nephrectomy compared to embolization (8.4 versus 4.2 days,  $p=0.001$ ). After nephrectomy, 60.6% received blood transfusions compared to 46.2% after embolization ( $p=0.51$ ) with a median number of two erythrocyte concentrations in both groups.

After embolization, nine patients (69.2%) developed post-embolization syndrome. After graft nephrectomy, fifteen patients (45.5%) had Clavien-Dindo score  $\geq 3$  versus four patients (30.8%) after embolization ( $p=0.51$ ). Thirteen patients (39.4%) required readmission after nephrectomy, versus four patients (30.8%) after embolization ( $p=0.74$ ), with comparable lengths of stay during re-admission (median 8.5 days versus 7 days). Two patients underwent subsequent graft nephrectomy after embolization due to infected necrosis and persistent graft intolerance syndrome.

After graft nephrectomy, one patient died of sepsis present before and one of sepsis developed after the procedure. Two embolization patients died of sepsis already present before embolization (mortality rate 2/33 versus 2/13,  $p=0.57$ ).

## Conclusions

Percutaneous embolization of the kidney allograft resulted in shorter hospital admissions than graft nephrectomy, but complications did not significantly differ. Post-embolization syndrome was a common finding. Infection is a risk factor for adverse outcomes after embolization.

# The Impact Of Age On Infection-Related Mortality And Death-Censored Graft Survival In Kidney Transplant Recipients

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## Background

Older kidney transplant (KT) recipients have a lower risk of graft loss due to rejection, but a higher risk of infections. In selected patients, less intensive immunosuppressive regimens (IS) may reduce the infection risk without increasing the risk of rejection. We investigated whether an age threshold could be determined to identify KT recipients who might benefit from less intensive IS.

## Methods

Data on KTs performed at Radboudumc since 2000 were obtained from the NOTR. Age-related differences in mortality and graft loss were analyzed using Cox regression with adjustment for recipient BMI and sex, donor age, sex, and type, cold ischemia time, prior KTs, preemptive KT, and year of KT. To investigate whether hazards reached a plateau at a certain age, analyses were repeated with recipient age dichotomized at various cut-off points (50, 55, 60, and 65 years).

## Results

2671 KTs were included (mean recipient age 51 years, 61% male, 55% living donor, 21% preemptive). With increasing age at time of transplantation, the hazard of mortality post-transplantation increased (all-cause: hazard ratio [HR] 1.07 per year of increasing age [95% CI 1.06;1.08]; infection-related: HR 1.03 [1.01;1.06];

malignancy-related: HR 1.02 [1.00;1.05]). The hazard of all-cause and infection-related death continued to increase with advancing age, without reaching a plateau, while the hazard of malignancy-related deaths plateaued around the age of 60 at time of transplantation.

The hazard of all-cause graft loss also increased with advancing age (HR 1.03 [1.02;1.04]), but the hazard of death-censored graft loss (mainly due to rejection) decreased (HR 0.98 [0.97;0.99]), indicating that with increasing age, a larger proportion of the patients died with a functioning graft. The hazard of death-censored graft loss plateaued between the ages of 55 and 60 years.

## Conclusions

While the risk of infection-related death continues to increase with advancing age, the age-related decrease in the risk of death-censored graft loss already plateaued between the ages of 55 and 60 years at time of transplantation. Since 44% of KT recipients are currently aged 55 or older, these data do not allow to identify a specific subset of KT recipients who might benefit from less intensive IS.

# Prospective CDC Crossmatching For Postmortal Donor Kidney Transplantation: Only For Immunized Patients?

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## Background

The presence of complement-binding donor-specific HLA antibodies (DSA) pose a high risk for hyperacute rejection after kidney transplantation. Therefore, a prospective CDC crossmatch must be performed before kidney transplantation if the patient is immunized. Pretransplant DSA that are only detectable by sensitive (Luminex-based) methods also increase the risk of a rejection episode after transplantation, but often do not result in a positive donor-recipient CDC crossmatch. However, performing a prospective CDC crossmatch increases the cold ischemia time of the donor kidney. The aim of this single-center study was to guide decision-making when to perform a prospective CDC crossmatch.

## Methods

Patients receiving a kidney transplantation offer from a postmortal donor between January 2023 and September 2024 were analyzed for the presence of pretransplantation DSA, including MFI values of these DSA (Immuncor/Werfen) and combined with results of prospective/retrospective donor-recipient CDC crossmatches.

## Results

For 209 deceased donor kidney offers, 71 prospective CDC crossmatches were performed in a 20-month period. In total, 4 prospective CDC crossmatches were positive, all in highly immunized patients. Three out of 4 received the kidney offer through the Acceptable Mismatch-program. The positive CDC crossmatches could be explained by multiple high MFI Luminex DSA (highest DSA MFI average >15,000) that were not listed as unacceptable and/or antigens that required additional testing. None of the CDC crossmatches performed for patients receiving a 2<sup>nd</sup> or 3<sup>rd</sup> kidney transplantation were positive if no DSA were present (n=22). For 30 patients receiving their first kidney transplantation in the presence of only Luminex DSA, all CDC crossmatches (both prospective and retrospective) were negative. In this group, the average DSA MFI was 2500 and none were >6500 MFI.

## Conclusions

Prospective CDC crossmatches remain necessary to test the patient-donor compatibility in immunized patients. However, in patients without CDC-reactive antibodies receiving their first postmortal kidney transplantation, the presence of pretransplant DSA correlates with an increased risk of acute rejection but this does not result in positive CDC crossmatches. Therefore, we propose to

omit the prospective CDC crossmatch for this specific patient group to decrease the cold ischemia time.

07

# Tacrolimus Exposure Is Associated With Acute Rejection In The Early Phase After Kidney Transplantation: A Joint Modeling Approach

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## Background

Conflicting reports exist regarding the relationship between tacrolimus exposure and the risk of acute kidney allograft rejection. The lack of consensus could be explained by use of methodological approaches that disregard important properties of analysis of longitudinal measurements and time-to-event data. Here, we use joint models to study the relationship between repeated measurements of tacrolimus pre-dose concentrations ( $C_0$ ) and time to acute kidney allograft rejection.

## Methods

This was a post-hoc analysis of a randomized-controlled trial in which *de novo* kidney transplant recipients (KTRs), received either a standard, bodyweight-based tacrolimus starting dose or a *CYP3A5* genotype-based starting dose. Joint modeling was performed by coupling a mixed-effects model for tacrolimus  $C_0$  and a Cox proportional hazards model for the risk of rejection. Only the first episode of rejection was considered. The longitudinal submodel included time and recipient age as fixed effects. Three sets of independent variables were considered for the survival submodel, accounting for recipient age, peak panel reactive antibodies (PRA), and human leukocyte antigen (HLA) mismatches. The area under the curve of tacrolimus  $C_0$  was used as the association structure linking both submodels.

## Results

A total of 229 KTRs was included, of which 24 recipients (10.5%) experienced rejection in the first three months after transplantation. A total of 3,069 tacrolimus  $C_0$  samples was available for analysis, with a median number of 13 (IQR 11-16) measurements per recipient. The joint model with the survival submodel adjusted for recipient age and peak PRA, demonstrated that tacrolimus  $C_0$  was associated with the risk of allograft rejection. A one-unit increase in the time-normalized area under the log-transformed tacrolimus  $C_0$  curve represented a change of -2.65 in the log of the relative hazard (95%-credibility interval: -5.05 – -0.36; *p-value* = 0.022). In other words: a one unit decrease in the area under the log-transformed tacrolimus  $C_0$  curve was associated with a 14-fold increased risk of rejection.

## Conclusions

A negative association between the cumulative effect of tacrolimus  $C_0$  and acute rejection was demonstrated by using joint modeling. Our findings corroborate with previous studies stating that KTRs with lower exposure to the immunosuppressive are at higher risks of rejection.

08

# Polyneuropathy In Kidney Transplant Recipients: A Cross-Sectional Study With Prospective Data Collection

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## Background

Polyneuropathic symptoms are highly prevalent among dialysis patients. However, initial studies on polyneuropathy in KTR reported a prevalence of only 2%, despite evidence indicating that small and large fibre function do not significantly improve after transplantation. To better understand polyneuropathy in KTR, prevalence, type of polyneuropathy, as well as associated clinical characteristics were assessed.

## Methods

This cross-sectional cohort study included KTR at the earliest 12 months post-transplantation. Participants were subjected to a structured neurological assessment including history taking, neurological examination, quantitative sensory testing, and nerve conduction studies. Based on the neurological assessment characteristics, participants were classified as having no/possible, or probable/definite large fibre polyneuropathy, or small fibre neuropathy by an expert panel. Furthermore, polyneuropathy subtypes were classified as follows:



axonal versus demyelinating, pure sensory, pure motor, and sensorimotor polyneuropathy. In logistic regression analyses, potential associations with clinical characteristics were assessed.

### Results

We included 160 KTR with a mean age of  $59.8 \pm 11.6$  years at a median of 6.1 [3.9 to 13.1] years post-transplantation. In total, 91 KTR (57%) were classified as having polyneuropathy, with 16 KTR (10%) who had received the diagnosis before study inclusion. Of the KTR with polyneuropathy, 58 KTR (36%) were categorised as definite large fibre polyneuropathy and 7 KTR (4%) as small fibre polyneuropathy. None of the patients demonstrated neurophysiological characteristics of demyelination. KTR with large fibre polyneuropathy presented with sensor-predominant polyneuropathy (40 KTR (48%)) and sensorimotor polyneuropathy (44 KTR (52%)). Overall, 33% of those with large fibre polyneuropathy reported experiencing either no symptoms or one symptom. Higher age (odds ratio (OR)=1.04 (1.01-1.08),  $P=0.01$ ), male sex (OR=2.59 (1.23-5.57),  $P=0.01$ ), diabetes (OR=6.06 (1.50-41.17),  $P=0.03$ ), and higher urea levels (OR=1.13 (1.04-1.24),  $P=0.01$ ) were significantly associated with polyneuropathy in KTR.

### Conclusions

Polyneuropathy is highly prevalent in KTR, predominantly manifesting as axonal sensory or sensorimotor large fibre polyneuropathy. Next to higher age and male sex, it was associated with diabetes and higher urea levels. Our findings highlight that polyneuropathy may be underdiagnosed in KTR, especially if the diagnosis is solely based on history taking.

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## Direct Implantation Of Kidney Graft On Endovascular Stent In The External Iliac Artery: A Feasibility Study

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### Background

With increasingly ageing population, both end-stage renal disease and peripheral artery disease become more prevalent. Peripheral artery disease is increasingly treated with endovascular procedures. Endovascular stenting of the external iliac artery (EIA) is often considered a contraindication for kidney transplantation, as clamping of the artery will lead to probable injury to the stent. In this study, we describe our first experiences of kidney transplantation with a graft placed on an endovascular stent.

### Methods

We performed one kidney transplantation with a graft placed on a self-expandable metal stent and one kidney transplantation with a graft placed on a covered stent as part of an endovascular repair of the aortic bifurcation, using endovascular balloon occlusion for occlusion of the proximal side of the EIA in both cases.



## Results

One recipient received a graft of a donation after circulatory death donor. The recipient experienced a short period of delayed graft function, but has a good kidney function at one year after transplantation, with an eGFR of 52 mL/min. The other recipient received a graft from a living donor. He experienced an episode of rejection after transplantation, but has an excellent kidney function at six months after transplantation, with an eGFR of 75 mL/min.

Both recipients experienced no complains of ischemia of the ipsilateral limb.

## Conclusions

This study shows our preliminary experience with direct implantation of a kidney graft on an endovascular stent in the external iliac artery. This demonstrates that implantation of a kidney graft on an endovascular stent can be safe and feasible and is not necessarily a contraindication for kidney transplantation.

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# Ready For Discharge, But Not Yet Ready For Home: Project Revastart In The Context Of Shortening Hospital Stays And Optimal Rehabilitation For The Patient After Organ Transplantation Or LVAD Implantation. (Original in Dutch)

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## Background

After heart, liver and lung transplantation (HTX, LTX and LoTX respectively), but also Left Ventricular Assist



Device (LVAD) implantation, patients may be medically ready after the procedure, but have not yet recovered enough to go home immediately due to deconditioning. The Revastart project has been set up for these patients in a rehabilitation center near the transplant institute. This project combines geriatric rehabilitation care (GRZ) and medical specialist rehabilitation (MSR) to bridge the period between medical readiness and discharge home. As a result, further recovery takes place in a rehabilitation setting instead of a prolonged hospital stay until discharge home.

### Methods

In the run-up to the start of this project, monthly consultations took place between healthcare providers from the transplant institute and healthcare providers from both the GRZ and MSR organizations. Clear guidelines from both the hospital and RevaStart have been designed to enable patients to be transferred. A specific training program was set up by healthcare providers from the hospital, focused on wound care, lifestyle rules and medication policy, which was followed by all RevaStart healthcare providers. Afterwards, the first patient was transferred to RevaStart. A multidisciplinary meeting (MDO) takes place every week to ensure that contact remains between the hospital and RevaStart about transferred patients. If indicated, healthcare providers also visit patients at RevaStart. Data was collected retrospectively from patients discharged to RevaStart.

### Results

The first patient was transferred in November 2023, and since then 2 LVAD, 3 HTx, 5 LTx and 2 LoTx patients have now been referred to RevaStart with an average age of 57.4 years, of which 17% are women. The median rehabilitation time was 5 (IQR 3-6) weeks, after which all patients could be discharged to their own living environment. Of the 12 patients, only 1 patient was returned to the hospital from RevaStart after a week. This patient was ultimately discharged from the hospital to his own living environment.

### Conclusions

Since the start of the project, 12 patients have now been transferred for rehabilitation. This has ensured that patients recuperate faster and more often outside the hospital, resulting in a significant reduction in hospital stay. This contributes to achieving the right care in the right place.

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# Trajectories Of Fatigue Among Kidney Transplant Recipients Prior To- And Post-Transplantation

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### Background

Fatigue is common in kidney transplant recipients (KTR). Yet, little is known on how fatigue evolves over time in KTR. Therefore, this study aimed to identify distinct fatigue trajectories from before transplantation (Tx) to 24 months after Tx, to explore covariables associated with these trajectories, and to assess how these trajectories affect health-related quality of life (HRQoL) and rehospitalization.

### Methods

Longitudinal data were used. Fatigue was assessed using the 8-item Checklist Individual Strength Revised prior to- and at 6-, 12-, and 24-months post-Tx. Fatigue trajectories were identified by Latent Class Growth Analysis. HRQoL was assessed by the Short Form-12 at 12- and 24-months post-Tx, and rehospitalization was defined as the total days readmitted within the first post-Tx year.

### Results

In total, 500 KTR were included (36.6% female, age 55±13 years). Four trajectories were identified: persistent low fatigue (9.0%), resolved mild fatigue (24.8%), severe fatigue that improved to mild fatigue (43.0%), and



persistent severe fatigue (23.2%). Univariable associated covariables were female sex, unemployment, receiving a kidney from a living donor, anemia, use of proton pump-inhibitors, poor sleep quality, depression, anxiety, lower personal control levels, and higher use of the coping styles avoidance, expression of emotions, palliative-, and passive reactions. In multivariable analysis using the persistent low fatigue trajectory as reference, no significant associations were found for the resolved mild fatigue trajectory. Depressive symptoms remained significantly associated with the severe fatigue that improved to mild fatigue trajectory and the persistent severe fatigue trajectory (aOR=2.8, 95% CI [1.3, 5.9],  $p=0.009$  and aOR=3.1, 95% CI [1.4, 6.7],  $p=0.004$ , respectively). Recipients within the persistent severe fatigue trajectory reported significantly lower HRQoL at 12- and 24-months post-Tx and a longer duration of rehospitalization within the first year post-Tx compared to the other trajectories.

### Conclusions

Four distinct fatigue trajectories were identified in KTR. A significant subset of KTR experienced persistent severe fatigue post-Tx, accompanied by reduced HRQoL and prolonged rehospitalization. Symptoms of depression appears to be an important factor in the course of fatigue, suggesting that addressing these symptoms could be a target for interventions to improve fatigue outcomes in KTR.

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# Unmet Care Needs In Dutch Solid Organ Transplant Recipients: A Cross-Sectional Study

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### Background

Solid organ transplant recipients (SOTRs) may experience unmet care needs post-transplant, with possible harmful effects, such as pain, distress or adverse events that may hamper successful treatment. However, little is known about unmet care needs in SOTRs. Therefore, identifying unmet care needs is essential to empower transplant professionals to provide optimal, supportive care. This study aimed to gain insight into the prevalence of unmet care needs among Dutch SOTRs, to examine sociodemographic, clinical, and personal characteristics associated with unmet care needs, and the influence of unmet care needs on health-related quality of life (HRQoL).

### Methods

In March 2023, a cross-sectional, single center study was conducted among Dutch kidney-, liver-, lung- and heart transplant recipients whom received their transplant 6-24 months earlier. A questionnaire was used to assess unmet care needs, sociodemographic and personal characteristics (anxiety, depression, self-efficacy, social support) and HRQoL. Clinical characteristics were assessed by medical record view. Descriptive statistics and Kruskal-Wallis test were used to gain insight into unmet care needs, multivariable regression analysis to explore factors associated with unmet care needs, and Mann-Whitney U test to assess the influence of unmet care needs on HRQoL.

### Results

Of all participants ( $n=182$ ), 176 (96.7%) SOTRs reported care needs, of which 166 (94.3%) reported unmet care needs. Median number of unmet care needs was 9.5 and were mainly (60%) found in the 'daily life and social interaction' domain. The number of care needs did not differ between types of transplantation ( $p=.355$ ). Lower levels of self-efficacy and more symptoms of depression were associated with more unmet care needs ( $p<.001$ ). SOTRs with  $>10$  unmet care needs scored significantly lower on both the physical (median 56.89) and mental (median 71.00) component scores ( $p<.001$ ) of HRQoL.

### Conclusions

Almost all SOTRs experience unmet care needs. Screening for unmet care needs, along with attention to level of self-efficacy and depressive symptoms, is necessary to be able to provide tailored interventions by transplant professionals.



## Evaluation Of Sexual Complaints In The First Year After Kidney Transplantation. (Original in Dutch)

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### Background

Sexual health is an important aspect of quality of life, but often remains underexposed. Patients also appear to experience sexual complaints after kidney transplantation. Whether and how this changes after a kidney transplant is unknown. PROMs can be used to systematically evaluate subjective experiences regarding sexual health in patients after kidney transplantation.

### Methods

In the 'Patient-Reported Outcome in kidney Transplant recipients: Input of Valuable Endpoints (POSITIVE)' study, 54 men (59±14 years) and 25 women (54±16 years) were followed at the Maastricht UMC+ from January 2021. They completed a MTSOSD-59 questionnaire before the transplant, 6 weeks, 3, 6 and 12 months after kidney transplantation. The questionnaire contains three items about sexual complaints. The change in occurrence and severity of sexual complaints was analyzed.

### Results

Before the transplant, 39% of men reported difficulty becoming sexually aroused and a reduced interest in sex, and 44% reported erection problems. These complaints are serious in 9-16% of men. In 44% of women there is difficulty becoming aroused and a reduced interest in sex, of which 4 to 8% are serious. Less than 5% of women have menstrual complaints. After 3 months, 19% of men have reduced interest in sex ( $p<0.05$ ), 19% have difficulty

getting aroused and 30% have erection problems. This remains at the same level after 6 and 12 months, with the severity of the complaints also decreasing. At 6 months, 12% of women have reduced interest in sex ( $p<0.05$ ) and 8% have difficulty becoming aroused ( $p<0.05$ ), with the complaints not being experienced as serious. This remained unchanged until 12 months after kidney transplantation.

### Conclusions

Sexual complaints are present in approximately 40% of men and women at the time of kidney transplantation. After kidney transplantation, both the frequency and degree of sexual complaints decrease in men and women. To further investigate sexual health after kidney transplantation, measurements will also need to be taken 2 years after kidney transplantation in this MUMC+ cohort and the LUMC cohort will be added.

## ACtive Care After TranSplantation: An Integrated Lifestyle Intervention Model In Complex Patients (ACT-SLIM) (Original in Dutch)

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## Background

Kidney transplant patients are 'complex patients' with multiple health problems. The lifestyle program 'Active Care after Transplantation' (ACT) improves physical functioning after transplantation (1). Patients in the intervention groups had 8-9% better fitness and showed twice as much recovery of strength. After 3 months of lifestyle intervention, they also reported an 8-10% higher quality of life than in the control group. Both patients and healthcare providers are strongly motivated to implement such a lifestyle program. This study is an implementation process, with the following goals: 1) Gain insight into obstacles and opportunities based on the ACT study: which obstacles and opportunities are available for sustainable implementation. 2) The prospective collection of experiences and results during the introduction of the program at three UMCs: these are used to set up an implementation plan. 3) Further development towards a broadly applicable implementation plan with solutions adapted to the context of a UMC.

## Methods

We use two implementation frameworks (CFIR and RE-AIM) to develop and evaluate the following. 1) Setting up a referral network so that patients have easy access to lifestyle care. 2) Further training of lifestyle professionals and paramedics in the field of kidney diseases to ensure the quality of care. 3) Training healthcare professionals in effective referral conversations and to promote cultural change with regard to lifestyle care. 4) Exploring financing options for lifestyle programs. 5) Integrating the program into the existing infrastructure for lifestyle care. 6) Applying additional strategies that are specifically tailored to the setting of a UMC. We do all this in collaboration with the most important stakeholders: university medical centers, patient organizations, paramedics and social organizations that promote exercise after transplantation. Various training materials have already been developed in the ACT study, such as educational material about kidney diseases, training protocols, lifestyle coaching manuals, aftercare instructions and nutrition manuals.

## Results

**EXPECTED RESULTS:** We expect that the ACT program will have a major positive impact on lifestyle care for kidney transplant patients.

## Conclusions

The program will contribute to better fitness, increased strength, improved daily functioning, faster physical recovery and more perceived mental support after transplantation.

## Reference

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# Challenges And Insights Of Implementing PROMs In Solid Organ Transplantation: Experiences And Lessons Learned

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## Background

In our transplant center, a comprehensive approach has been chosen to implement value-based healthcare (VBHC), meaning that all organ transplantation departments are collaborating. This approach is unique and has not been implemented in this way before. The VBHC dashboard is integrated into the electronic patient file. The aim of this study was to measure the extent to which VBHC has been integrated into the outpatient clinic.

## Methods

Patient Reported Outcome Measures (PROMs) was implemented, post-transplant, in phases from July 2023 to October 2024 starting with kidneys and lung transplant recipients, followed by liver and heart transplant recipients. Questionnaires used were the Patient Reported Outcomes Measurement Information System and the Basel Assessment of Adherence to Immunosuppressive Medication Scale (PROMIS and BAASIS). The PROMIS measures physical health (e.g. fatigue, pain), mental health (e.g. anxiety), social health (e.g. activities). In addition, participants had the possibility to respond to an open question on which topics they wanted to discuss with their healthcare provider (HCP).

## Results

Overall, PROMIS response rate was 78% (n= 1594), and BAASIS response rate was 77% (n= 1577). Of the responders 58% were men with a mean age of 57 years. Per department, for kidney the response rate (BAASIS and PROMIS) was 64% (n = 868), lung 87% (n = 323), liver 72% (n = 379), heart 76% (n = 206). The number of questionnaires opened by the HCP during the consultation ranged between 5% to 15%. Open questions were completed by 1558 participants, and topics they wanted to discuss were related to medication, fatigue and pain.

## Conclusions

VBHC changes the way we interact with patients to a person-centered approach. Therefore, effective communication and information-sharing by the HCP are crucial. However, a low percentage of HCP open the questionnaires during the consultation. By discussing the outcomes of a questionnaire during the consultation, problems can be promptly addressed to optimize care which is in line with the goal of VBHC. To do that HCP need to adapt the way they run their outpatient clinic. By combining our efforts, we can further optimize the quality of care.

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# Return To Work After Living Liver Donation

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## Background

Living liver donor programs usually advise donors that they can return to work and normal activities six to eight weeks after surgery, however there is little published data to support this advice.

## Methods

We studied the actual time it took for donors to return to work after living liver donation at our centre using a survey. Donors were asked to retrospectively answer questions about their recovery time when they were able to return to work /study and how they were able to reintegrate into their workplaces or study. Donors were eligible to participate if they donated part of their liver between May 2004 and December 2024.

## Results

Of the 66 donors eligible to participate in the study, 44 (67%) donors have so far responded. Six donors were lost to follow up and unable to be contacted for participation in the research. Mean age at donation was 34 years (18-58 years). 41 (62%) of donors were female. 42 (63%) donors were first or second degree relatives of their recipients, 21 (32%) donors were known to their recipient and 3 (5%) unrelated undirected donations took place.



31 (70%) of donors returned to work 5 weeks (3 – 12 weeks) after donation. 43 donors were working or studying before donation, and one donor participated in volunteer activities. After donation, all 44 donors returned to their pre donation activities. Of the 44 respondents, 17 donors returned to work with the help of the Uitvoeringsinstituut Werknemersverzekeringen (UWV), company doctors or direct managers. Adequate rest in the recovery phase immediately after donation, focusing on mental and physical health as well as adequate support both from the hospital and workplace/managers were what contributed most to a successful and confident return to work for living liver donors.

### Conclusions

When living liver donors can return to normal activities and employment after liver donation varies widely and is influenced by many factors Data collection for this study is still ongoing, a more in depth analysis of return to work patterns and influencing factors will be completed once all data has been collection from donors, in December 2024.

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# Removal Of A Magnetic Double-J Stent After Kidney Transplantation On The Nephrology Outpatient Clinic By The Nurse Specialist Nephrology.

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### Background

During kidney transplantation a double-J stent is inserted through the ureter of the graft to prevent stenosis at the anastomosis with the bladder of the patient.

Before introduction of the new stent, cystoscopy was necessary to remove the double-J stent at the outpatient clinic urology. Coordination of antibiotic prophylaxis for this procedure was difficult.

### Methods

From September 2023, a Magnetic Black Star Double-J Stent was inserted during kidney transplantation. After 2 weeks this stent was removed with a Magnetic Retrieval Device through a single bladder catheterisation by one of the nurse specialists nephrology.

After the introduction of the new catheter, the nurse specialist prescribed and checked the use of adequate antibiotic prophylaxis.

### Results

From the start till October 1th 2024, all 59 new transplant patients received a magnetic stent. In 4 of the patients who received a magnetic stent primary removal by the urologist was considered necessary.

All patients received antibiotics before the procedure.

In 46 from the 55 patients the double-J stent could as planned be successfully removed by the nurse specialist. For 9 patients an additional visit at the urology treatment room was necessary due to failure to remove the stent in eight patients and in one patient due to extreme fear for he procedure. At the urology department, in 2 of these patients removal of the stent through single catheterisation with the aid of ultrasound was possible, in 7 cases cystoscopy was needed to remove the stent.

In the first 14 days after removal of the double-J stent 4 positive urine cultures were found, only one of these patients was admitted in the hospital due to urinary tract infection.

### Conclusions

A magnetic double-J stent could successfully be removed in 84% of the cases on the nephrology outpatient clinic by the nurse specialist. The nurse specialists took care of correct antibiotic prophylaxis. In the first 14 days after removal of the stent 7% of the patients were treated for urinary tract infection.

# Optimization Of A Vascularized Human Kidney Organoid Mouse Model To Study The Role Of A Specific T Cell Subset In Fibrosis In Kidney Transplantation

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## Background

Long-term kidney allograft function is often compromised by the development of fibrosis, arising from both immune-related (antigen-dependent) and non-immune-related events. Immune-related events are driven by mismatched HLA and non-HLA antigens. Previous studies indicate that circulating non-HLA antigen-reactive CD4+ T cells correlate with the degree of fibrosis in kidney transplant recipients, yet their specific role remains unclear. A vascularized human kidney organoid mouse model allows for studying human immune responses in transplantation by injection of immune cells, such as peripheral blood mononuclear cells (PBMCs). Understanding whether isolated T cell populations or lines can successfully graft in this model is essential for studying the role of these T cell subsets.

## Methods

To assess the role of a specific T cell subset, sorted CD4+ T cells were expanded using anti-CD3/anti-CD28-coated beads and exogenous IL-2 and IL-15 for two

weeks. The expanded cells were either frozen for later use or tested immediately. Two weeks after transplantation of kidney organoids into immune-deficient mice, different doses (2 and 5 million) of CD4+ T cells were injected intraperitoneally to facilitate engraftment. After four weeks, blood samples were collected, and spleen and organoids were harvested for analysis. T cell populations in the blood and spleen were quantified using flow cytometry.

## Results

Mice injected with 5 million CD4+ T cells exhibited substantially higher CD3e gene expression in implanted kidney organoids compared to those without T cell injection, confirming successful T cell infiltration. After injecting 2 or 5 million fresh CD4+ T cells, median levels of human CD45+ lymphocytes in the spleens of four mice per group were 35% and 87%, respectively, indicating stronger engraftment with the higher dose. In contrast, after injecting 2 or 5 million frozen CD4+ T cells, median levels of human CD45+ lymphocytes in the spleens of two mice per group were 71% and 88%, respectively, suggesting that frozen CD4+ T cells perform comparably to fresh cells in this model.

## Conclusions

Five million CD4+ T cells, either fresh or frozen, successfully engraft in a vascularized kidney organoid mouse model, enabling detailed studies on the role of non-HLA antigen-reactive CD4+ T cells in induction of fibrosis in kidney transplantation.

# Circulating Sphingosine, Sphingosine-1-Phosphate And Long-Term Mortality In Kidney Transplant Recipients

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## Background

Kidney transplantation is the preferred treatment for renal failure; however, recipients face high mortality rates, often due to infections. Sphingosine-1-phosphate (S1P), derived from sphingosine, plays a crucial role in inflammation regulation and cell survival. Elevated S1P levels are linked to reduced severity of infections. Circulating very long-chain saturated fatty acids (VLSFA), which are positively associated with peanut intake and inversely associated with all-cause and infectious disease mortality in kidney transplant recipients (KTR), might contribute to circulating S1P levels. This study aimed to explore associations between plasma sphingosine, S1P, VLSFA, and long-term mortality in a prospective cohort study of stable outpatient KTR.

## Methods

The study included 680 outpatient KTR with a functional graft of 1 year. Plasma sphingosine and S1P were measured with liquid chromatography – mass spectrometry. VLSFA were measured with gas chromatography coupled with a flame ionization detector. Univariate and multivariable linear regression analyses were used to assess the association between sphingosine, S1P and potential determinants. Cox regression analyses were used to prospectively study the associations of sphingosine and S1P with all-cause and cause-specific mortality.

## Results

VLSFA were among the top predictors of S1P (std.  $\beta = 0.13$ ,  $p = 0.001$  in multivariable adjusted analyses). During a median (interquartile range) follow-up of 5.4 (4.8 – 6.1) years, 141 (21%) KTR died with 39 (28%) deaths due to severe infections. Circulating sphingosine was positively associated with infectious disease mortality, with a hazard ratio (HR) (95% confidence interval) per doubling of 1.63 (1.08 – 2.47),  $p = 0.02$ , while S1P was inversely associated with all-cause and infectious disease mortality, with a HR per doubling of 0.54 (0.31 – 0.93),  $p = 0.03$  and 0.17 (0.06 – 0.48),  $p < 0.001$ , respectively, all independent of adjustment for potential confounders. S1P mediated 12% ( $p < 0.01$ ) of the association between VLSFA and infectious disease mortality.

## Conclusions

Circulating sphingosine was positively associated with infectious disease mortality. S1P was positively associated with VLSFA and inversely associated with all-cause and infectious disease mortality. Further studies are needed to assess the effect of VLSFA-containing foods on circulating S1P and on the risk of (fatal) infections in KTR.

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# COVID-19 Booster Triggers Broad Antibody Functionalities In Kidney Transplant Recipients Initially Non-Responsive To Vaccination

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## Background

COVID-19 remains a significant threat to kidney transplant recipients (KTRs), who exhibited weak immune responses to priming vaccine doses due to immunosuppressive therapy. Although additional vaccine doses enhanced SARS-CoV-2-specific immune responses, the



variability in response timing and its impact on the quality of the immune response remains poorly understood. This study aimed to evaluate and compare immune responses between two groups of KTRs: initial responders, who developed antibodies after two priming doses of the mRNA-1273 vaccine, and late responders, who only responded after receiving additional vaccine doses.

### Methods

Age- and sex-matched initial and late responders were selected from the Dutch Renal Patients COVID-19 VACCINATION (RECOVAC) study. Initial responders received two doses of the mRNA-1273 vaccine, with detectable antibodies 28 days after the second dose. Late responders did not seroconvert after the initial doses, but developed antibodies 28 days after additional vaccinations. Serum samples and PBMCs collected 28 days post-initial or booster vaccination were analyzed for antibody and T-cell responses. Specifically, assays were conducted to measure binding antibodies, neutralizing antibodies, and Fc-mediated antibody functions, including antibody-dependent cellular cytotoxicity (ADCC), antibody-dependent cellular phagocytosis (ADCP), and antibody-dependent complement deposition (ADCD). T-cell responses were evaluated by measuring cytokine production by T-cells, specifically IL-21, IFN- $\gamma$ , and various T-helper cytokines.

### Results

Binding antibody levels increased significantly in both initial and late responders 28 days after vaccination ( $p < 0.0001$ ). No significant difference between the two groups in binding antibody levels was detected. Neutralizing capacity was also similar between initial and late responders. Fc-mediated functionalities, including ADCC, ADCP, and ADCD, did not differ significantly between the groups. T-cells did not differ in the production of IFN- $\gamma$  and T-helper cytokines; however, IL-21 production was higher in early responders ( $p < 0.01$ ).

### Conclusions

The study findings indicate that immune responses are comparable between initial and late responders among KTRs. This implicates that KTR who initially did not respond to the COVID-19 priming vaccination, can still develop a qualitatively similar immune response after booster vaccination. Despite eventual antibody development and increased levels after repeated vaccination, the overall immune response remained limited, highlighting a potential constraint in the effectiveness of vaccination in this vulnerable population.

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## Pharmacometabolomics Unveils Incomplete Mycophenolate Mofetil Prodrug Activation In Kidney Transplant Recipients

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### Background

Current immunosuppressive treatment after transplantation commonly includes mycophenolate mofetil (MMF) and a calcineurin inhibitor to prevent graft rejection. As a prodrug, MMF is converted into its active form, mycophenolate (MPA), by the carboxylesterase (CES) enzymes which is considered to occur rapidly and completely. Recent research utilizing the innovative pharmacometabolomics (PMx) technique, however, identified an unknown/unreported MMF glucuronide metabolite in several kidney transplant recipients (KTR), indicating that CES enzyme activity could be saturated or inhibited.

### Methods

Untargeted 'SWATH' PMx data was used to determine relative MMF prodrug abundances (ratio of MMF and glucuronidated MMF signals over the sum of all MMF-related signals) in urine samples from 321 (derivation cohort) and 403 (validation cohort) KTR with PMx confirmed MMF use. Beta regression was performed to associate relative MMF prodrug abundances with clinical participant data. Additionally, *in vitro* experiments using human S9 liver



extract were performed to investigate the influence of potential CES inhibitors on MMF activation.

### Results

Beta regression linked an impaired MMF activation with increasing MMF dose and kidney function as well as with cyclosporine (CsA) use. Regarding the latter, in vitro experiments revealed a decreased MMF activation caused by the pharmaceutical excipient Kolliphor® EL, which is present in CsA capsules, rather than by CsA itself.

### Conclusions

Substantially reduced MMF prodrug activation was observed in large numbers of KTR, potentially due to CES enzyme inhibition or saturation. However, other factors may also affect MMF activation, which require elucidation to improve immunosuppressive therapy.

### Background

Following a kidney transplantation, mismatches between recipient and donor HLA can trigger alloreactivity, which may result in rejection of the transplanted organ. Although the focus lies mainly on the mature protein that is displayed on the cell surface, recent studies have indicated that also the leader peptide of HLA class I alleles, which guides the molecules to the cell surface and is presented by HLA-E, may affect the outcome of a transplantation. The leader peptide of HLA-B contains a dimorphism at position -21, with either a Methionine (M) or a Threonine (T) on the second position of the peptide that is presented by HLA-E. This dimorphism has been shown to affect the outcome of a stem cell transplantation, but the effect on kidney transplantation remains unknown.

### Methods

In this study, we examined the role of this dimorphism on the risk of developing T-cell-mediated rejection (TCMR). The cohort consisted of 351 kidney transplantations performed in our center between 2006 and 2015. HLA typing was available for a minimum of HLA-A, -B, -C, and -DR.

### Results

Recipients homozygous for the -21M leader peptide variant were found to have a significantly increased risk of developing early TCMR (hazard ratio (HR) 4.52, 95% confidence interval (CI) 2.35-8.71,  $p < 0.0001$ ). The impact of this genotype was exclusively observed in the first two weeks after transplantation. In addition, the observed effect was independent of the leader peptide variants present in the donor, as well as mismatching of the HLA-B leader peptide. Strikingly, the hazard ratio doubled among CMV-seropositive recipients (hazard ratio 9.26, 95% CI 4.11-20.87,  $p < 0.0001$ ). Among CMV-seronegative recipients, we did not find a significant difference between the different HLA-B leader peptide recipient genotypes.

### Conclusions

Combined, this study suggests that recipients homozygous for the M-variant of the HLA-B leader peptide have an increased risk of developing early TCMR, an effect that may depend on the CMV serostatus of the recipient. Although these findings need validation and the underlying working mechanism currently remains speculative, this study indicates that the HLA-B leader peptide of the recipient may strongly affect the risk of early TCMR after kidney transplantation.

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# HLA-B Leader Peptide Dimorphism Is Associated With The Risk Of Early T-Cell-Mediated Rejection After Kidney Transplantation

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# Finding The Optimal Sterilization Method For Human Decellularized Livers: Assessing Microbiome, Matrix Proteins, And Biocompatibility

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## Background

Liver tissue engineering holds great promise for addressing the growing demand for transplantable organs. Decellularization technology has been widely used to create liver matrices that may serve as native scaffolds for tissue engineering. However, to meet the quality criteria toward clinical applications, it is essential to assess the presence of microorganisms and potential pathogens. Only then, safety and compliance with medical device regulations is ensured. Sterilization procedures can, however, negatively impact the ECM quality. Therefore, this study aimed to evaluate the effectiveness of five sterilization techniques.

## Methods

Human livers (N=3), deemed unsuitable for transplantation, were decellularized by perfusion with 4% Triton-X-100 and 1% ammonia solution. The resulting ECM was sterilized using Gamma radiation, UV radiation, exposure to Supercritical Carbon Dioxide (sCCO<sub>2</sub>), Peracetic acid, or Antibiotic-Antimycotic treatment. The microbial burden was determined using standardized microbiological methods. The effect on the ECM composition and biomechanical properties, including

collagen content and fiber orientation, was assessed. Crosslinking or denaturation of proteins was studied using two-photon microscopy and collagen staining. Additionally, the biocompatibility of the sterilized matrices was evaluated by measuring cell viability after recellularization with intrahepatic cholangiocyte organoids and HepG2 cells.

## Results

Peracetic acid and UV radiation were not effective to remove micro-organisms, demonstrating a poor sterilization. Assessing how these techniques affected the ECM by microscopy, showed that the overall structure of collagen fibers was altered, and modifications in fiber-to-fiber orientation of collagens were found after exposure to UV and Gamma radiation. Cells remained viable and proliferated in all scaffolds, confirming that none of the sterilization methods affected the biocompatibility of the scaffolds.

## Conclusions

Exposure to UV radiation and Peracetic acid were not effective for sterilization. However, while Gamma radiation did remove microorganisms well, this technique showed alterations in protein composition and fiber orientation. No technique hampered the biocompatibility. We therefore suggest sCCO<sub>2</sub> or Antibiotic-Antimycotic treatment to sterilize scaffolds after decellularization as it results in an overall effective removal of pathogens, while causing only little damage to the matrix proteins. This study demonstrates the importance of sterilization of decellularized liver matrices for tissue engineering and potential clinical applications.

# Everolimus-Based Immunosuppression Leads To An Expansion Of Donor-Specific Regulatory T Cells With A Significant Increase In The Ratio Of Donor-Specific Treg/Teffector Cells

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## Background

Everolimus-tacrolimus-prednisolone maintenance immunosuppression (EVR-IS) allows for a lower trough level of tacrolimus as compared to mycophenolate mofetil-tacrolimus-prednisolone-based immunosuppression (MMF-IS) in kidney transplant recipients. We observed that EVR-IS leads to expansion of regulatory CD4<sup>+</sup> T cells (Tregs) while the effector memory T cell population remains largely unaffected. Previously, we have shown that MMF-IS is associated with progressive loss of donor-specific effector memory T cells, in particular within the CD4<sup>+</sup> T cells. Whether EVR-IS induced changes in T cell subpopulations are reflected in frequencies of donor-specific T cells is not known but important to interpret the clinical significance of Treg expansion.

## Methods

PBMCs from 20 kidney transplant recipients (10 EVR-IS and 10 MMF-IS) prior to, and at 12 and 24 months after transplantation were short-term stimulated with CD3-depleted donor cells. The activation-induced marker CD137 was used to identify donor-reactive regulatory (Treg) and effector (Teff) T cells by multiparameter flowcytometry. Tregs were identified as CD4<sup>+</sup>CD25<sup>++</sup>CD127<sup>-</sup> T cells.

## Results

The proportion of donor-specific Tregs increased in the EVR-IS arm as compared to a decrease in the MMF-IS arm. Average percentages of CD137<sup>+</sup>Tregs at 12 months after transplantation were 0.19% versus 0.05% for EVR-IS versus MMF-IS ( $P < 0.05$ ), respectively. The percentage of donor-specific CD4<sup>+</sup> Teff declined in both treatment arms but at a higher rate for MMF-IS compared to EVR-IS, resulting in 0.14% and 0.06% CD137<sup>+</sup> CD4<sup>+</sup> Teff at M12, respectively. In contrast, within this period the donor-specific CD8<sup>+</sup> Teff decreased by 60% for EVR-IS (from 0.91% to 0.31%) whereas the decline was delayed for MMF-IS and only reached at 24 months. The resulting ratios of donor-specific Tregs/CD4<sup>+</sup> Teff and Tregs/CD8<sup>+</sup> Teff significantly increased ( $P = 0.01$ ) for EVR-IS from 1.2 to 1.9 and 0.3 to 0.9 prior to and at 24 months after transplantation, respectively. Within the MMF-IS arm these ratios decreased after transplantation.

## Conclusions

EVR-IS leads to a significant expansion of donor-specific Tregs combined with a decline over time of donor-specific CD8<sup>+</sup> Teff and CD4<sup>+</sup> Teff. The resulting increase in the Treg/Teff ratio may explain the observation that an EVL-IS regimen allows for lower tacrolimus trough levels.



# Puberty Stage Specific Changes In T-Cell Subpopulations In Healthy Individuals And Pediatric Kidney Transplant Recipients.

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## Background

During adolescence an increase in early graft loss is observed in pediatric kidney transplant(KTx) recipients in comparison to adjacent age-groups, regardless of therapy compliance. Given the importance of T-cell activity in renal graft rejection, we hypothesize that pubertal hormonal changes shift the immune system towards a more pro-inflammatory phenotype. To support this hypothesis, this study explored the changes in T-cell subpopulations over the course of puberty in healthy individuals and KTx-recipients.

## Methods

Healthy individuals, median age 17 years(range: 8-29),and KTx-recipients, at least 1 year post transplantation, median age 16.5 years(range:7 to 30), were included in this multi-center, observational study. Pubertal maturation was assessed by stratifying participants into four different puberty stages(Pre-, early, late, and post-puberty), using skeletal age and Tanner stage. Peripheral blood samples were used to determine multiple differentiation stages of CD4, CD8, and Tcr- $\gamma\delta$  Tcells subpopulations, using 8-color flow cytometry. Differences in absolute cell counts, and relative proportions across puberty stages were tested using the Kruskal Wallis. Post-hoc pairwise comparison between stages was performed using Dunn's test with Bonferroni

correction for multiple testing with statistical significance set at  $\alpha=0.05$ .

## Results

In 66 healthy individuals (42% male, pre-:15%, early-:12%, late-:9%, and post-puberty:64%), absolute naïve CD4 T-cell and recent thymic emigrant(RTE) CD4 T-cell counts decreased over the course of puberty( $p=0.014$ ,  $p=0.021$ ), while absolute CD4 effector memory cell counts increased( $p=0.008$ ). In post-hoc analysis, higher absolute cell counts were observed during early-puberty compared to post-puberty in naïve CD4 T-cells and Tcr- $\gamma\delta$  V $\delta$ 1 T-cells ( $p=0.013$ ,  $p=0.037$ ). In 100 KTx-recipients(61% male, pre-:19%, early-:13%, late-:12%, and post-puberty:56%), similar patterns were observed. Absolute naïve CD4 and naïve CD8 T-cell counts decreased over the course of puberty( $p=0.022$ ,  $p=0.02$ ), with post-hoc analysis observing a significant difference between pre- and post-puberty( $p=0.021$ ,  $p=0.046$ ). In RTE Tcr- $\gamma\delta$  T-cell, absolute counts decreased during puberty( $p=0.006$ ), with post-hoc testing revealing a difference between pre- and post-puberty ( $p=0.007$ ).

## Conclusions

Healthy individuals and KTx-recipients demonstrate a similar shift from a less mature to a more experienced and active immune profile over the course of puberty.

# Biomarkers Of Standard Criteria And Marginal Donor Lungs During Ex Vivo Lung Perfusion: A Comparative Study

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## Background

Ex Vivo Lung Perfusion (EVLP) has become an established method to assess and recondition donor lungs before lung transplantation (LTx). In this study, we explored several biomarkers of standard criteria and marginal donor lungs during EVLP. Novel findings could guide future interventions, such as thrombolysis, to enhance lung quality and expand the donor lung pool.

## Methods

EVLP was performed for minimal 180 min with 18 standard criteria (logistical) and 15 marginal (medical) donor lungs. The following biomarkers were measured in perfusate after 90 and 180 min: d-dimer, Prothrombin Fragment 1+2 (F1+2), Plasminogen Activator Inhibitor-1 (PAI-1), urokinase Plasminogen Activator Receptor (uPAR), IL-1 $\beta$ , IL-6, IL-8, TNF- $\alpha$ , syndecan-1, hyaluronan and Vascular Cell Adhesion Molecule-1 (VCAM-1).

## Results

In the logistical and medical group, 16/18 and 12/15 were transplanted respectively. Both groups showed significantly increased levels of all measured biomarkers. Remarkably, d-dimer, F1+2, uPAR, IL-6, IL-8, syndecan-1, hyaluronan and VCAM-1 were significantly higher in the medical group. Declined donor lungs had significantly higher levels of syndecan-1 and hyaluronan and lower pO<sub>2</sub> compared to all transplanted donor lungs. Lung function during EVLP was similar between the transplanted logistical and medical groups, as primary graft dysfunction (PGD). No significant correlations between PGD were observed.

## Conclusions

Marginal donor lungs sustained more injury as reflected in higher levels of fibrin degradation, pro-inflammatory cytokines, glycocalyx shedding and endothelial activation. Declined donor lungs exhibited significantly higher glycocalyx shedding. Therefore, (marginal) donor lungs could potentially benefit from thrombolysis, reducing inflammation and endothelial preservation during EVLP to further enhance lung quality.

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# Comparative Analysis Of Transcriptomic And Proteomic Responses In Kidney Grafts Undergoing Normothermic Perfusion

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## Background

The shortage of donor kidneys has increased the use of marginal grafts, highlighting the need for better objective viability assessment to ensure successful transplantation. Normothermic machine perfusion (NMP) provides a unique opportunity to evaluate kidney function under

near-physiological conditions before transplantation, allowing for dynamic pre-transplant observation of organ function. This study aimed to understand the relationship between transcriptomics and proteomics during NMP, providing insights into ex vivo kidney physiology and identifying potential biomarkers to improve graft viability assessment and predict transplant outcomes.

### Methods

Thirty pigs underwent double nephrectomy with paired randomization to receive either 75 minutes of warm ischemia or no ischemia, followed by NMP. Renal biopsies were collected at multiple time points (pre-NMP, 1 hour, 2 hours, 3 hours, and 6 hours) for transcriptomic and proteomic analyses. Only genes present in both omics datasets were included for further evaluation. Correlation analysis and unsupervised clustering were used to assess the relationship between tissue-based transcriptomics and proteomics during NMP, focusing on the impact of ischemia and perfusion on kidney physiology.

### Results

Transcriptomics and proteomics analyses revealed distinct temporal patterns throughout the NMP process. Of the 5,600 overlapping gene-protein pairs analyzed, only 27% showed positive correlation between mRNA expression and protein abundance, while 5% showed negative correlation, and the majority (68%) exhibited no clear correlation. The proteomic changes typically lagged behind transcriptomic changes, with an average delay of 3 hours. This temporal delay indicates that mRNA expression changes precede the protein synthesis process. Approximately 20% of gene-protein pairs exhibited similar expression trends, clustering together in unsupervised clustering analysis, suggesting a synchronized response to ischemia and NMP conditions in these genes.

### Conclusions

Proteomic changes lagged behind transcriptomic changes during NMP, with an average delay of 3 hours. This suggests that transcriptomics is a more reliable marker for assessing graft viability during the early stages of NMP. When eventually transformed to point-of-care biomarkers, early transcriptomic alterations may provide rapid insights into the graft's condition, whereas proteomic changes require more time to become evident.

# The Pig As A Translational Model For Renal Normothermic Machine Perfusion: Insights From Transcriptomics And Proteomics

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### Background

Normothermic machine perfusion (NMP) is increasingly being explored as a promising platform for preserving and functionally assessing donor kidneys. However, detailed insights into renal physiology during NMP remain limited, especially regarding its translational relevance across species. Porcine kidneys are often used as a preclinical model to study the effect of NMP. Here, we aimed to investigate the pig as a model for studying human renal NMP by integrating transcriptomic and proteomic analyses.

## Methods

Twenty discarded human and 60 pig kidneys were subjected to six hours of NMP. RNA sequencing and LC-MS/MS analyses were performed on cortical tissue biopsies taken before the initiation of NMP and at 1, 2, 3, and 6 hours of NMP. The differential expression of 50 pre-defined hallmark gene sets was analyzed, summarizing the cellular processes to assess biological activity. By comparing the changes in protein and gene expression over time between human and pig kidneys, the interspecies differences in molecular responses to NMP were assessed.

## Results

Over 6 hours of NMP, 48 out of 50 hallmark gene sets exhibited significant (adj.P<0.05) differential expression in the pig transcriptome, reflecting dynamic cellular changes during perfusion across almost all cellular processes. Importantly, all these transcriptomic alterations demonstrated a positive correlation between human and pig kidneys, with 30 out of 50 being significant (adj.P<0.05). This underscores a strong interspecies concordance in gene expression dynamics under NMP. In contrast, proteomic analyses revealed less pronounced concordance, with 39 out of 50 hallmark gene sets positively correlating, of which four were significant (adj.P<0.05). These were related to stress responses. This highlights a species-specific difference in protein regulation and post-transcriptional mechanisms.

## Conclusions

Our findings suggest the pig is a robust and translationally relevant model for studying renal NMP, particularly at the transcriptomic level. These results provide a framework for understanding the molecular processes underpinning NMP and support using porcine models to optimize clinical kidney preservation and viability assessment strategies. Further investigation into proteomic divergences may reveal insights into species-specific adaptations during perfusion.

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# Hypothermic Oxygenated Perfusion And Static Cold Storage Induce Significant Transcriptomic Changes In Porcine Hearts With Minimal Variation Between Preservation Methods

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## Background

Effective heart preservation is essential for increasing the availability of transplantable hearts and improving outcomes. While techniques like hypothermic oxygenated perfusion (HOPE) are promising, a deeper understanding of the molecular changes in preserved hearts is needed to refine these techniques and develop biomarkers for graft assessment. In this study, we analysed the transcriptional profiles of hearts preserved with static cold storage (SCS) and HOPE, focusing on the molecular mechanisms activated after reperfusion.

## Methods

Twenty-one porcine slaughterhouse hearts were preserved with SCS (n=14) or HOPE (n=7) for 4 hours,



followed by 4 hours of reperfusion with normothermic machine perfusion (NMP). Serial biopsies from the left ventricle were collected during both preservation and reperfusion for bulk RNA sequencing. Differential gene expression analysis and pathway enrichment were performed, comparing temporal gene expression profiles between SCS and HOPE, as well as between surviving and non-surviving hearts in the SCS group. Cardiac function was assessed during NMP, with survival defined by cardiac output > 3 L/min, left atrial pressure < 15 mmHg, and mean aortic pressure > 60 mmHg.

### Results

During NMP, both SCS and HOPE groups exhibited large transcriptomic changes, particularly in pathways related to immune responses and cell death. Interaction analysis showed that these changes were not specific to HOPE or SCS but occurred in hearts preserved by both methods. We observed no significant changes in transcriptomic activity during cold preservation, indicating that transcriptional changes may primarily occur upon rewarming. All hearts in the HOPE group met the survival criteria, whereas only 4 hearts in the SCS group met these criteria. Comparisons between surviving and non-surviving hearts within the SCS group revealed no significant gene expression differences during preservation or reperfusion.

### Conclusions

This study presents the first comprehensive analysis of molecular changes in cardiac *ex vivo* machine perfusion using whole transcriptome analysis. Upregulation of gene signatures associated with ischemia-reperfusion injury were observed during NMP. Despite differences in survival outcomes between SCS and HOPE, the absence of preceding transcriptomic differences suggests survival may be influenced by mechanical or physiological factors. Future studies incorporating proteomics and metabolomics could enhance biomarker discovery and deepen our understanding of preservation effects.

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# Prolonged Ex Situ Oxygenated Hypothermic Machine Preservation In Donation After Circulatory Death Donor Hearts

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### Background

Novel organ preservation strategies including oxygenated hypothermic machine perfusion (HOPE) are shown to successfully preserve donor hearts, and to even extend preservation time in donation after brain death hearts. However, up to date, no serial report is available on prolonged HOPE of donation after circulatory death (DCD) hearts. In this study, we aim to evaluate whether DCD hearts can be successfully preserved using HOPE for a prolonged period.

### Methods

This study is implemented in the existing infrastructure of organ donation in the Netherlands. DCD donor hearts that were declined for clinical transplantation are included. Hearts are preserved for either 4 or 8 hours using HOPE. During HOPE, hearts are continuously perfused with oxygenated XVIVO Heart Solution supplemented with erythrocytes at an aortic root pressure of 20 mmHg and a temperature of 8°C. After preservation,



hearts are evaluated during normothermic machine preservation (NMP, 2 hours) using pressure-volume loop analyses.

### Results

A total of 6 hearts are included in the study: 2 hearts were preserved with HOPE for 4 hours and 4 hearts for 8 hours. All hearts were functionally evaluated during NMP with ex vivo pressure-volume loop analyses. At the end of NMP, mean maximal left ventricular pressure was  $87 \pm 53$  mmHg and  $80 \pm 19$  mmHg in the 4 and 8 hour groups, respectively, at a pre-load of 20 mmHg. End-systolic elastance (Ees) was used for assessment of left ventricular contractility. Mean Ees was  $1.52 \pm 0.2$  mmHg/mL in the 4 hour group, and  $1.57 \pm 0.5$  mmHg/mL in the 8 hour group.

### Conclusions

These preliminary results suggest that a preservation time up to 8 hours with HOPE is feasible and results in comparable left ventricular function when compared to 4 hours of preservation. To draw firmer conclusions we will perform additional experiments and assess more outcome parameters.

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# Optimization Of Donor Kidneys With Sevoflurane During Normothermic Machine Perfusion

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### Background

Volatile anesthetics, like sevoflurane, have shown to reduce ischemia reperfusion injury in various organs, including kidneys, in multiple studies. The potential mechanisms of protection involve inhibition of opening mitochondrial permeability transition pores, protection of the endothelial cells and glycocalyx, inhibition of cell death pathways, inhibition of inflammatory. Normothermic machine perfusion (NMP) of kidneys creates a therapeutic window of opportunity to add pharmacological substances with the aim to reduce injury, enhance repair and detect biomarkers to evaluate organ function before transplantation. We hypothesize that administration of sevoflurane during NMP reduces injury and improves kidney quality.

### Methods

We set-up a slaughterhouse porcine model with administration of sevoflurane using a vaporizer during NMP and tested the feasibility and stability. Then executed 16 experiments (8 paired kidneys, n8/group), with or without sevoflurane. Kidneys were retrieved and subjected 30mins warm ischemia time then flushed with UW solution, preserved cold storage for 24h, after which 6h NMP was initiated. Sevo-NMP group (n=8) was treated with 4% sevoflurane for the first 1h during the 6h NMP while the Control-NMP group was treated without sevoflurane. Perfusate, urine, and tissue samples were collected and physiological measurements were recorded. Two groups data were analyzed with multiple paired t test.

### Results

There are no differences in intrarenal resistance, perfusate flow rate, fractional sodium excretion, lactate, weight gain between two groups. The Sevo-NMP group showed higher urine production at 30mins (p=0.02) and higher oxygen consumption at 60mins (p=0.01). Total protein and cumulative protein in urine in Sevo-NMP group are markedly increased at multiple timepoints. Creatinine clearance in Sevo-NMP group is also higher than Control-NMP group within the first hour. Both AST and LDH in the perfusate of Sevo-NMP group showed significantly higher levels compared to the Control-NMP group at multiple timepoints. Sevo-NMP group 30 min fractional potassium excretion was reduced (p=0.01) while urea in the urine was increased statistically (p=0.05).





## Conclusions

Administration of sevoflurane during the kidney normothermic machine perfusion is feasible. Vaporizer setting 4% of sevoflurane can promote glomerular filtration rate and kidney metabolism but may cause potential renal cell damage.

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# The Creation Of A Cardiac Bioreactor - Ex Situ Heart Perfusion As A Platform For Therapeutic Intervention

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## Background

Attempts at treating heart disease by regenerative therapeutics are hampered by problems associated with delivery of the therapeutic agent to the heart when administered in vivo. However, by isolating the organ in a metabolically and immunologically favorable condition during ex situ heart perfusion (ESHP), it is possible to directly manipulate those factors that complicate delivery of the therapeutic agent and hence improve the success rate of cardiac regenerative therapy. By creating such a cardiac bioreactor, selective and isolated curative treatment of heart disease outside of the body (ex situ) becomes a possibility. In this abstract, we introduce the RegMed XB Cardiovascular Moonshot and discuss our

steps towards the creation of a cardiac bioreactor for curative treatment of heart disease and biological modification of the organ.

## Methods

The influence of hemofiltration and hemoadsorption on quality of normothermic ESHP were assessed. An optimized protocol for normothermic ESHP was designed and successfully used for extended preservation of (very) marginal porcine hearts without decline in graft quality. As a proof-of-concept, mRNA delivery to the heart using lipid nanoparticles during ESHP was tested for biological modification.

## Results

Hemofiltration improved normothermic machine perfusion, while there was no clear benefit of hemoadsorption. Using an optimized perfusion protocol, improved normothermic preservation was achieved and length of ESHP without functional decline of the graft was extended. Successful delivery and translation of mRNA was achieved during 6 hours of normothermic ESHP using lipid nanoparticles.

## Conclusions

We demonstrated that it is possible to successfully preserve and biologically modify hearts for an extended amount of time during ESHP. This opens up the possibility for selective and isolated treatment of heart disease and/or biological modification of heart grafts to improve outcome after heart transplantation.

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# Short Storage Duration And Washing Of Red Blood Cells Improves Liver Functionality During Normothermic Machine

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## Background

Normothermic machine perfusion can be performed to extend preservation time and assess the viability of liver grafts for transplantation. Red blood cells (RBC) form a crucial part of the perfusate in NMP, facilitating the gas exchange needed for metabolism at normothermia. Extended storage lesion of RBCs is detrimental for oxygen kinetics, energy reserves, osmoregulation, and metabolic waste products. Washing RBCs (resuspending in a fresh medium) improves overall morphology and removes accumulated waste products, providing a standardized and improved start to NMP. Therefore, the aim of this study is to investigate the effect of storage duration and washing of RBCs on the functionality of livers in viability assessment criteria during NMP.

## Methods

Between November 2020 and November 2023, 37 liver NMPs were included in this study. NMPs were performed using young RBCs (n=10, storage duration 11–21 days), old RBCs (n=17, storage duration 22–31 days) and RBCs washed with an autotransfusion system (n=10, storage duration 12–31 days). The primary outcomes was functionality in viability assessment criteria in perfusate (glucose, lactate, pH), bile (pH) and delta between perfusate and bile (glucose, bicarbonate, pH).

## Results

Starting perfusate conditions of perfusate using washed RBCs had higher pH ( $p=0.043$ ), and lower lactate ( $p=0.003$ ) and glucose ( $p<0.001$ ). Throughout perfusion, perfusate lactate was higher when using old RBCs ( $p<0.001$ ). Washing RBCs reduced bile ( $p<0.001$ ) and perfusate ( $p=0.009$ ) glucose during NMP, however no differences were found in delta glucose ( $p=0.164$ ). Young RBC perfusions had a significantly higher delta pH compared to old ( $p<0.001$ ) and washed RBCs ( $p=0.004$ ). Delta bicarbonate was also higher using young RBCs compared to old RBCs ( $p<0.001$ ). In young, old and washed RBC perfusions, utilization rate was 90%, 70.6%, and 90% ( $p=0.323$ ), respectively, leading to similar post-transplant rates of non-anastomotic strictures, graft and patient survival.

## Conclusions

Liver NMPs using young and washed RBCs perform better in viability assessment criteria compared to old RBCs. Perfusate composed with washed RBCs did not lead to improvements in viability assessment compared to young RBCs, despite increased resemblance to physiological

electrolyte levels prior to connecting the liver graft. In NMP, RBC condition is critical and potentially influences the decision to transplant a liver.

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# Cardiovascular Risk Management After Solid Organ Transplantation

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## Background

Cardiovascular disease (CVD) is the leading cause of mortality after solid organ transplantation. Dyslipidemia, hypertension and diabetes are risk factors for the development of CVD, and management of these risk factors is therefore essential to prolong patient survival after transplantation. However, recent studies in other populations indicate that there is an underutilization of medication for cardiovascular risk management, in particular lipid lowering therapy.

We aimed to investigate the adequacy of cardiovascular risk management, divided into lipid-, hypertensive- and diabetes management at 1 year after solid organ transplantation. Furthermore, we aimed to investigate whether the cardiovascular risk management differs between solid organ transplant programs (heart, liver, lung, kidney).



## Methods

Cross-sectional data from solid organ transplant recipients 1 year after transplantation were used. The threshold of the cardiovascular risk management parameters, LDL cholesterol, systolic blood pressure (SBP), diastolic blood pressure (DBP) and HbA1c, above which medication is advised, was derived from the national Dutch guidelines for cardiovascular risk management in combination with the guidelines of the departments of the different solid organ transplantation programs. Based on these guidelines, the proportion of patients receiving adequate treatment was assessed.

## Results

We included 1017 recipients (23 heart-, 127 liver-, 143 lung-, and 724 kidney transplant recipients), among which 61.4% males, with a mean age of 57 ±13 years. Adequacy of lipid management differed between the transplant programs ( $p<0.001$ ), with proportions of recipients reaching the target goal of  $<2.6\text{mmol/L}$  ranging from 28% in the lung transplant group to 51% in the kidney transplants group. No between-group differences were observed for antihypertensive management (range 30-42%;  $p=0.12$ ). For diabetes management, significant differences were observed between groups (range 85-100%;  $p=0.01$ ), with the heart transplant recipients showing the highest adherence rate of 100%. Overall, only 16% of recipients met all recommended target values, with no significant differences between organ transplant programs (range 13-22%;  $p=0.52$ ).

## Conclusions

There is still considerable progress to be made in cardiovascular risk management among solid organ transplant recipients, particularly in antihypertensive and lipid management. Opportunities lie with recipients above target values, who are not yet treated or who can benefit from optimisation of treatment.

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# Successful Kidney Transplantation In Patients With Hyperoxaluria: 10 Years' Experience

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## Background

Patients with (enteric) hyperoxaluria are often declined for kidney transplantation because of the high delayed graft function (DGF) and graft failure risk, associated with oxalic acid deposition and toxicity. We established a guideline aimed at prevention.

## Methods

Between 2014-2024, 41 patients with primary or enteric hyperoxaluria with plasma oxalic acid concentration above 40  $\mu\text{mol/L}$  were offered treatment according to the guideline. It was left to the patient and the treating nephrologist whether and in which components of the guideline to participate. The effect of pre-transplant characteristics and participation to (components of) the guideline on DGF and primary non function (PNF) was studied.



Graft and patient survival were compared to a control cohort transplanted in our center in the same period (N=1859).

### Results

Causes of hyperoxaluria were: Primary (n=3), gastric bypass (n=13), pancreatic insufficiency (n=5), other enteric causes (n=16), unknown (n=4). The guideline was followed by 32 patients (78%) regarding dietary oxalic acid restriction; 27 (66%) medication to decrease dietary oxalic acid absorption and deposition in the kidney; 17 (41%) intensification of dialysis before transplantation; 25 (61%) dialysis right before transplantation and 33 (80%) oxalic acid free tube feeding.

Eighteen patients had direct function (44%); 11 living; 3 DBD, 4 DCD donors. Eighteen patients had DGF (44%); 3 living, 5 DBD, 10 DCD donors. Five patients had PNF (12%); 2 living, 2 DBD, 1 DCD donor. The only variables with a significant effect in univariable binary logistic regression analysis on DGF/PNF were: dialysis intensification before transplantation ( $p=0.005$ ), living kidney donation ( $p=0.013$ ) and dialysis in the 24 hours before transplantation ( $p=0.014$ ).

Comparing pre-transplantation characteristics in the hyperoxaluria to the control population, showed significantly more: hemodialysis; time on dialysis; comorbidity.

Significantly more patients in the hyperoxaluria population had DGF/PNF (44% and 12%) compared to the controls (21 and 4%;  $p<0.001$ ). Graft function at month 3 and year 1, graft survival censored for death and patient survival were comparable.

### Conclusions

Kidney transplantation is successful in the majority of this complex hyperoxaluria population. Modifiable factors that decrease the high DGF/PNF risk are: intensified dialysis, living donor transplantation and dialysis in the preceding 24 hours.

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# Unraveling The Impact Of Multiple Mycotoxin Exposures On Post-Kidney Transplant Outcomes Through Uniting Epidemiological And Multi-Omics Designs

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### Background

Mycotoxins are hazardous contaminants produced by molds, capable of inducing a range of adverse health effects, including organ damage, immune dysfunction, and carcinogenesis. Global consumption of plant-based foods may lead to both acute and chronic exposure to mycotoxins, as they can accumulate in ripening crops such as corn, cereals, soybeans, and peanuts, during growth, transport, and processing. This study investigates the impact of multi-mycotoxin exposure on post-kidney transplant morbidity and mortality, informed by dietary surveys from patients with kidney disease.

### Methods

We quantified the mycotoxin levels in plasma samples from kidney transplant recipients (KTR) ( $n_1 = 632$ ) and a control group ( $n_2 = 392$ ) using ultra-high-performance liquid chromatography-tandem mass spectrometry (UPLC-MS/MS) with matrix-matched calibration. Clinical phenotypes were assessed through a multi-omics



approach, incorporating untargeted metabolomics via UPLC-high-resolution MS and functional profiling of microbiomes using shotgun metagenomic sequencing. Advanced machine learning and deep learning techniques were applied for feature selection and integrative data analysis.

### Results

Our preliminary findings indicated the presence of multiple mycotoxins - ochratoxin A (OTA), tenuazonic acid (TeA), enniatin B (EnnB), citrinin, deoxynivalenol, T-2 toxins, cyclopiazonic acid, and zearalenone - in plasma samples from the Dutch population. Notably, the levels of OTA, TeA and EnnB in KTR were significantly higher than those in the control group (Mann-Whitney U test;  $p < 0.01$ ). Additionally, OTA exposure appeared correlated with significant alterations in gut microbial composition, including reduced fecal microbiota diversity, a decrease in the relative abundance of *Firmicutes*, and an increase in the relative abundance of *Proteobacteria* and *Escherichia coli*. KTR with high OTA exposure had significantly lower survival rates than those with low or no exposure (Cox regression; hazard ratio for death, 2.63; 95% confidence interval, 1.07 to 6.42;  $p = 0.034$ ).

### Conclusions

While OTA has long been suspected as a contributor to human nephropathies, our study provides further evidence of OTA toxicity, especially in patients with end-stage kidney disease. Insights gained from this research highlight the critical impact of OTA exposure on post-transplant outcomes. These findings underscore the need for tailored dietary and nutritional strategies aimed at minimizing OTA exposure, which could improve the prognosis and long-term outcomes for KTR.

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# Self-Reported Health And Quality Of Life Among Liver, Kidney, Heart And Lung Transplant Recipients: Insights From The Value-Based Healthcare System

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### Background

Next to survival, Quality of life (QoL) is an important outcome after solid organ transplantation. We investigated differences in patient self-reported QoL and health before and after transplantation and compared QoL and self-reported health between recipients of heart, lung, liver and kidneys.

### Methods

QoL and health was measured via our value-based healthcare system using the PROMIS (Patient Reported



Outcome Measurement Information System) Global Health questionnaire in patients before and after solid organ transplantation between July 2023 and October 2024. The questions (GH01) 'In general, would you say your health is' and (GH02) 'In general, would you say your quality of life is' were scored on a scale ranging from 1 (poor) to 5 (excellent). Statistical analysis of this retrospective data was performed in SPSS.

### Results

The questionnaire was completed by 158 patients before transplantation and 1521 times after transplantation (either once or multiple times per person over time).

The self-reported health rating increased significantly between pre- and post-transplant among lung recipients (mean before 1.94, 1 year after 3.10) and liver recipients (mean before 2.53, 1 year after 3.17). Among kidney recipients there was a significant increase in health rating among those <12 months and >12 months post-transplant ( $p=0.017$ ).

Before transplantation the self-reported health rating of lung patients is significantly lower than that of the liver patients. On the QoL rating pretransplantation, lung patients also score significantly lower than liver patients ( $p<.001$ ). The self-reported quality of life score increased after transplantation, but was only significant among lung recipients ( $p=0.000$ ) and heart recipients ( $p=0.027$ ).

### Conclusions

An increase in QoL is observed in all organ recipients after transplantation. The largest improvement is observed among lung transplant recipients who have the lowest pretransplantation QoL scores. After the initial increase, increases in QoL over time seemed to be limited. Further refinements are needed for data comparability, but the value-based healthcare system already offers valuable insights into large cohorts, proving invaluable for future research.

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# Medication Adherence Among Heart, Lung, Liver And Kidney Transplant Recipients: Insights From The Value-Based Healthcare System

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### Background

Non-adherence to immunosuppressive medication (IS) in solid organ transplantation (SOT) is associated with an increased risk of transplant rejection and graft loss. A joint initiative was taken to gain insight into medication adherence between recipients of different organs with the ultimate aim of promoting adherence in clinic.

### Methods

The Basel Assessment of adherence to immunosuppressive Medication Scale (BAASIS) questionnaire was implemented as a post-transplant patient-reported outcome measure (PROM) in phases from July 2023, starting



with kidney, followed by heart, lung and liver transplant recipients. The BAASIS measures both taking (1 or more missed dosages of IS in the last 4 weeks) and timing (>2 hours before or after agreed time) of medication, persistence (stopped medication without consultation with the healthcare provider (HCP)) and adjustment (changing dosage without consultation with HCP). Recipients received questionnaires 3, 6, 9 and 12 months and yearly after SOT.

### Results

1577 BAASIS questionnaires were completed (response 77%, 60% Male), by 202 heart, 193 lung, 371 liver and 816 kidney transplant recipients. Overall, 11% of SOT recipients were non-adherent on the taking scale (10% heart, 10% lung, 12% liver and 11% kidney transplant recipients). 25% of SOT patients were non-adherent on the timing scale (24% heart, 18% lung, 34% liver and 22% kidney recipients). Liver recipients had a higher incidence of non-adherence in the timing scale, 0-6 months up to 45% and > 10 months up to 35%, whilst other SOT recipients showed an increase up to 27% >12 months. 3 kidney transplant recipients completely stopped their medication without consent from their physician. 15 recipients changed the dosage of IS without consent from or informing their physician (3 heart, 2 liver, 2 lung and 8 kidney recipients).

### Conclusions

Most recipients after SOT take their IS at the correct time, in the correct dosage and do not alter their medication use on their own initiative. More than 10% admitted to be non-adherent. However, the adherence of recipients who did not (yet) complete the questionnaire, remains unknown. BAASIS is a useful tool to stimulate discussion about medication adherence with transplant recipients during their outpatient visits.

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## Diet, Dietary Guideline Adherence And Clinical Determinants Of Diet In Kidney Transplant Recipients

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### Background

Even though diet-related morbidity in kidney transplant recipients (KTR) is high, thorough dietary assessments in KTR are scarce. In this study, we studied diet and dietary guideline adherence in KTR, in comparison to the general population. Furthermore, we aimed to identify KTR at risk for poor diet.

### Methods

We analyzed cross-sectional dietary data from three day food diaries in KTR <1 year after transplantation, from different study centers throughout The Netherlands, obtained at baseline in the Active Care after Transplantation Study (NCT01047410). Food groups and nutrient intake were evaluated according to Dutch food-based dietary guidelines and Dutch Dietary Reference Values. Results in KTR were compared to existing data in the general population. Potential associations of clinical characteristics with dietary intake were assessed using linear regression.

### Results

167 KTR were included (40% female, age 51.9 ± 13.5 years, median [interquartile range] 147 [94-227] days after transplantation). Adherence to dietary guidelines was low for intake of fruits (recommendation: >200 g/



day, median intake [interquartile range]: 110 [41-190] g/day, percentage of the population adhering: 22%), vegetables (recommendation: >200g/day, intake: 137 [83-211] g/day, adhering: 28%), fiber (recommendation: >25 g/day, intake: 20.5 [16.3-25.8] g/day, adhering: 26%) and plant-to-animal protein ratio (recommendation: >50% of total protein intake from plants, intake: 37 [31-45] %, adhering: 12%). Although adherence to guidelines was poor, the diet of KTR was to a large extent similar to that of the general population and slightly healthier in some aspects, including lower intake of salt, red meat, sugary beverages, and soft drinks, along with higher intake of soft fats. Having a deceased donor was associated with lower vegetable intake (st.β (95%CI)=-0.45 (-0.75, -0.14), p=0.004) and polypharmacy (≥5 daily medicines) was associated with a lower plant-to-animal protein ratio (st.β(95%CI)=-0.43 (-0.82, -0.05), p=0.03).

### Conclusions

In summary, dietary guideline adherence in KTR was low and comparable to the poor adherence in the general population. Considering the very high burden of diet-related morbidity in KTR, better dietary adherence deserves priority as a prevention target in this population, in particular in patients with a deceased donor and with polypharmacy.

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# Safety And Efficacy Of PTA And PTA With Stent Placement For Portal Vein Stenosis After Pediatric Liver Transplantation; Findings From The PORTAL Registry

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### Background

Portal vein stenosis (PVS) after pediatric liver transplantation (pLT) is often treated with percutaneous transluminal angioplasty (PTA), optionally with additional stent placement (stent). This study aims to determine the efficacy and safety of PTA and stent.

### Methods

This study included all PTA and stent for PVS after pLT from the Portal vein Obstruction Revascularisation Therapy After Liver transplantation (PORTAL) registry. The PORTAL registry contains data from a 20-year cohort originating from 21 centers across 18 countries on 6 continents. Outcome measures included adverse events (<30 days postprocedural), technical success, and primary- and secondary patency after intervention.

### Results

A total of 181 patients were initially treated with PTA, and 26 with stent. Adverse events did not differ significantly between PTA and stent (all p>0.050). These included bleeding (n=9, 5%), thrombosis (n=5, 3%), infection (n=7, 4%), reintervention (n=4, 2%), retransplantation (n=4, 2%), death (n=8, 4%) and other (n=6, 3%). PTA and stent achieved technical success in 97% and 89%, respectively (p=0.089). One-year primary patency for PTA was 75%, and 84% for stent (p=0.277). 48 patients received endovascular reintervention after PTA, of which 35 PTA and 12 stent. Reintervention with PTA obtained a one-year primary patency of 78%, which was 100% for reintervention with stent (p=0.085). Ten-year secondary patency after PTA and stent, was 97% and 100%, respectively (p=0.978).

### Conclusions

PTA and stent both obtained excellent safety and efficacy, even if performed after a prior PTA. Given its minimally invasive nature, PTA appears to be a particularly favorable modality for addressing PVS after pLT.



# Impact Of Prior Kidney Transplantation On Symptom Burden And Health-Related Quality Of Life In Incident Dialysis Patients

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## Background

Dialysis patients with prior kidney transplantation (KT+) have higher mortality and hospitalization rates compared to dialysis patients without prior KT (KT-). Graft failure can also negatively impact mental health. This study therefore compared symptom burden and health-related quality of life (HRQoL) between KT+ and KT- dialysis patients in the first year of treatment.

## Methods

Adult incident dialysis patients were included in this multicenter prospective cohort study (DOMESTICO). Symptom burden (Dialysis Symptom Index) and HRQoL (Short Form-12) were assessed at initiation of dialysis and three, six, and twelve months later. Linear mixed models, adjusted for confounders, were used to compare symptom burden and HRQoL between KT+ and KT- patients during the first year of dialysis treatment.

## Results

161 KT+ and 1475 KT- patients were included (mean age 55 vs 65 years; mean Charlson Comorbidity Index 3.1 vs 3.8). Symptom burden did not significantly differ between KT+ and KT- patients in the first year of dialysis treatment (mean difference [95% confidence interval] in number of symptoms 0.1 [-0.6; 0.8] and overall symptom severity score 0.8 [-1.5; 3.0]). At dialysis initiation, physical and mental HRQoL were significantly lower in KT+ compared to KT- patients (mean difference with 95% confidence interval [-2.4; -0.9] and -2.0 [-3.7; -0.3], respectively). During the first year of dialysis treatment, physical HRQoL remained significantly lower in KT+ patients (-2.1 [-3.3; -0.8]), but mental HRQoL was not significantly different between groups (-0.8 [-1.9; 0.4]).

## Conclusions

Symptom burden did not significantly differ between KT+ and KT- patients. KT+ patients had lower physical HRQoL at initiation of dialysis treatment and during the subsequent year compared to KT- patients, which suggests that physical HRQoL involves more domains in addition to symptom burden. Mental HRQoL was lower in KT+ patients at initiation of dialysis. Our results indicate that patients with kidney graft failure that (re)initiate dialysis require extra attention to their physical and mental health, especially at the initiation of treatment.

# Psychosocial Care Around Transplantation. (Original in Dutch)

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## Background

In the past 15 years, the number of transplants in the Netherlands has almost doubled from approximately 7,000 to 12,000. The number of dialysis patients (HD/



PD/THD) has remained approximately the same in the same period around 6,000 (1). While the number of dialysis patients has been fairly stable over the past 15 years, the number of transplant recipients has almost doubled. This also has consequences for psychosocial care for transplant recipients in the Netherlands.

### Methods

Research question: What psychosocial care is provided around transplantation and what needs do the transplant patients have? We focused on a number of methods: inventory of the psychosocial care provided in the Netherlands by means of a questionnaire to all social workers working in Nephrology; inventory of the needs of transplant recipients using questionnaires; organization of two focus groups with transplantees to supplement the questionnaires; organization of a focus group with the Renal Social Work Group in the United Kingdom where we looked at how they organized psychosocial care and what we can learn from it.

### Results

From this research we would like to make the following recommendations. These are divided between the regional hospital and the university medical center (UMC). Many of the recommendations are already included in the Kidney Donation and Transplantation Roadmap (2), in which psychosocial care is seen as a standard part of regular care.

### Conclusions

Recommendations for the regional hospital include the following: 1. Do not offer psychosocial care after transplantation on a demand-driven basis, but organize a standard introductory meeting upon return to the regional hospital. 2. Pay more attention to psychosocial care in conversations with nephrologist and nurse practitioner. 3. Introduce PST form as part of the standard psychosocial pre-transplant care (3).

Once the PST is well integrated into the care, the transition from the regional hospital to the UMC for transplantation can occur. 4. A psychosocial sign-out from UMC to the regional hospital is also necessary.

Recommendations for UMCs include: 1. Promote development of expertise of social workers in regional hospitals when it comes to transplant-related psychosocial care. 2. Introduce PST form as part of the standard psychosocial pre-transplant care (4). 3. Organize a standard introductory meeting with the social worker after transplantation. 4. Followup contact after the initial introduction in the first year is considered desirable. This

corresponds to research previously conducted at the UMCU (4).

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## The Heart Dashboard: A New Way Of Monitoring Dutch Heart Transplantation Waiting List, Transplantations And Outcomes

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### Background

In 2023 and 2024 there have been several developments to improve the distribution and analysis of waiting list, donation and transplant information in the Netherlands. In the public domain both trends and characteristics of all organ transplant programs are visible from the middle of 2023. With input from the LOTTO, the NTS developed a lung and heart dashboard. Here, we report trends, patient characteristics and outcomes from the last 10 years from the heart dashboard, which is available since July 2024.





## Methods

Trends in waiting list and transplant numbers over time as well as information about recipient characteristics were obtained using the heart dashboard.

## Results

After an increase in the number of patients listed for heart transplantation from 2015 until 2021, the last three years the waiting list numbers (both on the total as well as on the active waiting list) have dropped. The number of new registrations remained more or less constant, indicating that the decline is due to the increase in the number of transplants. This rise from 38 transplants in 2017-2019 until a record number of 74 transplants in 2023 is possibly related to the start of the DCD heart program in March 2021, as the number of DBD transplants after an initial drop in 2021 remained stable at approximately 31 in the last two years. In 2023/2024 we see that almost 60% of heart transplantations is performed with the heart of an DCD-donor, with very good 1-year graft survival rates. Looking into the characteristics of heart transplant recipients in the last 10 years we see that the majority is male with a non-ischaemic determined heart failure. Most patients are transplanted from a LVAD. The median waiting time until transplantation is 1,4 year (IQR: 0,5-2,6); the longest waiting times are seen in patients with ischaemic heart diseases.

## Conclusions

With the new heart dashboard it is easier to monitor waiting list and transplant trends and identify factors that influence heart waiting list and transplant outcomes.

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# Medication Training Within Transplant Care Pathways. (Original in Dutch)

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## Background

The method of medication training has remained unchanged over the past 25 years, although automated overviews are used instead of written medication cards. The current training method and resources used are no longer in line with the patient's situation, the nurse's working method and the processes within the care pathways.

## Objective

In December 2025, medication coaching will be provided in a structured manner within the transplant care pathways with the support of clear information and the therapy compliance of the newly transplanted patient will be promoted.

## Methods

Project group: The project group is multidisciplinary and there is also the participation of an outpatient pharmacist and client panel members. The project group meets at least once a month.

## Analysis

- 1) Literature research into therapy compliance and questionnaires.
- 2) Experiences from three other UMCs will be shared.
- 3) the current process will be re-evaluated

## Findings

The current method of training does not take into account the patient's acquired knowledge and experience. The patient has a learned method before transplantation. Adjusting learned behavior takes a number of weeks. For the patient, the term therapy adherence has a negative connotation, based on non-adherence. The patient does not receive clear instructions and these are not consistent with the home situation. The medication intake schedule is unclear. The medication box is unclear and not easy to use. The patient information is fragmented and ambiguous. Patients are given a baxter role upon discharge if they do not comply with the medication training. A baxter role in the first phase is high risk. Experiences from the annual prescription project and the benefits of collaboration with the outpatient pharmacy are not used sufficiently.

The point of development are divided into the following topics: Information provision, Medication training and Patient guidance.



## Results

Results so far: 1) A patient information brochure for all transplant patients. 2) The information from the brochure is reflected at other moments in the care pathway. 3) Clarity in who provides what information to the patient and when. 4) Medication coaching instead of training. 5) The patient determines together with the healthcare provider which interventions are the best solution for his/her personal situation. 6) Interventions are followed and evaluated in an unambiguous manner.

## Conclusions

Still to be developed: 1) imbedding in electronic patient record system. 2) Medication coaching in screening phase. 3) Communication with referrers. 4) Additional supporting resources to be developed.

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# Nausea And Pain In Postoperative Living Liver Donors: PCEA Or PCA. (Original in Dutch)

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## Background

Many living liver donors experience a lot of nausea and pain postoperatively. This keeps donors in the hospital longer. To reduce pain after surgery, liver donors receive Patient Controlled Epidural Analgesia (PCEA), which has a side effect of nausea. A Patient Controlled Epidural (PCA) is often used as an alternative in other patient categories and this form of pain relief could also be used in living liver donors, providing adequate pain relief and less nausea.

## Methods

A literature study was conducted in which the PubMed database was searched for studies that compared two groups of living liver donors, a group with a PCEA and a group with a PCA, with regard to nausea and pain. The quality of the included studies was assessed using an assessment form from the Wenckebach Institute. The priority was to obtain a systematic review or RCT. However, there were few studies that included all the criteria, which meant that the quality of the study was omitted.

## Results

Two studies were included, which are retrospective studies. One of the two studies showed that living liver donors with a PCA received significantly ( $p < 0.001$ ) more opiates and had more pain than patients with a PCEA. In addition, patients with a PCEA were more likely to feel nauseous in the morning than patients with a PCA, and vomiting was rare in both patients with a PCEA and a PCA. Another study showed that living liver donors with PCEA needed fewer opiates than the group with PCA and also experienced fewer complaints of nausea and/or vomiting. The PCEA group had a longer hospital stay and longer time to return to a normal diet.

## Conclusions

The PCEA leads to better pain management postoperatively. The studies concluded different results regarding nausea, vomiting and length of stay. It is recommended that more research is conducted on the cause and possible treatment of postoperative nausea and pain in living liver donors to improve postoperative quality and comfort for the patient.



# The PRELIVERT-study: Preoperative pREhabilitation In Patients Planned For LIVER Transplantation

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## Background

Patients who qualify for liver transplantation (LT) are mostly frail due to their underlying liver disease. Frailty is comprised by a decreased functional capacity, impaired aerobic capacity, and sarcopenia. It is well known that frailty leads to both increased pre- and post-transplant morbidity and mortality. For various surgical populations prehabilitation was demonstrated to be feasible, effective, and to improve surgical outcomes. Few studies on this subject have been conducted in the patient population awaiting LT.

## Methods

PRELIVERT is a single-center prospective cohort study. Sixty patients who are anticipated to be wait-listed for LT will be included. Participants will follow an eight-week home-based program consisting of physical training, nutritional guidance, and smoking cessation. Effectiveness will be measured by a cardiopulmonary exercise test, a 6-minute walking test and muscle strength at start and completion of the program. The primary outcome is feasibility of the program, defined as a compliance of at least 75%. Secondary outcomes are effectiveness of the program and postoperative results including length of hospital stay, postoperative complication- and readmission rates. Postoperative outcomes will be compared to a matched historical cohort.

## Results

Patient accrual started in September 2024 and preliminary results are expected for March 2025.

## Conclusions

The PRELIVERT-study is designed to investigate the feasibility of a prehabilitation program in patients anticipated to be waitlisted for LT.

# Evaluating The Impact Of Paramedical Care On Outcomes During The Hospital Phase Of Solid Organ Transplant Recipients : Protocol Of A Systematic Review

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## Background

Organ transplantation is an invasive, high-risk procedure with significant costs. There is increasing focus on improving physical capacity and lifestyle both pre- and post-transplant to enhance transplant outcomes and quality of life, and to reduce the risk of re-transplantation, morbidity, and mortality. Several studies have demonstrated the positive effects of (pre)habilitation on transplant outcomes. However, research focusing on paramedical care (e.g., physical therapy and dietetics) during the hospital phase and its impact remains limited.

To improve our understanding of our paramedical care during the hospital phase, we are working to optimize our paramedical care pathways across the continuum of care, from pre- to post-transplantation. As part of this initiative, we aim to conduct a systematic review of all published studies examining the impact of paramedical care during the hospital phase of solid organ recipients.

### Methods

We will search multiple databases for studies between 1946 up to 08 May 2024. Two independent reviewers screened the references to identify comparative studies that reported on the effectiveness of exercise and nutritional interventions during the in-hospital phase following heart, lung, liver or kidney transplantation. Independent reviewers will extract clinical outcomes, such as re-admissions, length of stay and complications, as well as outcomes related to the exercise intervention, including exercise capacity, muscle strength and nutritional status. A narrative summary will provide an overview of the data.

### Results

A total of 4672 papers met our inclusion criteria. We included 12 RCTs that focused on diverse physiotherapy interventions and 30 RCTs on nutritional support. Both with very diverse interventions and small sample sizes. We will assess the risk of bias of the RCTs with the Risk of Bias tool 2 of Cochrane and rate the certainty of evidence with the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.

### Conclusions

The review will focus on factors that may influence the provision of care and the clinical reasoning process, ensuring that care teams are well-informed. By addressing these critical elements, we aim to support healthcare providers in delivering optimal, patient-centered care throughout the transplant journey and improve their quality of life.

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# Cognitive Testing By Assessment Of Speed Of Forgetting In Solid Organ Transplant Donors And Recipients

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### Background

Many solid organ transplant recipients report to experience impaired memory. Traditional methods assessing cognitive impairment are often confronting for patients, time consuming, costly, and cannot be repeated due to retest effects. We explore a remote, minimally burdensome memory test to assess forgetting speed as a measure of cognitive health in solid transplant donors and recipients. This study aims to evaluate the feasibility of the system, compare cognitive abilities across transplant types, and examine factors linked to cognitive ability.

### Methods

Invitations to participate were sent by e-mail to 3047 participants of a large biobank and cohort study. Participants were asked to complete up to three 8-minute, remote memory assessments in which they memorized picture-term paired associates. For each participant, an individual Memory Index (MI) was inferred from the accuracy and response times measured throughout the session.



## Results

In total, 1444 participants (420 (potential) donors, and 69 heart, 239 liver, 158 lung, 528 kidney, 30 other/combined transplant recipients; mean age=59.6±12.5 years, 47% female), completed at least one memory assessment (response rate: 47.4%). We found that an individual's MI was correlated with age ( $r=-0.45$ ), education level ( $p=0.27$ ), self-perceived memory health ( $r=-0.12$ ) and HRQoL ( $r=0.17$ ), as well as various measures of physical fitness, underlining the sensitivity of the measure. We found that transplant recipients had worse MI scores than donors (77.26±13.52 versus 74.34±13.79,  $P<0.001$ ). Using penalized regression and random forest machine-learning approaches, we found that the MI consistently outperformed traditional neuropsychological assessments in predicting biological markers such as kidney function (eGFR) and AGE Reader cardiovascular risk.

## Conclusions

We demonstrated the feasibility and effectiveness of a remote, low-impact screening tool for the assessment of cognitive health in solid transplant donors and recipients. The response rate suggests high participant engagement. Memory Indexes derived from 8-minute sessions were sensitive to demographic variables, HRQoL, and physical fitness markers, and outperformed traditional neuropsychological assessments in predicting key biomarkers. Overall, our results support the usage of digital screening as a scalable and repeatable measure of cognitive health.

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# Migration, Organ Transplantation And Organ Trade: Exploring The Health-Related Harms And Needs Of People Who Sell Their Kidneys And Of Individuals With End-Stage-Renal-Disease In A Migration Context.

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## Background

The number of forcibly displaced people is proliferating globally. Concurrently, there is a growing scarcity of organs for transplantation. This scarcity is fuelling a global trade in organs that mainly consists of trade in living donor kidneys. Research suggests that in particular migrants are vulnerable to being targeted to sell their kidneys. Also, migrants experiencing chronic kidney disease, in particular those with end-stage-renal-disease (ESRD) face barriers in access to dialysis and transplantation. However, research addressing the health-related harms and needs of migrants who sell their kidneys and of migrants with ESRD is scarce. There is also limited research that addresses the experiences and needs of healthcare providers who care for these populations. In this study protocol we outline three main aims: (1) explore the physical, psychological, and socio-economic health-related harms and needs of migrants who consider or have engaged in kidney sale; (2) investigate the health-related harms and needs of migrants



experiencing ESRD; and (3) examine the experiences, knowledge, and needs of healthcare professionals providing care to these groups.

### Methods

This study will be conducted from 2025 until 2029 through qualitative fieldwork in The Netherlands, Jordan, Tunisia, Turkey and Spain. These countries are selected because they host high numbers of migrants and/or because they report kidney sales. Semi-structured interviews will be conducted with migrants who have sold a kidney/considered selling their kidney, with migrants experiencing ESRD and with healthcare providers who treat these migrants. Respondents will be recruited at locations such as asylum centres, refugee camps, dialysis clinics, hospitals, and NGOs.

Data will be analysed through a mixed inductive and deductive approach, wherein theories will be derived from the collected data, while also applying theoretical models related to migration, mental -and -physical health to interpret the data. This approach allows us to capture the multi-layered context of migration and health vulnerability.

### Results

The abstract presents a study protocol, no results is available yet.

### Conclusions

Results will offer insights and improve understanding of migrants' needs, ultimately guiding policies and healthcare practices to enhance support and services for migrants facing health disparities and exploitation in organ transplantation.

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# Equity In Kidney Transplant Allocation For Antillean Patients Within Eurotransplant

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### Background

The Antilles are a group of islands in the Caribbean that are still part of the Kingdom of the Netherlands. The population of these islands is ethnically diverse, shaped by the historical transatlantic slave trade and migration. Since 1998, patients with kidney failure residing on these islands can enter the waiting list of Eurotransplant. However, the Eurotransplant donor database consists mainly of donors of Caucasian descent, which may result in a smaller donor pool for patients from the ethnically diverse Antilles. We compared the prevalence of broad HLA antigens between patients residing on the Antilles, patients residing in the Netherlands and Eurotransplant kidney donors.

### Methods

A cross-sectional analysis of the Amsterdam kidney transplant waiting list as of 14-03-2024 was conducted. Patients residing on the Antilles or in the Netherlands were compared with deceased donors screened between January 2021 and January 2024. The primary outcome was the prevalence of broad HLA antigens and the percentage of overlap between patient groups and donors. Secondly a ratio between the prevalence of broad HLA antigens between patient groups and the donors was calculated. Descriptive statistics, a Mann-Whitney U test and a Brown-Forsyth test were used to analyse the data.

### Results

A total of 186 patients on the waiting list and 295 donors were included to assess HLA prevalence. The overlap of broad HLA antigen prevalence with the donors was 75.8% for Antillean patients as compared to 87.7% for Dutch patients. The ratio's calculated were not significantly different. However, the variance of the ratio's between groups was found to be significantly different ( $p = 0.04$ ).

### Conclusions

Patients residing in the Antilles on the Eurotransplant waiting list appear to have a lower compatibility with donors, in terms of broad HLA antigens, compared to patients residing in the Netherlands. This suggests a different distribution of (more rare) broad HLA antigens among the Antillean population. Such a disparity may lead to a reduced donor frequency and potentially longer waiting times for Antillean patients. To explore this further, we will investigate differences in donor frequency





and waiting times between patients living in the Antilles and those living in the Netherlands.

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## Impaired Hand Dexterity And Mortality Risk In Kidney Transplant Recipients.

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### Background

Hand dexterity, a physical function which requires the interplay between sensory and motor function of the human body, is frequently impaired among kidney transplant recipients (KTR). Impaired hand dexterity is associated with worse daily functioning, and we hypothesize that it is also a marker of overall tissue damage. To test this hypothesis, we set out to investigate whether impaired hand dexterity is associated with mortality in KTR.

### Methods

Prospective data of outpatient stable ( $\geq 1$ -year post-transplant) KTR were included. Impaired hand dexterity was defined as a time required to complete the 9-hole peg test longer than the 95<sup>th</sup> percentile of an age- and sex-matched reference population. Cox regression analyses were performed to assess the association with mortality.

### Results

We included 309 KTR (mean age 55 $\pm$ 13 years, 42% female). The prevalence of impaired hand dexterity was 23%. After a median follow-up time of 6.0 years [IQR 4.1- 7.1 years], 67 (22%) of these patients died. In univariable analysis, impaired hand dexterity was significantly associated with increased mortality (Hazard Ratio [HR]: 2.16, 95% CI: 1.31 – 3.57,  $p=0.0026$ ). This association

remained independent of adjustment for potential confounders, including age, sex, time since transplantation, eGFR, donor type, history of dialysis, and diabetes (HR: 2.17, 95% CI: 1.29 – 3.68,  $p = 0.0037$ ).

### Conclusions

Impaired hand dexterity is independently associated with an increased risk of mortality in KTR. Hand dexterity assessment may, therefore, be of interest as a potential test to be included in follow-up of KTR and deserves inclusion in future studies.

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## Everolimus-Based Immunosuppression Allows For Regulatory T-Cell Expansion While Maintaining Effector Memory T-Cells

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### Background

Everolimus (EVR) is known for its limited nephrotoxicity and potential to employ tolerance-inducing mechanisms as compared to mycophenolate mofetil (MMF) following



transplantation. EVR might be beneficial for elderly patients with increased frailty and comorbidity, presenting with a different risk profile for kidney transplantation. The aim of this study was to evaluate the T-cell differentiation and exhaustion marker profile after kidney transplantation in everolimus-tacrolimus-prednisolone (EVR-IS) compared to standard MMF-tacrolimus-prednisolone immunosuppression (MMF-IS).

### Methods

Blood samples were collected prior to and at month 12 and 24 after kidney transplantation in the multicenter OPTIMIZE study (EudraCT number: 2018-003194-10). Recipients of  $\geq 65$  years at time of transplantation were randomized to either MMF-IS or EVL-IS. Circulating T-cells (N=86 EVR-IS and N=83 MMF-IS) were characterized in detail for differentiation status, transcription factor expression and exhaustion markers using multiparameter flowcytometry. Data were analyzed by assessing predefined T-cell subsets and marker expression and by unsupervised analysis (FlowSOM).

### Results

MMF-IS resulted in a significant decrease of % of central (CD45RA-CCR7+, Tcm) and effector (CD45RA-CCR7-, Tem) memory CD4+ as well as CD8+ T-cells and regulatory CD4+ T-cells (CD25++CD127-, Tregs) at M12 which stabilized at M24. In contrast, EVR-IS lead to an increased proportion of Tregs at M12 ( $P < 0.05$ ) while % of CD4+ and CD8+ Tem remained stable after transplantation. Unsupervised analysis of the data revealed 3 clusters of cells to be significantly different comparing EVR-IS to MMF-IS at M12, largely confirming the traditional analysis. One cluster corresponded to Tregs (2.4-fold higher in EVR-IS). Another cluster consisted of CD4+ T-cells with characteristics of less differentiated (CD27dimCD28+) Tem co-expressing the proliferation marker Ki-67 (1.9-fold higher in EVR-IS) and the third cluster contained CD8+ T-cells with a terminal differentiated Tem profile co-expressing the transcription factor Tbet, (2-fold lower in EVR-IS). The expression of exhaustion markers did not differ between the two arms with no significant changes in time after transplantation.

### Conclusions

EVR-IS leads to expansion of Tregs whereas % of CD4+ and CD8+ Tem are maintained, in contrast to the effects of MMF-IS. The data suggest that tolerance induction by EVR could be an important mechanism which allows for lower levels of tacrolimus in elderly transplant recipients.

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# One-Year Outcomes Of Hepatic Artery Stenosis After Pediatric Liver Transplantation: Results From An International, Multicenter, Real-World Registry

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### Background

Hepatic artery stenosis (HAS) after pediatric liver transplantation (pLT) could lead to progression to hepatic artery thrombosis, graft failure, biliary complications, and death. However, there is a lack of robust studies investigating outcomes of HAS after pLT. This study aimed to determine one-year graft and patient survival rates and identify risk factors associated with adverse outcomes in patients who develop HAS after pLT.

### Methods

We analyzed data from patients who developed HAS after pLT from the HEPatic Artery Stenosis and Thrombosis after Liver Transplantation in Children registry. This registry includes data from 24 centers across 20 countries and six continents, spanning a 20-year period during which 8,469 pLTs were performed. Clinical characteristics were examined at three timeframes: pre-transplant, immediate post-transplant, and after HAS diagnosis. Risk factors for graft loss and mortality after HAS were identified using multivariate Cox regression analyses, with model assumptions verified using Schoenfeld residuals.



## Results

HAS was reported in 119 patients (estimated 1.4%; 51% female; median age 4.2 years). The overall one-year graft and patient survival rates after HAS diagnosis were 93% (95% CI: 89–98) and 97% (95% CI: 93–100), respectively. Multivariate Cox regression analysis identified dialysis requirement at HAS diagnosis as the sole independent risk factor for both one-year graft loss ( $p < 0.01$ ) and mortality ( $p = 0.01$ ).

## Conclusions

HAS after pLT is associated with favorable one-year outcomes, with risk factors for unfavorable outcomes generally lacking. In patients requiring dialysis at the time of HAS diagnosis, other factors are more likely to contribute to multi-organ failure and poor outcomes. Future studies are needed to identify best clinical practice and treatment strategies for patients with HAS.

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# Fractionated Dosing Of Prednisone To Prevent Hyperglycemia After Liver Transplantation. (Original in Dutch)

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## Background

In postoperative orthotopic liver transplant (OLT) patients at the University Medical Center Groningen, Prednisolone is prescribed from day one post-operatively to prevent rejection of the new liver. The immune system is well suppressed, but the side effects of Prednisolone cause complications for the patient. One of these is the development of hyperglycemia. In practice, the question has arisen whether there is added value to administer a fractionated dose of twice daily (BD) instead, without reducing the effectiveness of Prednisolone.

## Methods

Based on a literature search, the PubMed database was searched for studies relating to Prednisolone use in transplant patients. The articles were assessed for quality.

## Results

Of the 25 studies, two studies were ultimately included. The study by Yates et al. was a blind RCT in which 44 kidney transplant patients were included and randomized into an intervention (BD) and control group (once daily, QD). Mean blood glucose was lower in the BD group compared to the QD group ( $7.9 \pm 1.7$  vs.  $8.1 \pm 2.3$  mmol/L,  $p < 0.001$ ). In addition, median peak blood glucose times were lower in the BD group than in the QD group (BD) ( $10.4$  [9.5, 11.4] vs.  $11.4$  [10.3, 13.4] mmol/L,  $p < 0.001$ ). The study by Decker et al. had an observational design, in which 51 patients (16 kidney transplant and 35 glomerulonephritis) from the QD group required more anti-diabetic medication compared to the BD group ( $p = 0.008$ ). These were mainly kidney transplant patients, whose kidney function did not deteriorate. In the BD group, a lower amount of Prednisolone was given per day compared to the QD group, without causing rejection ( $p = 0.008$ ).

## Conclusions

Prednisolone with twice daily dosage appears to have a positive effect on the number of days in which (kidney) transplant patients experience hyperglycemia and does not appear to have an adverse effect on the (kidney) transplant. Nevertheless, a follow-up study in OLTs with more patients is desirable to confirm the conclusion in practice.

# Caveat Of Biliary Ph As Biomarker Of Bile Duct Viability During Normothermic Machine Perfusion Of Donor Livers

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## Background

*Ex-situ* normothermic machine perfusion (NMP) enables assessment of livers before transplantation. Many groups include hepatocyte assessment criteria, with an increasing interest in biliary pH for cholangiocyte viability. However, when measuring biliary pH, we have noted variations in the results depending on the time interval between collection and processing of samples, questioning the robustness of biliary pH as a biomarker. Our aim was to determine the impact of carbon dioxide (CO<sub>2</sub>) exchange between bile and air on biliary pH and whether the method of bile collection and processing can influence the measured pH value.

## Methods

We prospectively analyzed the composition of bile samples collected with or without the use of mineral oil (MO) during NMP and during liver surgery. Bile samples were analyzed for partial pressure of CO<sub>2</sub> (pCO<sub>2</sub>), pH, bicarbonate (HCO<sub>3</sub><sup>-</sup>) and glucose immediately as well as 5, 10, 15 and 30 minutes after collection. Continuous data were presented as median and interquartile range (IQR).

## Results

Bile was collected during seven NMP procedures and from five patients undergoing liver surgery. In bile

collected without MO, biliary pCO<sub>2</sub> decreased with increasing time between collection and analysis. In parallel, biliary pH increased. In bile collected under MO, the decrease in biliary pCO<sub>2</sub> was less pronounced and biliary pH remained stable. The difference in biliary pH was clinically meaningful, as biliary pH was 7.47 (7.43-7.58) after 30 minutes in samples collected under MO, compared to 7.70 (7.58-7.90) when samples were collected without MO. In contrast to pCO<sub>2</sub> and pH, HCO<sub>3</sub><sup>-</sup> and glucose values remained stable over time in both groups and no significant differences were observed between the two sampling methods.

## Conclusions

This study indicates that biliary pH is critically influenced by diffusion of CO<sub>2</sub> from bile samples after collection. If biliary pH is used as a viability marker during NMP, it is crucial to prevent interface contact between bile and ambient air. We advocate to collect bile under MO and to analyze samples as quickly as possible, preferably within 5 minutes.

# Carboxyhemoglobin, Smoking Exposure, And Mortality In Kidney Transplant Recipients

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## Background

Smoking increases mortality risk in kidney transplant recipients (KTRs). KDIGO recommends annual tobacco use screening for KTRs. However, self-reported smoking

is often unreliable, and urinary cotinine testing as the golden standard is costly. Carboxyhemoglobin (COHb) has emerged as a reliable and effective biomarker for identifying active smokers in KTRs. This study aims to investigate the association between COHb levels, smoking exposure, and mortality in this population.

### Methods

Plasma COHb was obtained from blood gas analysis. Smoking status was determined by a questionnaire. Cox regression analyses were performed to evaluate the association with mortality.

### Results

Among 1328 stable KTRs (mean age  $57 \pm 14$  years, 49% female, median time post-transplant 12 [IQR 12-85] months), the median COHb level was 0.93% [IQR 0.83-1.23%]. The prevalence of active smokers and delayed graft function were higher following the increasing COHb level ( $p = 0.025$  and  $p < 0.001$ , respectively). Triglyceride, C-reactive protein level, and urinary albumin excretion were significantly higher following the increasing COHb level ( $p < 0.001$ ,  $p < 0.001$ , and  $p = 0.026$ , respectively). Kidney function did not differ following the increasing COHb level. During a median follow-up of 4 years, 189 (14.2%) patients died. Higher COHb level was independently associated with higher mortality risk (hazard ratio [95%CI] per standard deviation increase = 1.23 [1.11-1.37],  $p < 0.001$ ). This association remained significant independent of adjustment for potential confounders, including smoking status.

### Conclusions

COHb, which was previously known as a reliable biomarker for detecting active smokers and more accessible than urinary cotinine, is independently associated with a higher risk of mortality in KTRs.

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## Electronic Nose For Detecting Impaired Glucose Metabolism In Heart Transplant Recipients

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### Background

Post-transplant diabetes mellitus (PTDM) is very common in heart transplant recipients (HTR), with a 5-year post-transplant incidence of 34%. PTDM is associated with increased risk for severe renal dysfunction, retransplantation and death. As such, early recognition of PTDM is warranted. An oral glucose tolerance test (OGTT) is the preferred test to screen for both prediabetes and diabetes. However, an OGTT is time-consuming and cumbersome which can discourage patients from screening procedures. As potential alternative and less burdensome test to distinguish between normal and impaired glucose tolerance, we assessed the diagnostic accuracy of exhaled breath analysis using an electronic nose (eNose) to distinguish between normal and impaired glucose tolerance.

### Methods

HTR, more than 1 year post-transplantation, who underwent OGTT screening were included. A positive control group consisted of known diabetic HTR who were fasting at time of the measurement. Exhaled breath analysis was performed using an eNose (SpiroNose) pre-glucose loading. eNose parameters were combined with clinical relevant parameters for PTDM (time after HTx (in years),



fasting glucose level (mmol/L), Prednisolon use, weight (kg)) in a multivariate logistic regression model.

## Results

In total, 67 HTR were included; 31% were female, median age was 57 [range 40–65] years, time after transplantation was 7.9 [3.5–12.5] years. Of these HTR, 17 had a normal test (fasting glucose 5.3 [4.3–5.8] mmol/L; HbA1c 35 [29–39] mmol/mol), 26 prediabetes (fasting glucose 5.9 [4.6–7] mmol/L; HbA1c 41 [32–50] mmol/mol) and 24 PTDM (fasting glucose 7.8 [4.4–17] mmol/L; HbA1c 57 [35–96] mmol/mol), indicating that 75% of the tested patients had impaired glucose metabolism (prediabetes or PTDM).

Pre-glucose loading, eNose alone discriminated between normal and impaired results with an AUROC of 0.68 (95% CI 0.53–0.82), 69% accuracy, 70% sensitivity, and 65% specificity. Incorporating clinical parameters improved performance to an AUROC of 0.88 (95% CI 0.79–0.96), 77% accuracy, 70% sensitivity, and 100% specificity.

## Conclusions

Impaired glucose metabolism is a frequent finding in HTR. Exhaled breath analysis using eNose technology has the potential to non-invasively monitor HTR for impaired glucose tolerance. To possibly replace OGTT as a screening tool further confirmation in a larger cohort is warranted.

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# Systematic Review & Meta-Analysis: Pre-Lung Transplantation Body Composition And Post-Lung Transplantation Outcome

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## Background

Lung transplantation (LTx) is a life-saving intervention for patients with end-stage pulmonary disease. Patients referred for LTx undergo evaluation of their medical and physical suitability. The impact of pre-transplantation body composition on post-transplant outcomes is increasingly recognized. However, guidance regarding body composition measures is lacking.

Studies have indicated that not just the quantity, but also body fat distribution and proportion of lean muscle mass can influence short and long-term outcomes in different solid organ transplantation. Therefore, this study aimed to systematically assess the relationships of various body composition parameters before LTx with outcomes post-lung transplantation, including hospital and ICU length of stay, duration of mechanical ventilation, and short-term and long-term mortality.

## Methods

A systematic literature search was performed in six databases for articles until the 22nd of April 2024. We included studies on LTx recipients (age > 18 years) providing an association between pre-transplant body composition parameters and post-transplant outcomes. A meta-analysis was performed on the articles assessing the relationship between BMI classification and all-cause mortality.

## Results

41 articles met the inclusion criteria, of which five articles were included in the meta-analyses. In the multivariate analysis, being underweight was significantly associated with increased all-cause mortality (pooled HR of 1.35 (95% CI, 1.10–1.66,  $I^2=0\%$ ,  $p$ -value < 0.001). Overweight and obesity were not significantly associated with mortality (pooled HR of 1.06 (95% CI, 0.94–1.19,  $I^2=0.01\%$ , 1.15 (95% CI, 0.69–1.89,  $I^2=70\%$ ), respectively). Other studies reported that a favorable change in BMI was more predictive of mortality than baseline BMI. Low albumin was associated with post-operative parameters and was stated as a more sensitive marker of malnutrition because BMI changes more slowly. Multiple studies showed that quality and quantity of muscle measured by CT scans were associated with short-term post-transplant outcomes and survival.





## Conclusions

Various body composition parameters are associated with post-transplant outcomes. Due to the considerable heterogeneity among the studies and the absence of comparative analyses across different body composition metrics, no conclusions can be drawn regarding which measures provide the best yield. For future studies, we recommend focusing on mutual comparison between body composition parameters and outcomes to support clinical recommendations in future guideline development.

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# Heart Failure Post Lung Transplantation: A Single Center Experience

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## Background

Lung transplantation (LTx) is a treatment option in carefully selected patients with end-stage respiratory failure. Prior to LTx, a thorough assessment of cardiovascular comorbidities will take place, with heart failure being a contraindication to LTx. Despite extensive cardiovascular examination prior to LTx, there is a group of patients who develop heart failure after LTx when they are stable and in follow-up at the outpatient clinic. New-onset heart failure (HF) is a condition that affects quality of life and limits survival post LTx.

There is limited data on HF postLTx. Therefore, investigate the incidence and risk factors of heart failure after LTx.

## Methods

We retrospective included all LTx patients between 2018 and 2023. Heart failure was assessed by echocardiography and defined accordingly A left ventricular ejection fraction (EF) <40%; called HFrEF. An EF 41-49% is called HFmrEF, and an EF >50% with diastolic dysfunction is called HFpEF. Multivariable regression was performed. With known riskfactors for heart failure: hypertension, atrial fibrillation, endocrine causes, and medications such as corticosteroids. Data were analysed using spss 28.

## Results

In this study 218 LTx patients were included, 117 male. The median age was 58 years (51-62). Twentytwo, patients developed heart disease. Heart diseases such as chronic atrial fibrillation (n=4), Dressler's syndrome (n=4), pericarditis constructiva (n=3), and STEMI (n=1) were excluded from the analysis. Of the 218 patients, 4 patients developed HFrEF 3 patients developed HFmEF en 3 patients developed HFpEF. A total of 10 patients (4%) developed one of the three forms of heart failure.

Seven of these patients were men. The median time to onset of HF after transplantation was 23 months. Age, sex, transplant indication, BMI, pack years, atrial fibrillation post transplantation, hypercholerolemia or NTprobnp did not predict HF post LTx.

## Conclusions

The incidence of heart failure post-LTx is 4%. In our single center retrospective study we couldn't identify risk factors for the onset of heart failure post LTx. However a national survey would increase our knowledge of HF post LTx.

# Urinary Polyamines Are Associated With Reduced Risks Of Graft Failure And Mortality In Kidney Transplant Recipients

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## Background

Polyamines are polycationic molecules derived from amino acids that are essential in cellular processes such as growth, differentiation, and DNA stability. In kidney disease, polyamines are involved in regulating oxidative stress, inflammation, and immune responses, which are key factors in kidney transplantation outcomes. We evaluated the associations of urinary polyamine excretion with graft failure and mortality in kidney transplant recipients (KTR).

## Methods

We conducted a prospective cohort study of 589 outpatient KTR with a functioning graft of beyond one year. Baseline clinical data, dietary intake data, and laboratory and urinary polyamine measurements were collected.

## Results

In multivariable association of dietary intake and urinary polyamine excretion, total protein, fiber, and alcohol intake showed positive associations with urinary N<sup>1</sup>-acetylspermidine, N<sup>8</sup>-acetylspermidine and N-acetylputrescine (St.  $\beta > 0.05$ ,  $p < 0.05$ ).

During a median follow-up of 8.2 years, 98 KTR developed graft failure. Longitudinal analyses showed that N<sup>1</sup>-acetylspermidine (HR: 0.64 [95% CI: 0.49-0.84]) and N<sup>8</sup>-acetylspermidine (HR: 0.64 [95% CI: 0.46-0.88]) had a strong inverse association with graft failure after

adjusting all confounders. Urinary N<sup>1</sup>-acetylspermidine excretion presented significant interaction with eGFR. For urinary N<sup>8</sup>-acetylspermidine excretion, significant interaction with total alcohol intake was observed.

During a median follow-up of 8.2 years, 157 KTR died. Higher urinary total polyamines (HR: 0.59 [95% CI: 0.45-0.77]), N<sup>1</sup>-acetylspermidine (HR: 0.69 [95% CI: 0.58-0.81]), N<sup>8</sup>-acetylspermidine (HR: 0.61 [95% CI: 0.51-0.74]) and spermidine (HR: 0.76 [95% CI: 0.62-0.92]) excretion were associated with lower risk of all-cause mortality after adjustments. Significant interaction was found between urinary total polyamine excretion and proteinuria with the risk of mortality. Urinary N<sup>1</sup>-acetylspermidine excretion showed an interaction with antihypertensive use. Urinary spermidine excretion demonstrated significant interactions with proteinuria.

## Conclusions

Urinary N<sup>1</sup>-acetylspermidine and N<sup>8</sup>-acetylspermidine excretion were independently associated with reduced risks in long-term graft failure and all-cause mortality. Further researches are needed to investigate whether urinary polyamines are modifiable factors for long-term graft outcomes in different populations.

# Effect Of Antithymocyte Globulin Treatment On Transplant Function In Lung Transplant Patients With Progressive Chronic Lung Allograft Dysfunction

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## Background

Chronic lung allograft dysfunction (CLAD) remains a leading cause in limiting long term survival post lung transplantation (LTx). In LTx patients with progressive CLAD, not responding to initial augmentation with methylprednisolone, no consensus for treatment exists. One option is cytolytic therapy with antithymocyte globulin (ATG), a polyclonal T-lymphocyte immunoglobulin. It depletes circulating T-lymphocytes, prompts apoptosis of B-cell lineages and modulates cell surface interactions that mediate the leukocyte endothelium interaction. These mechanisms are thought to be contributing to the development of CLAD. The aim of this study is to determine the effect of ATG therapy on transplant function and survival or re- LTx in patients with progressive CLAD.

## Methods

We evaluated retrospectively all patients who received a LTx between 2004 and 2022 in our center. LTx patients included had progressive CLAD defined as failure to stabilize lung function after initial augmentation with methylprednisolone and were treated with ATG. Patients who received ATG were divided into responders and non-responders. Response was defined as stabilization or improvement of FEV1 six months post-ATG treatment compared to the last FEV1 measurement prior to ATG treatment. Non-response was defined as a further decline in FEV1 > 5% 6 months -post ATG treatment compared to the last FEV1 measurement prior to ATG treatment. Survival was assessed by Kaplan-Meijer analysis.

## Results

A total of 672 patients received a LTx. From these patients 26 patients (3.9%) had progressive CLAD and were treated with ATG. From these patients 15/26 (58%) were responders. Responders showed a significantly higher median FEV1 at 6 months post ATG 1,73L (1,12 L-2,59 L) compared to the non-responder's 0,93L (0,73L-1,53L),  $p = 0.02$ . The effect on FEV1 persisted the first year after ATG and patients remained in the same CLAD stage. Long-term survival or time to re-transplantation was significantly better in responders when compared to non-responders.

## Conclusions

In LTx patients with progressive CLAD, administration of ATG was effective in more than half the patients limiting further progression of CLAD and improved long-term outcome. Further research should focus on predictors of improved outcome in order to select LTx patients in an early stage of CLAD who might benefit from ATG.

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# SCARCE: aSymptomatic respiratory viral Carriage in pre-lung transplant patients and the effect on eArly-post lung tRansplant Course

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## Background

Community acquired respiratory viruses (CARV) can be found in asymptomatic persons. Lung transplant (LTx) recipients are at particular risk for CARV due to their high immunosuppressive regimen. We analyzed CARV carriage in LTx candidates immediately pre-LTx and studied its influence on the early post-LTx course in recipients transplanted while positive for a CARV.

## Methods

All adult LTx recipients transplanted from January 2017 to August 2023 were included. Routinely obtained pre-LTx



viral swabs were tested for a CARV. Data were collected from the LTx database and Electronic Patient Records. Primary outcome was incidence of primary graft dysfunction (PGD) 72 hours post-LTx. Secondary outcomes were duration of mechanical ventilation, intensive care unit (ICU) length of stay (LOS), total hospital LOS, 30-day and 90-day mortality rate, PGD at 48 hours and rejection therapy within the first month post-LTx. Statistical analyses were done using Mann-Whitney U test for quantitative variables and Fisher's exact or Chi-square test for qualitative variables.

### Results

23 (10.4%) out of 222 LTx recipients tested positive for a CARV pre-LTx. Viruses found were rhinovirus (43.5%, n=10), SARS-CoV-2 (21.7%, n=5), other coronaviruses (13.0%, n=3), para influenza virus (13.0%, n=3) and human metapneumovirus (8.7%, n=2). Overall, 10.8% of recipients developed PGD grade 2-3 at 72h. Recipients who were CARV-positive had a 9.5% incidence of PGD grades 2,-3, compared to 10.9% in CARV-negative recipients ( $p = 1.00$ ). Duration of mechanical ventilation, ICU LOS, total hospital LOS, 30-day and 90-day mortality rate, and occurrence of acute rejection did not differ between both groups.

### Conclusions

We found no association between asymptomatic pre-LTx viral carriage and early post-LTx outcomes, suggesting routine CARV testing in asymptomatic candidates is unnecessary and may lead to unwarranted refusals with increasing waiting list mortality. Therefore, we do not recommend routine pre-LTx CARV testing.

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# Outcomes And Management Strategies Of Pregnancies After Heart And Lung Transplantation Across Europe

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## Background

Knowledge on pregnancy after heart or lung transplantation (HTx, LTx) remains scarce. This study aimed to assess short- and long-term outcomes of pregnancies after HTx and/or LTx across Europe and to analyze how centers approach the management of these patients.

## Methods

In this multicenter study, HTx and LTx centers in Europe provided data on patients with pregnancies >20 weeks of gestation and answered questions about their management of HTx and LTx patients with a pregnancy wish. Descriptive statistics were used.

## Results

We included 48 pregnancies from 40 patients across 12 centers. Hypertension occurred in 50%, 23% and 33% and preeclampsia in 14%, 15% and 33% in HTx, LTx and HLTx respectively. No graft rejection during pregnancy was reported with graft function remaining stable in most patients after delivery. There was one medical abortion and one neonatal death (both LTx). Preterm birth rates were 27% and 72% and low birthweight 10% and 56% for HTx and LTx. During follow-up (range 4-30 years post-Tx), 6/40 mothers (15%) died (1 HTx, 2 LTx, 3 HLTx), with their 8 children aged between 0-11 years. Chronic lung allograft dysfunction was reported in 3 LTx patients, requiring re-Tx in two. On long-term follow-up no specific physical health problems were mentioned in 29/30 alive children. In the management questions, it stood out that the opinion towards a pregnancy differed per physician from reluctant (36%) to positive (64%) and there were many differences in the management.

## Conclusions

This international cohort study shows rather reassuring outcomes for pregnancies after HTx and/or LTx. Despite high rates of pregnancy complications, most children are born healthy and long-term graft function and overall survival appear unaffected in most patients. Nonetheless, in line with overall survival, many children will lose their mother early in life, which remains important for pre-conception counseling. Lastly, the study highlights large differences in the approach towards a pregnancy after HTx and LTx between centers.

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# Effect Of Calcineurin Inhibitor Type On De Novo Malignancy After Heart Transplantation: A Single-Center Analysis Over 37 Years Of Post-Transplant Care

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## Background

Changes in immunosuppressive therapy after heart transplantation (HTx) have led to improved survival. Whether this is accompanied by an increased risk of fatal malignancies remains unclear. This analysis describes incidence, type and influence of calcineurin type on malignancies and survival.

## Methods

In this retrospective, single-center study, all transplant recipients between 1986 - 2023 were reviewed for type, clinical course, and outcome of de novo malignancies post-HTx, including calcineurin inhibitor type used, being either ciclosporin A (CsA) (period 1; 1986-2002) or tacrolimus (TAC) (period 2; 2003-2023), next to standard therapy with mycophenolate and prednisone.

## Results

In 617 HTx procedures, 461 de novo malignancies occurred in 202 patients (mean age at HTx  $50.5 \pm 10.2$  years, 73% male, median follow-up  $17 \pm 8$  years), with



no differences in incidence with regard to EBV-status or CMV-mismatch. Cutaneous malignancies had the highest incidence (70%), mainly squamous or basal cell carcinoma. Recurrence was >50% following the first event but mortality was low (2%). Melanoma was observed in 3% of all cases. Post-transplant lymphoma (PTLD; 6%), prostate (4%), lung (3%), and breast cancer (2%) were the most common non-cutaneous malignancies. Interestingly, the incidence of cutaneous malignancies decreased (72 vs 55%), while non-cutaneous malignancies increased (28 vs 45%;  $p=0.07$ ) over time. Death due to non-cutaneous malignancy was higher than death due to graft failure (43.8 vs 15.7 %), overall survival was similar for both periods ( $p=0.62$ ).

### Conclusions

Cutaneous malignancies are the most common type post-HTx, while non-cutaneous malignancies account for the highest mortality rate. Transition from CsA to TAC over time was associated with a non-significant increase in non-cutaneous malignancies without a clear impact on survival. Regular skin check-ups and yearly controls to monitor non-cutaneous malignancies are warranted.

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# Battling Aspergillus After Lung Transplantation: Risk Factors, Statins, And The Impact On Chronic Lung Allograft Dysfunction

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### Background

Invasive pulmonary aspergillosis (IA) poses significant challenges for lung transplant (LTx) patients, with unclear risk factors and preventive strategies. The effectiveness of nebulized Amphotericin B (AmB) or statins for IA prevention and the effect of IA on chronic lung allograft dysfunction (CLAD) and mortality remain unclear.

### Methods

Data was collected from all LTx patients transplanted between 1-12-2013 and 1-1-2022. IA, including definitive, possible and probable IA, was defined according to the European Organization for Research and Treatment of Cancer criteria. Pre-specified risk factors were compared between patients with and without IA post-LTx and were entered in a logistic regression model. Two additional logistic regression models were built with factors that might be associated with both statin or AmB prophylaxis and IA. A matched case-control study was conducted for the association between statins and IA, with matching based on follow-up time.

### Results

Aspergillus was cultured in 110 /275 (40%) patients post-LTx, 89/110 (81%) were classified as probable IA. Mycophenolatmofetil (MMF) use, airway stenosis, Aspergillus cultured pre-LTx, CLAD and acute rejection (AR), were significantly associated with an increased risk of IA. Statin use was associated with a decreased risk, while AmB prophylaxis was not. A significant statin effect could not be confirmed by the case control analysis. There was no significant difference in all-cause mortality between patients with and without IA (34% vs 29%).

### Conclusions

The high incidence of IA post-LTx necessitates more effective strategies. Targets for intervention include prior positive cultures, airway stenosis, AR, the use of MMF, and possibly prophylaxis with the statins instead of nebulized AmB.



# Lung Retransplantation A Single Center Dutch Experience

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## Background

Lung transplantation (LTX) is a treatment option in patient with an end-stage respiratory disease. Development of chronic lung allograft dysfunction (CLAD) restricts long-term survival in LTx. In selected cases a Lung retransplantation (LRTX) might be considered. International registry data has shown that long-term survival of patients with a LRTX is impaired when compared to survival of patients who received a first LTx. Since long term survival in Dutch LTx patients is superior when compared to international registry data, we aimed to investigate the long-term survival of patients who received a LRTX in the largest Dutch lung transplant center.

## Methods

Patients > 18 years were included who received a LRTX in our center from 1990-2023. Demographics and patients characteristics were summarized and survival was assessed by Kaplan-Meijer curve with GraphPad prims 10.1.0.

## Results

From 1990-2023 a total of 896 LTx were performed. From this group 20 patients (2.2%) received a LRTX for CLAD: 14 bilateral, 5 unilateral and 1 heart-lung transplantation. The initial diagnoses were: pulmonary fibrosis n = 1, cystic fibrosis n = 5, pulmonary arterial hypertension n = 4, emphysema n = 7, other n = 3. Median age of LRTX was 41 [25-48] years. Time between the 1e and 2e LTx was 4.0 [1.1-7.7] years. One year survival was 85%,

median survival was 2.1 [1.5-5.0] years with no difference between unilateral or bilateral LRTX.

## Conclusions

LRTX is uncommon and is mainly performed in a young patients. LRTX early outcome is good. Long-term survival is significantly worse than the median survival of Dutch LTx patients who received a first LTx, but is comparable to international registry data. Future research could focus on identifying the reasons for this poor survival in LRTX to better select patients who are suitable for LRTX.

# Case Report “Prehabilitation And Rehabilitation Of A Lung Transplant Patient After Post Covid-19 Associated Acute Respiratory Distress Syndrome (ARDS) : Navigating Challenges During The Pandemic”

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## Background

In this case, we discuss the physiotherapeutic approach for an Intensive Care Unit (ICU) patient with COVID-19-associated Acute Respiratory Distress Syndrome (ARDS), who was placed on the high-priority waiting list for lung transplantation (LoTX).

A 56-year-old man was transferred via trauma helicopter from a peripheral hospital to an academic center for LoTX screening. The patient was in a medically induced coma (RASS -5). Initially, pulmonary recovery was the goal, as ventilator settings had already been reduced, and a CT scan of the thorax showed signs of an active phase of ARDS. In case of no recovery, Plan B was to initiate LoTX screening for a diagnosis of non-resolving COVID-19 ARDS. In consultation with the patient, physiotherapeutic treatment goals were established. Physiotherapy care was delivered on the ICU according to the ICU Physiotherapy Guidelines. Therapy was limited by anxiety and severe desaturation during mechanical ventilation. By week 3, there was no change in lung imaging and recovery was no longer expected and the patient was accepted for LoTX. In week 5, the patient began training in the physiotherapy gym outside the ICU. The patient was transported to the gym in a chair over a distance of 100 meters while on mechanical ventilation, using the ventilator transport cart. This was partly initiated to provide the patient with a psychological boost due to anxiety and the prolonged stay in the ICU. The patient enjoyed being away from the ICU during the session. Additionally, the physiotherapy gym offers the possibility of exergaming and access to other rehabilitation equipment, which facilitates the (p)rehabilitation process. On 24-4-2021, during week 6, a bilateral lung transplantation (LoTX) was performed. At the start of week 9, the patient's tracheostomy tube was removed, and later that week, he was transferred to the pulmonary ward. In week 14 he climbed up and down the stairs and he was discharged home. Outpatient physiotherapy continued in the primary care setting.

#### Methods

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#### Results

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#### Conclusions

Two year after the LoTX he was able to climb mountains.

No matter how challenging a situation may seem, always focus on the possibilities ahead, and keep your patients moving forward.

# A Transatlantic Veno-Venous ECMO Bridge For Lung Transplantation

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#### Background

This report details the challenging journey of a 58-year-old male with a progressive fibrotic lung disease due to sarcoidosis who needed a lung transplantation (LTx). Residing on the remote island of St. Eustatius, access to specialized medical care was limited, but he was entitled to receive appropriate medical care in the Netherlands.

#### Methods

For comprehensive cardiac workup, the patient was transferred to Colombia, where he underwent a coronary angiogram (CAG), cardiac ultrasound, CT scan, and PET scan, which showed pulmonary hypertension without coronary disease or active sarcoidosis. Upon returning to St. Eustatius, he experienced severe respiratory distress caused by a pneumothorax, necessitating the



insertion of a chest tube. He was, once again evacuated to Colombia (4900 ft) by plane for pleurodesis. He was accepted for bilateral LTx in the Netherlands on the condition that safe transport could be arranged. Air transport was carried out by using a Bombardier Challenger 604 at 41,000-49,000 ft (the patient was already at an elevation of 4,900 ft in Medellin). Awake femoral-jugular veno-venous Extracorporeal Membrane Oxygenation (vv-ECMO) was used (3,5 L/min).

### Results

Under the guidance of a highly experienced team, the transport was carried out without complications or equipment failure. The patient was listed for LTx at arrival in the Netherlands. Fortunately, a suitable lung offer was received shortly after, and the LTx was successfully performed without any complications.

### Conclusions

This case demonstrates that collaborative efforts among medical teams worldwide make vv-ECMO flight transport possible. When performed by an experienced team, it is a safe procedure for highly selected LTx candidates.

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# Urinary Endotrophin And T-Cell Mediated Rejection In Kidney Transplant Recipients

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### Background

Rejection remains one of the main problems in kidney graft survival. Until now, diagnosis has been based on findings from biopsy. However, the kidney biopsy procedure is an expensive and invasive procedure with a risk of complications. Thus, there is a need for non-invasive rejection biomarkers. Endotrophin, the C-terminal pro-collagen type VI $\alpha$ 3 fragment, has been shown to correlate with kidney interstitial fibrosis, kidney outcome measures, and survival in various kidney diseases and kidney transplantation. In this study, we investigated whether endotrophin is associated with T-cell mediated rejection (TCMR), allowing its use as a non-invasive biomarker.

### Methods

Plasma endotrophin and urinary endotrophin (indexed for creatinine) were measured in kidney transplant recipients (KTR) using the nordicPRO-C6TM enzyme-linked immunosorbent assay. The blood and urine samples were obtained on the same day as the biopsy procedure. In a subset of patients, the biopsy was stained for endotrophin and T-cells.

### Results

A total of 166 KTR were included in the analyses. One-hundred-forty-nine KTR who underwent indication biopsy had higher urinary endotrophin (13.3 [3.09-51.6] ng/mg vs 2.6 [2-5.4] ng/mg,  $p < 0.001$ ) and plasma endotrophin (15.6 [12.4-21.3] ng/mL vs 10.8 [9.7-11.6] ng/mL,  $p < 0.001$ ) than 17 KTR who underwent protocol biopsy. Among 149 KTR who underwent indication biopsy, 48 (32.2%) had TCMR (either borderline, acute, chronic, or mixed). Plasma endotrophin was not associated with higher odds of having TCMR (odds ratio (OR) [95% confidence interval (95%CI)] per doubling = 1.14 [0.71-1.83],  $p = 0.6$ ). On the contrary, urinary endotrophin was associated with higher odds of having TCMR (OR [95%CI] per doubling = 1.25 [1.07-1.45],  $p = 0.004$ ), and the association remained significant after adjusting for potential confounders, including plasma endotrophin level (adjusted OR [95%CI] per doubling = 1.38 [1.10-1.72],  $p = 0.005$ ). In a subset of patients, T-cell density in the biopsy was associated with endotrophin-positive myofibroblasts ( $p = 0.61$ ;  $p = 0.045$ ), urinary endotrophin



( $p = 0.67$ ;  $p = 0.017$ ), and interstitial fibrosis/tubular atrophy ( $p = 0.61$ ;  $p = 0.048$ ).

### Conclusions

These data indicate the potential use of urinary endotrophin as a non-invasive biomarker for fibrosis in the context of TCMR.

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## Activity Of 11 $\beta$ -Hydroxysteroid Dehydrogenase Type 1 And Graft Failure In Kidney Transplant Recipients.

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### Background

Long-term graft outcomes remains a paramount challenge in kidney transplant recipients (KTR). One emerging therapeutic avenue of exploration involves the enzyme 11 $\beta$ -hydroxysteroid dehydrogenase type 1 (11 $\beta$ -HSD1) with its pivotal role in intracellular amplification of glucocorticoid levels. It's activity has been implicated in various metabolic complications, however it's role on kidney graft survival is not yet known.

### Methods

In a prospective cohort study of 662 KTR and 103 healthy controls, 24-hour urinary tetrahydrocortisol (THF), allo-tetrahydrocortisol (alloTHF), and tetrahydrocortisone (THE) were measured using liquid chromatography

tandem-mass spectrometry. (THF + alloTHF)/THE was used as a measure of 11 $\beta$ -HSD1 activity. All included KTR were treated with prednisolone.

### Results

Activity of 11 $\beta$ -HSD1 was higher in KTR 1.7 [1.4-2.2] compared to controls (1.2 [0.94-1.4],  $P < 0.001$ ). During a median follow-up of 5.3 [4.5-6.0] years 12% KTR developed graft failure. In Cox regression survival analyses 11 $\beta$ -HSD1 activity was associated with graft failure (HR 1.93 95% [1.44-2.58];  $P < 0.001$  per unit increase of log<sub>2</sub>-transformed 11 $\beta$ -HSD1 activity), independent of sex, age, lipoproteins, glucose, donor status, and use of calcineurin inhibitors and only lost its significance after adjustment for renal function.

### Conclusions

Increased 11 $\beta$ -HSD1 activity is strongly associated with a higher risk of graft failure in KTR. Pharmacotherapeutic inhibition of 11 $\beta$ -HSD1 activity may be a potential strategy to reduce graft failure.

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## Prognostic Value Of Cell-Free DNA In Hypo- And Normothermically Machine-Perfused Kidneys: Associations With Post-Transplant Outcomes

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## Background

Recently, normothermic machine perfusion (NMP) at 37°C has been explored as a new tool to assess the quality of marginal donor kidneys, as it better simulates physiological conditions compared to hypothermic machine perfusion (HMP). During perfusion, cellular components are flushed out into the perfusate. One of these components is cell-free DNA (cfDNA) as a result of active secretion, inflammation, or cell death from tissue injury. Studies have suggested that cfDNA origin - either nuclear or mitochondrial - can be indicative of graft (dys) function. Therefore, this study aimed to quantify cfDNA levels and its origin in perfusate, as well as to evaluate associations between cfDNA and post-transplant outcomes (immediate function, delayed graft function, primary non-function).

## Methods

Perfusate was collected from 51 HMP and 6 NMP deceased donor kidneys. cfDNA was isolated using the QIAamp Circulating Nucleic Acid kit (QIAGEN) and quantified with the dsDNA High Sensitivity Assay (Invitrogen) on a Qubit 3 fluorometer. Mitochondrial and nuclear cfDNA were quantified by qPCR, using synthetic gene fragments for absolute quantification. cfDNA concentrations and copy numbers were normalized to perfusion time to obtain the release rate.

## Results

cfDNA was detected in kidney perfusates, with median release rates of 0.09 ng/μL/h in HMP and 20.1 ng/μL/h in NMP perfusates. Regardless of the perfusion method, most cfDNA originated from the mitochondria, with a 24-fold increase in mitochondrial cfDNA over nuclear cfDNA during HMP ( $p < 0.001$ ) and a 15-fold difference during NMP ( $p < 0.01$ ). Although cfDNA release rate and origin during HMP did not correlate with post-transplant outcomes, we did observe a lower mitochondrial cfDNA release from primary non-function kidneys compared to immediate function kidneys during NMP.

## Conclusions

Our findings demonstrate that cfDNA is detectable in both HMP and NMP kidney perfusates. Mitochondrial cfDNA is notably more abundant than nuclear cfDNA, which is likely the result of the higher number of

mitochondrial DNA copies compared to the diploid nuclear DNA. Our preliminary data suggest that cfDNA may hold the potential as a biomarker for post-transplant outcomes during NMP.

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# Exploring Proteomic Signatures Of Liver Viability During NMP: The Latest Insights Into Biomarker Discovery For Liver Transplantations

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## Background

Normothermic machine perfusion (NMP) has emerged as a promising technology to evaluate donor livers previously deemed unsuitable for transplantation. By mimicking normal physiological conditions, NMP supports metabolic activity and allows for real-time assessment of the liver function. Biomarkers, such as lactate clearance, pH, glucose metabolism, and bile production, are currently being used for assessing liver viability. However, their diagnostic value remains limited, highlighting the need for more reliable biomarkers to improve the viability assessment and predict post-transplant outcomes.

## Methods

This study aims to identify novel biomarkers for liver viability during NMP using mass spectrometry (MS)-based shotgun proteomics. A total of 24 human donor livers, representing a spectrum of viability from highly suitable



to highly unsuitable for transplantation, were included. Blood-based perfusate samples were collected in SST-tubes during the DHOPE-COR-NMP procedure at four timepoints: COR T-1 (baseline, pre-NMP), NMP T60, NMP T150, and NMP Tend. Proteomic analysis was conducted using off-line liquid chromatography-tandem mass spectrometry (nanoLC-MS/MS) to identify proteins and their temporal dynamics during NMP.

### Results

We were able to detect 2464 different proteins in 72 samples using this approach, with 382 proteins originating from the COR T-1 samples. The data analysis is currently ongoing, and no definitive results are available at the time of submittance. However, this approach is expected to reveal proteomic differences between suitable and unsuitable livers, with a focus on proteins related to tissue injury, repair mechanisms, and metabolic activity. These findings aim to provide insight into potential biomarkers that could offer real-time assessment of liver health during NMP.

### Conclusions

The identification of specific proteomic biomarkers through MS-based shotgun proteomics holds promise for improving the evaluation of donor liver viability during NMP. This approach could enhance the reliability of viability assessments and support better-informed decisions in liver transplantations.

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## A Single Day Protocol To Quantify Donor-Derived Cell-Free DNA As A Monitoring Tool For Allograft Injury After Kidney Transplantation

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### Background

Donor-derived cell-free DNA (ddcfDNA) is a promising minimally-invasive biomarker for the detection of allograft injury after kidney transplantation. Nevertheless, the added clinical value of ddcfDNA remains unclear. The current expensive and time-consuming NGS methods for the detection of ddcfDNA are inconvenient for clinical monitoring. Here we use a personalized digital (d)PCR-based method that enables quantification of ddcfDNA within one day.

### Methods

Plasma was collected at the time of a for-cause biopsy (n = 66), stable day 7 (D7, n=59) and stable month 6 (M6, n=74) after transplantation of in total 142 kidney transplant recipients. Using HoloGRAFT™ (Omixon), donor-specific copy number variant (CNV) markers were selected for every recipient. DPCR was used to measure at least two donor-specific assays in the plasma samples. DdcfDNA values were calculated as % of total cfDNA, as well as copies/ml plasma.

### Results

At the moment of a for-cause biopsy, the median (range) ddcfDNA concentration was significantly higher (82 [5-3571] copies/ml) compared to stable M6 (16 [0-335] copies/ml,  $p < 0.0001$ ), but comparable to stable D7 (91 [10-742] copies/ml). At the time of biopsy-proven acute rejection (BPAR) the ddcfDNA concentration was 165 (19-3571) copies/ml, which was significantly higher compared to the biopsies showing no rejection (non-AR, 43 [5-188] copies/ml,  $p < 0.0001$ ). For early biopsies, collected in the first 10 days after transplantation, the % ddcfDNA was comparable between BPAR (0.6 [0.2-9.5] %) and non-AR (0.6 [0.3-1.4] %) biopsies, while the concentration was significantly higher in the BPAR (154 [19-3571] copies/ml compared to the non-AR (86 [22-188] copies/ml,  $p < 0.05$ ). For late biopsies both concentration as well as % of ddcfDNA discriminated BPAR from non-AR biopsies. ROC analysis to discriminate BPAR





from non-AR showed an AUC of 0.86 with a sensitivity of 71%, specificity of 86%, PPV of 56% and a NPV of 92%.

### Conclusions

Personalized dPCR specifically targeting donor cfDNA is an affordable tool with a short turnaround time to monitor ddcfDNA values after kidney transplantation. DdcfDNA has the potential to augment clinical decision making by excluding the presence of allograft rejection and thereby possibly preventing unnecessary biopsies.

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# Circulating Bio-Adrenomedullin Concentrations, Body Composition And Mortality In Kidney Transplant Recipients

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### Background

Kidney transplantation improves survival and quality of life compared to dialysis, but presents risks, including cardiovascular complications and hypervolemia. Hypervolemia, prevalent among stable outpatient kidney transplant recipients (KTR), is linked to increased blood pressure and may affect overall outcomes. Bioactive adrenomedullin (bio-ADM) is emerging as a potential biomarker for hypervolemia, differing from N-terminal pro brain natriuretic peptide (NT-proBNP). In this study we examine bio-ADM levels in stable outpatient KTR, compare them with healthy controls, and explore

associations with extracellular water volume (ECW), body composition, and mortality.

### Methods

Data were analyzed from 1,012 KTR and 192 healthy donors. Bio-ADM levels were measured in plasma using immunoassay, and body composition was assessed via bioelectrical impedance analysis. Multivariable regression analyses and mediation analyses were used to evaluate the association of body composition and ECW with bio-ADM, while Cox regression was used to analyze associations with mortality.

### Results

Median age of the included KTR was 58 [interquartile range (IQR): 48, 67] years, 37.4% was female, mean ( $\pm$ SD) BMI was  $27.4 \pm 4.6$  kg/m<sup>2</sup> and mean eGFR was  $51.2 \pm 17.8$  mL/min/1.73m<sup>2</sup>. KTR exhibited significantly higher bio-ADM levels than healthy controls (32.6 vs. 20.7 pg/mL,  $p < 0.001$ ). In KTR, BMI was positively associated with bio-ADM (st.  $\beta = 0.40$ ,  $p < 0.001$ ), and mediation analysis showed that the association between BMI and bio-ADM was partially mediated by ECW and partially by fat mass. Neither BMI nor ECW were associated with NT-proBNP. Elevated bio-ADM levels were linked to increased mortality risk in KTR. This association remained independent of adjustment for age, sex, BMI, eGFR, NT-proBNP, and hs-CRP (HR = 1.23, 95% CI 1.06 to 1.42,  $p = 0.005$ ).

### Conclusions

These findings suggest that bio-ADM could be a valuable biomarker for identifying hypervolemia in KTR and may help pinpoint patients at heightened risk due to high ECW and fat mass. Bio-ADM's association with mortality further supports its potency for a role in guiding management strategies for stable outpatient KTR.

# Clinical Utility Of Plasma CXCL9 And CXCL10 For Guiding Anti-Rejection Therapy After Kidney Transplantation

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## Background

Previous studies have addressed the clinical utility of adding data on urinary chemokines C-X-C motif ligand 9 (CXCL9) and CXCL10 to model-based detection of kidney allograft rejection. However, the added value of these chemokines measured in plasma is unknown. We aimed to study whether adding early plasma CXCL9 and CXCL10 measurements to a prediction model for the need for anti-rejection therapy based on standard-of-care clinical parameters leads to higher model predictive ability.

## Methods

A baseline model was developed based on recipient age, donor age, the number of HLA mismatches at the A, B, and DR loci, and the need for dialysis in the first three days after transplantation. We performed a principal component analysis (PCA) on the plasma chemokines measured at day three to summarize them into one predictor. We added the predictors' first principal component to the baseline model to evaluate improvement in

model predictive ability. We assessed model discrimination through the area under the receiver operating characteristic curve (ROC-AUC), calibration through flexible calibration curves, and clinical utility through net benefit (NB) analysis. We assessed model optimism through bootstrapping.

## Results

Forty-two out of 157 patients (26.7%) required anti-rejection therapy between day three and day twenty-one after transplantation. Seventeen patients (10.8%) presented biopsy-proven acute rejection. Models with the chemokines presented higher optimism-corrected discriminative ability (ROC-AUC 0.774 versus 0.755) and better calibration in the lower end of predicted probabilities than the baseline clinical model. Both the baseline model and the extended model guided the decision on whether to biopsy patients or not better than standard intervention strategies. However, minimal improvement in net benefit was observed for models with chemokine information compared to the baseline model across reasonable thresholds for intervention (delta NB ranging from 0.008 to 0.013).

## Conclusions

This study provides evidence that adding plasma CXCL9 and CXCL10 information could improve the performance of a standard-of-care prediction model for rejection. However, the viability of adopting this strategy in practice could be restricted due to the limited gain in net benefit provided by the chemokines.

# Effect And Toxicity Of A Mitochondrial Antioxidant Therapy, Ubiquinone, In Porcine Precision Cut-Kidney Slices

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## Background

During the process of ischemia-reperfusion injury (IRI), the transient shortage of oxygen and nutrients leads to formation of reactive oxygen species (ROS) that are primarily produced in the mitochondria. Oxidative stress, or the disbalance between large amounts of ROS and reduced quantities of antioxidants, is associated with inferior graft and patient outcomes. Therefore, scavenging ROS with a mitochondrial antioxidant therapy, like ubiquinone, prior to transplantation could be an interesting strategy to improve (mitochondrial) preservation and ultimately graft function. The aim of this study was to find the optimal dosing range of ubiquinone for kidney tissue in a pre-clinical animal precision-cut kidney slices (PCKS) model.

## Methods

Porcine kidneys endured 30 min of warm ischemia and thereafter were preserved on oxygenated hypothermic machine perfusion. PCKS were created from cortex biopsies and incubated with mitochondrial antioxidant therapy ubiquinone, (MitoQ) in various concentrations (0.1, 0.5, 1.0, 5.0 and 10.0  $\mu\text{mol/L}$ ) during the first 24 hours of incubation, either in an oxygenated hypothermic or normothermic incubation

set-up. This was followed by 24 hours of normothermic incubation. Primary endpoint was real-time mitochondrial respiration, measured by high-resolution respirometry (Oroboros). Secondary endpoints were tissue ATP, tissue TBARS and incubation medium injury markers (LDH and ASAT). Statistical analyses were performed using a two-way ANOVA or Kruskal Wallis test, depending on normality distribution.

## Results

Mitochondrial maximum respiration and maximal respiratory capacity was significantly higher in 0.1  $\mu\text{mol/L}$  MitoQ treated PCKS after 24 hours of normothermic incubation compared to control and PCKS treated with  $>0.5$   $\mu\text{mol/L}$ . Treatments groups of  $>1$   $\mu\text{mol/L}$  had comparable levels of tissue ATP, TBARS and incubation medium LDH and ASAT levels ( $P>0.05$ ). PCKS treated with 5 and 10  $\mu\text{mol/L}$  had significant inferior function in all endpoints: mitochondrial respiration, ATP and injury markers ( $P<0.05$ ).

## Conclusions

Treatment with 0.1  $\mu\text{mol/L}$  MitoQ in normothermic conditions shows superior mitochondrial functioning of in the PCKS compared to control. However, MitoQ administration of  $>5$   $\mu\text{mol/L}$  showed tissue toxicity, and emphasizes the importance of this dose-finding study in a pre-clinical animal model. Future studies will use the next step in pre-clinical machine perfusion studies, to include kidney functions like filtration and reabsorption.

# Derivation And Validation Of A New Donor Risk Score Incorporating Graft Steatosis And Donor Diabetes Mellitus

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## Background

Graft steatosis is a risk factor for adverse outcomes after liver transplantation, and the concomitant presence of diabetes mellitus (DM) further increases risk. Incorporation of these factors in donor risk scores is of important, as the prevalence of metabolic dysfunction is increasing in the donor population. We aimed to derive and validate a simple donor risk score (DRS) based on presence of DM and graft steatosis and other readily available donor factors.

## Methods

We analysed all consecutive first adult full-graft DBD liver transplantations performed in the Eurotransplant region from 2010-2020. Presence of steatosis was assessed by imaging. Cases were randomly allocated to a derivation and validation group. We used backward selection Cox-regression to identify donor and graft factors associated with retransplantation-free survival of the recipient. Identified risk factors were used to create a point-based DRS, the performance of which was assessed in the validation dataset and across clinically relevant subgroups.

## Results

A total of 12174 transplants were analysed, 7650 were allocated to the derivation dataset. Median donor age was 57 (IQR 45–68), 54% was male, 484 (10.7%) had DM and 1050 (23.2%) had signs of steatosis. In the derivation dataset, donor age >50 ( $p<0.001$ ), GGT>ULN ( $p<0.001$ ), donor DM ( $p=0.002$ ), presence of graft steatosis ( $p=0.007$ ) and non-local graft procurement ( $p<0.001$ ) were associated with impaired re-transplantation-free survival. A point-based model was built allocating a point for each risk factor, yielding a DRS ranging from 0–5 points. In the validation dataset ( $n=4524$ ), a higher risk score was associated with worse retransplantation-free survival. Retransplantation-free survival at 5 years was 71.6% for recipients of a low risk graft (0-1 risk factor, 22% of cohort), 62.7% for recipients of an intermediate risk graft (2-3 risk factors, 67% of cohort) and

51.1% in recipients of a high risk graft (>3 risk factors, 11% of cohort;  $p<0.001$ ). Higher risk grafts were associated with poorer outcomes regardless of recipient age and recipient MELD score.

## Conclusions

This validated risk score based on donor age, GGT, presence of donor DM, graft steatosis and non-local procurement predicts retransplantation-free survival in DBD liver transplantation and can be used for rapid assessment of graft quality in clinical practice.

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# Long-Term Health In Offspring Of Female Orthotopic Liver Transplantation Recipients – A Prospective Dutch Cohort Study

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## Background

Research on long-term health outcomes of offspring born to mothers with a liver transplantation (LiTx) is limited. Existing studies focus on short-term outcomes and have small sample sizes. This is one of the first cohort studies including long-term (age >12 years) outcomes.

## Methods

This is a multicenter prospective cohort study (offspring born between 1988 and July 2024). Data were collected using questionnaires and maternal electronic health records. Offspring was identified through the Dutch LiTx centers. Questionnaires covered pregnancy outcomes, infection, medication history, and physical development. The following definitions were used: low birth weight (LBW): <2500g and preterm birth: <37 weeks gestation. For offspring <8 years, developmental milestones were assessed using the Van Wiechen scheme (VWS) and questions about reading, writing and biking. For those ≥8 years, quality of life was evaluated through the Positive Health Questionnaire, which scores six dimensions: quality of life (QoL), participation (P), mental well-being (MW), daily functioning (DF), bodily functions (BF), and meaningfulness (MF). Participants rate each dimension from 0 (very negative) to 100 (very positive). Results are presented with {reference value}.

## Results

Out of n=123 eligible participants, n=64 (52%) completed the questionnaire. 19% (n=12) had LBW {10%}. 24% (n=15) were born preterm {8}. Only 73% (n=46) followed reference growth curve {90%}. 89% (n=54) had an healthy age-adjusted body mass index {48%}. Of participants aged <8 (n=31), VWS milestones were reached in 94% (n=29) of cases {81-100%}. For participants aged 3.5-8 years, 100% (n=17) recognized letters, 88% (n=15) wrote letters and 94% (n=16) biked independently. For those ≥8 years (n=33), health dimension scores were: QoL 88, P 87, MW 78, DF 87, BF 84, and MF 81.

## Conclusions

Maternal LiTx offspring has increased rates of premature birth and low birth weight, as well as lower rates of reaching the reference growth curve compared to the general population. However, long-term outcomes appear favorable, with higher age-adjusted rates of healthy BMI and developmental milestones attainment than the general population. Also, five of six health dimensions are rated above 80, graded as excellent in literature.

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# Intra-Operative Placement Of Biodegradable Biliary Stent To Prevent Biliary Complications After Liver Transplantation: The First Results Of The Archimedes Pilot

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## Background

Surgical failure of the biliary anastomosis, both anastomotic strictures (AS) and biliary leaks, remain significant complications following liver transplantation (LT). They contribute substantially to patient morbidity and impose a considerable burden on healthcare systems. Recent studies suggest that the intra-operative placement of biodegradable biliary stents may reduce the incidence of biliary complications after LT.

## Methods

Between January 2024 and November 2024, we conducted a pilot study in which eight consecutive patients underwent standard duct-to-duct biliary anastomosis during LT (DCD 6/8; DBD 2/8), followed by the insertion of a CE marked Archimedes biodegradable stent through the anastomosis while not crossing the ampulla. These stents have a slow degrading profile with minimal strength retention up to 11 weeks. During the first post-operative week, stent position was confirmed radiologically. Stent degradation was assessed on each consecutive imaging performed for clinical reasons



during follow-up. The incidence of biliary complications (AS and leaks combined) was assessed at 6-months post-LT and was compared to the incidence in a historic cohort.

### Results

During this study period 8 stents were successfully placed, 4 stents with diameter of 8fr (n=4) and 10fr (n=4). Technical success rate was 88% (n=1 stent migration within 48 hours). The stents degraded completely within 3 months in 6/7 patients, while in one patient the remains of the stent were radiologically visible up to 9 months post LT. This patient showed no signs of biliary complications. The expected incidence of biliary complications based on the historic cohort was 28%. The actual incidence of biliary complications was 14% (1/7). This patient developed a biliary leak post-operatively, no patients developed an AS.

### Conclusions

The intra-operative placement of a biodegradable biliary stent is feasible during LT. The placement of the stent reduced the overall biliary complications with 50%. This pilot data suggests that intraoperative stent placement may lead to clinically relevant reduction of biliary complications and hence lower morbidity and costs. A randomized clinical trial is warranted to confirm these preliminary findings.

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## Outcomes After Transplantation Of Liver Grafts Donated After Euthanasia

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### Background

In an attempt to decrease donor organ shortage, some countries allow transplantation of organs donated after euthanasia (Donation After Circulatory Death [DCD] Type V, DCD-V). Similar to grafts from DCD Type III (DCD-III), DCD-V organs experience a period of warm ischemia, which can lead to post-transplant complications. Donor warm ischemia time is shorter in DCD-V donors, potentially resulting in improved outcomes. However, recent transplants with DCD-V livers showed higher incidences of postoperative complications, necessitating thorough evaluation of DCD-V liver transplant outcomes.

### Methods

In this retrospective study we analyzed all liver transplantations performed at the three Dutch liver transplant centers between January 1<sup>st</sup> 2013 and November 1<sup>st</sup> 2023 with DCD-V grafts. As a comparator cohort, patients who received DCD-III grafts in the same period were analyzed. Minimal follow-up was 12 months. Primary outcomes were 1-year graft survival and postoperative complications, including ischemic cholangiopathy (IC) at one year.

### Results

Between 2013 and 2023, 74 DCD-V liver transplant procedures were performed. Median donor age was 53 (IQR 39-59) years. Indication for euthanasia was psychiatric illness in 39% (28/74), neurological or neurodegenerative disorder in 46% (34/74), and other indications in 15% (11/74). In the comparator cohort of 353 DCD-III liver transplants, median donor age was 54 (IQR 39-62, p=0.264) years.

In the DCD-V group 68% of the livers were treated with machine perfusion vs. 72% in the DCD-III group (p=0.493). One-year graft survival rates were comparable in the DCD-V and DCD-III groups (86% vs 88%). The incidence of PNF did not differ between the groups (3% vs. 1%, p=0.401). At 1-year overall biliary complication rate was 54% in the DCD-V group vs. 38% in the DCD-III group (p=0.011). IC was noted in 31% of DCD-V livers vs. 15% in DCD-III livers (p<0.001).





## Conclusions

Livers donated after euthanasia represent a valuable source of donor livers, however these livers seem to have an increased risk for post-transplant biliary complications, especially intrahepatic biliary strictures. More research is needed to determine the underlying cause of this increased risk for biliary complications. Moreover, the role on machine perfusion in reconditioning and selection of DCD-V livers warrants further research.

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# Poor One-Year Outcomes Of Hepatic Artery Thrombosis After Pediatric Liver Transplantation: Results From An International, Multicenter, Real-World Registry

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## Background

Hepatic artery thrombosis (HAT) after pediatric liver transplantation (pLT) is a severe complication that can lead to acute graft failure, often requiring urgent

re-transplantation. Despite its significance, the outcomes of HAT after pLT remain poorly characterized. This study aimed to determine the one-year incidence of graft loss and mortality and to identify associated risk factors in patients who develop HAT after pLT.

## Methods

We analyzed data from patients who developed HAT after pLT from the HEPatic Artery Stenosis and Thrombosis after Liver Transplantation in Children registry. This registry includes data from 24 centers across 20 countries and six continents, spanning a 20-year period during which 8,469 pLTs were performed. Clinical characteristics were examined at three timeframes: pre-transplant, immediate post-transplant, and following HAT diagnosis. Risk factors for graft loss and mortality after HAT were identified through multivariate Cox regression analyses, with model assumptions verified using Schoenfeld residuals.

## Results

HAT occurred in 3.4% of patients (n=287, 53% female, median age 1.8 years). Following the diagnosis of HAT, the cumulative incidence of graft loss was 44% (95% CI 38–49) at one month and 56% (95% CI 50–62) at one year. Mortality rates were 15% (95% CI 11–19) and 23% (95% CI 18–28) at these respective timepoints. Multivariate Cox regression analysis identified three independent risk factors for one-year graft loss after HAT: aspartate aminotransferase (AST)  $\geq 1000$  U/L, an international normalized ratio (INR)  $\geq 2$ , and dialysis at HAT diagnosis (each  $p < 0.05$ ). Independent risk factors for one-year mortality included cirrhotic primary diseases, living donor pLT, AST  $\geq 1000$  U/L, INR  $\geq 2$ , and dialysis at HAT diagnosis (each  $p < 0.05$ ).

## Conclusions

Patients with HAT after pLT experience notably high rates of graft loss and mortality, particularly within the first month following diagnosis and with signs of graft and multi-organ failure. Risk stratification according to risk factors identified at HAT diagnosis underscore the critical need for strategies to prevent graft loss and mortality after HAT.

# Liver Transplantation Should Not Be Rejected In Fit Individuals Aged 70 And Above.

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## Background

The need for liver transplantation (LTX) in elderly patients is increasing, as a result of the aging population. We aimed to expand the knowledge on liver transplantation in patients aged  $\geq 70$  years, and to evaluate the value of geriatric screening.

## Methods

Retrospective chart review was performed of patients of  $\geq 64$  years-old, screened for LTX at our center from 2018-2024. The primary outcome parameter was patient survival. Secondary outcome parameters were graft survival and complications.

## Results

Eighty-one patients who were screened for LTX were identified, of whom 28 patients were excluded from transplantation for various reasons (e.g. poor general condition, oncologic disease progression). The remaining 53 patients were divided into two groups: 64-69 years ( $n=38$ , 71.7%), and  $\geq 70$  years at screening ( $n=15$ , 28.3%); median transplantation age was 67 (IQR66-68, R65-69) and 71 (IQR70-72, R70-74) years respectively ( $p<0.001$ ). There were more males in the older group ( $n=15/100\%$  vs  $n=27/71.1\%$  ( $p=0.01$ )). HCC was more often indication for LTX in the elderly (35% vs 21%, ( $p=0.26$ )). No patients were excluded from transplantation based on extensive geriatric screening. Median follow-up was 18 months in the older vs 25 months in the younger group. Overall survival was comparable among groups with 92.1% in the younger vs 94.1% in the older group ( $p=0.96$ ). Also, graft

survival was comparable, with 97.4% in the younger vs 88.2% in the older group ( $p=0.17$ ).

At screening, the elderly group appeared more fit as measured by cardiopulmonary exercise testing (median 14.4 vs 13.4 ml/min/kg). Peroperatively, several trends were noted: more heart-beating donors among those  $\geq 70$  years (47.1% vs 27.0%,  $p=0.15$ ), as well as shorter duration of machine perfusion (193 vs 506 min,  $p=0.08$ ), and longer static cold ischaemia time (302 vs 248 min,  $p=0.04$ ). Postoperatively, complication rates were comparable, however there was a trend towards more delirium (35.3% vs 21.1%,  $p=0.26$ ) in the elderly group.

## Conclusions

Carefully selected patients of  $\geq 70$  years-old have comparable overall short term survival and graft survival vs patients of 60-69 years-old, with a similar complication rate. Patients of  $\geq 70$  years-old should not be excluded from LTX, solely based on their age.

# Rhesus Antagonism Is Associated With Higher Rates Of Non-Anastomotic Strictures Following Orthotopic Liver Transplantation In Patients Receiving Donation After Brain Death: A Single-Center, Retrospective Cohort Study

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## Background

Complications of liver transplantation (LT) include non-anastomotic strictures (NAS). Incidence rates of NAS vary between 11-31% and patients require multiple cholangiographic interventions using a combination of balloon dilatation and stenting, and/or re-transplantation. Risk factors include donation after circulatory death (DCD) as compared to donation after brain death (DBD) and increased ischemia times. Uncertainty remains with regard to the exact pathophysiological mechanisms involved, and immunological factors are believed to play a role as well. Expression of ABO antigens on biliary epithelial cells has been confirmed before, and ABO blood group incompatibility is associated with higher incidence of NAS. The aim of this research is to assess the effect of Rh antagonism on development of NAS after LT.

## Methods

This single-center, retrospective cohort study includes 678 orthotopic LTs performed between 2000-2023 (of which DBD=422, DCD=191, and machine perfused=65). The primary endpoint is NAS that required cholangiographic intervention. Rh antagonism is defined as a case in which a Rh negative recipient receives a Rh positive donor graft. Kaplan-Meier survival curves and Cox regression analyses are used for survival and risk factor analysis. Immunohistochemistry (IHC) on human liver biopsies is performed to assess the presence of Rh antigens on biliary epithelial cells.

## Results

Total incidence of NAS was 142 (20.9%), of which 14.9% for LT-DBD, 35.6% for LT-DCD, and 16.9% for machine perfused grafts. Fifty-two (7.7%) cases of Rh antagonism were identified. The overall cohort showed no significant effect of Rh antagonism on NAS development. However, when analyzed separately, in the DBD cohort Rh antagonism was associated with higher rates of NAS (**HR 2.749; p=.002**). This effect does not hold for transplantation after DCD.

## Conclusions

Rh antagonism increases the risk of development of NAS after LT with DBD.

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# Graft And Overall Survival In Patients With Portal Vein Stenosis After Pediatric Liver Transplantation; Results From The Multicenter Multinational PORTAL Registry

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## Background

Pediatric liver transplantation (pLT) can lead to complications such as portal vein stenosis (PVS), which could affect graft- and patient survival. This study represents the first global registry-based assessment of one-year patient and graft survival in individuals with post-pLT PVS.

## Methods

The study analyzed data from the Portal vein Obstruction Revascularisation Therapy After Liver transplantation (PORTAL) registry. This registry contains data from 21 centers, across 18 countries, 6 continents over a 20-year cohort.

## Results

We included 239 patients (47% male, 53% female; median age at pLT, 1.1 years; interquartile range, 0.7-3.1) diagnosed with PVS. The median age at detection of PVS was 2.7 years (interquartile range, 1.1-5.7). The one-year graft



survival rate was 96%, and the one-year patient survival rate was 99%. Multivariate analysis revealed that patients who received a venous jump/interposition graft during pLT were independently associated with decreased graft- and patient survival ( $p=0.003$  and  $p=0.015$ , respectively). Early onset ( $\leq 14$  days after pLT,  $p=0.017$ ), age at pLT  $< 1$  year ( $p=0.003$ ) and male gender ( $p=0.018$ ) were independently associated with a decreased graft survival.

### Conclusions

Our findings indicate that patients with PVS after pLT have excellent graft- and patient survival. Several risk factors to lower patient outcome were identified. Long-term outcomes could be enhanced by targeting these risk factors.

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# Safe Transplantation Of Extended Criteria Donor Livers: Two-Center Experience With Resuscitation And Viability Assessment Of 186 Livers Using Sequential Hypo- And Normothermic Machine Perfusion

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### Background

Liver machine perfusion is increasingly used to test and select extended criteria donor (ECD)-livers in an attempt to counter decreasing quality of available organs under the current organ shortage. A combined protocol of sequential hypothermic and normothermic machine perfusion, linked by one hour of controlled oxygenated rewarming (DHOPE-COR-NMP) can be used to resuscitate donor livers and subsequently perform viability assessment. We aimed to analyze long-term follow-up data from DHOPE-COR-NMP procedures for extended criteria donor (ECD)-livers performed in two centers.

### Methods

All ECD-livers treated with DHOPE-COR-NMP between March 2019 until August 2024, were included, guaranteeing a minimum follow-up period of 6 months. The primary outcome was death-censored graft survival. Secondary outcomes included overall patient- and graft survival, as well as post-transplant complications, such as non-anastomotic biliary strictures (NAS) and anastomotic strictures (AS).

### Results

A total of 186 DHOPE-COR-NMP procedures were performed. This resulted in 127 transplants (utilization rate 68%), of which 122 were ECD-DCD livers (96%). Death-censored graft survival and patient survival at 1 year was 90% and 91%, respectively. There was one case of primary non-function (0.8%). Portal vein thrombosis occurred 3 times (2.4%) and hepatic artery thrombosis occurred 5 times (3.9%). The 1-year cumulative incidence of NAS was 6%. Of all NAS cases, 2 patients were re-transplanted and one resulted in patient death. At one year, AS occurred in 26% of transplanted livers.

### Conclusions

This study shows that, graft resuscitation and subsequent viability assessment through DHOPE-COR-NMP allows for safe transplantation of ECD-livers with excellent outcomes. The incidence of NAS is low, especially considering the fact that this cohort mainly consisted of ECD-DCD livers.

# Long-Term Follow-Up After Hypothermic Oxygenated Machine Perfusion In DCD Liver Transplantation: Results Of A Randomized Controlled Multicenter Trial (DHOPE-DCD)

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## Background

Dual hypothermic oxygenated machine perfusion (DHOPE) reduces the risk of symptomatic non-anastomotic biliary strictures (NAS) within 6 months after donation after circulatory death (DCD) liver transplantation. However, 6-month protocol magnetic

resonance cholangiography (MRC) in the DHOPE-DCD trial revealed biliary irregularities in 65% of asymptomatic patients, and it remained unknown how many would develop symptoms with longer follow-up. Additionally, acute rejection within 6 months was nearly 2-fold lower in DHOPE-preserved livers, compared to static cold storage alone (SCS; Control group). This study evaluates the 5-year incidence of graft-related complications, including symptomatic NAS and acute rejection, in the DHOPE-DCD trial.

## Methods

We analyzed 5-year follow-up data of patients enrolled in the randomized, controlled, multicenter DHOPE-DCD trial, comparing DHOPE with SCS in DCD liver transplantation. Symptomatic NAS was defined as radiologically confirmed NAS in the presence of clinical symptoms or elevated cholestatic laboratory values. Acute rejection was either biopsy proven or based on biochemical response following treatment, in patients with adequate maintenance immunosuppression. Patients transplanted for immune-mediated disease, including autoimmune hepatitis, primary sclerosing, or primary biliary cholangitis were considered at increased risk for rejection.

## Results

A total of 78 patients were included in the DHOPE group and 78 in the Control group. The incidence of symptomatic NAS was 13% in the DHOPE group and 25% in Controls at 1 year (HR 0.42, 95%CI 0.19-0.94;  $p=0.035$ ), and 14% vs 26% at 5 years (HR 0.47, 95%CI 0.23-0.99;  $p=0.048$ ). Of the 114 asymptomatic patients with a protocol MRC at 6 months, 74 (65%) had radiological biliary irregularities, of which 10 (14%) became symptomatic. Two out of 40 asymptomatic patients with a normal protocol MRC (5%) developed symptomatic NAS within 5 years. Incidence of acute rejection was 10% in DHOPE recipients and 17% in Controls ( $p=0.269$ ). In patients with immune-mediated diseases, rejection was observed in 0% of DHOPE recipients and 32% of Controls ( $p=0.037$ ).

## Conclusions

This study demonstrates that the benefits of DHOPE persist beyond the initial 6 months after DCD liver transplantation. DHOPE significantly reduces the risk of symptomatic NAS up to 5-years post-transplantation and may reduce the risk of rejection, especially in patients transplanted for immune-mediated disease.

# Impact Of Hypothermic Machine Perfusion Duration On Deceased-Donor Kidney Transplant Outcomes

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## Background

Hypothermic machine perfusion (HMP) has been established as a standard method to preserve donor kidneys, improving transplant outcome compared to static cold storage. This study aimed to evaluate the effects of the duration of non-oxygenated HMP and oxygenated HMP (HMP-O<sub>2</sub>) on the outcomes of deceased-donor kidney transplants.

## Methods

Data were collected retrospectively from 1,786 deceased donor kidney transplantations performed in the Netherlands between 2017 and 2023. Among these, 1,244 kidneys underwent non-oxygenated HMP, while 542 underwent HMP-O<sub>2</sub>. Our analysis focused on assessing the impact of perfusion duration on one-year graft and patient survival, using logistic regression and Kaplan-Meier (KM) survival curves. Propensity score matching (PSM) was used to adjust for differences in donor characteristics such as age, weight, and other clinical factors.

## Results

After propensity score matching, the survival analysis showed no significant difference between the oxygenated and non-oxygenated HMP groups in terms of transplant outcomes, indicating that donor characteristics rather than the perfusion method influenced the outcomes. Subgroup analysis using KM curves, stratified by perfusion duration (using the median as a cutoff),

revealed that neither the duration of oxygenated nor that of non-oxygenated HMP significantly affected long-term graft or patient survival.

## Conclusions

These findings suggest that, in a real-world clinical setting and within certain limits, a longer duration of HMP does not compromise transplant outcomes. This could offer flexibility in transplantation logistics, potentially reducing nighttime surgical procedures and associated complications.

# Prolonged Preservation Of Livers Donated After Circulatory Death Using Dual Hypothermic Oxygenated Machine Perfusion.

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## Background

Liver transplantation with grafts donated after circulatory death (DCD) increases the risk of early graft failure due to ischemia-reperfusion (IR) injury-related complications. A 2-hour period of dual hypothermic oxygenated machine perfusion (DHOPE) has been shown to reduce IR injury-related complications, especially non-anastomotic biliary strictures (NAS). While prolonged DHOPE





may safely extend the preservation time for brain-death donor livers, its safety in DCD livers remains unclear. This study evaluates the safety and outcomes of prolonged DHOPE in DCD liver transplantation.

### Methods

Between June 2022 and August 2024, 22 DCD livers underwent prolonged DHOPE ( $\geq 4$  hours), with a median follow-up of 8 months post-transplant. A 1:1 time-matched control DCD group underwent DHOPE  $< 4$  hours. Outcomes included the 7-day peak value of alanine-aminotransferase (ALT; U/L), international normalized ratio (INR), and total bilirubin ( $\mu\text{mol/L}$ ), as well as graft loss due to primary non function (PNF) or early hepatic artery thrombosis (eHAT) within 2 months. Death-censored graft survival and NAS incidence were assessed at 6 months. Data are presented as medians and ranges.

### Results

The total preservation time was 12.0 hours (9.0-23.9) in the prolonged group and 8.8 hours (5.7-10.7) in the controls ( $p < 0.001$ ), with a respective DHOPE duration of 6.4 hours (4.7-19.7) and 3.0 hours (1.3-4.0). Peak ALT, INR, and bilirubin values were comparable between groups: ALT (1525 U/L (440-3997) vs. 962 U/L (335-4059),  $p = 0.132$ ), INR (2.2 (1.6-4.3) vs. 2.4 (1.3-4.7),  $p = 0.37$ ), and bilirubin (108  $\mu\text{mol/L}$  (23-282) vs. 71  $\mu\text{mol/L}$  (9-421),  $p = 0.37$ ).

Death-censored graft survival was not significantly different (86% vs. 100%,  $p = 0.23$ ), although in the prolonged group, three patients required re-transplantation due to one case of PNF (5%) and two after eHAT (9%). Symptomatic NAS occurred in two patients in the prolonged group (9%) and none of the controls.

### Conclusions

Prolonged DHOPE in DCD livers did not result in a significant increase in graft-related complications, including PNF, eHAT and NAS. While graft survival has to be monitored in longer follow-up, it now appears to be safe to extend DCD liver graft preservation. This approach can optimize transplant logistics and facilitate daytime surgeries for high-risk DCD liver recipients.

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## Additional Dual Hypothermic Oxygenated Perfusion After Normothermic Regional Perfusion In Liver Transplantation: No Added Benefit.

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### Background

Due to persisting organ shortage more livers from extended criteria donors (ECD), including donors after circulatory death (DCD), are accepted for transplantation. To reduce (biliary) complications of these ECD-DCD grafts, machine perfusion has shown to be crucial. Abdominal normothermic regional perfusion (aNRP) provides a platform for both viability evaluation and ischemic cholangiopathy reduction, while dual hypothermic oxygenated perfusion (DHOPE) serves only the latter. However, it remains unclear whether these perfusion techniques are complimentary. Previous studies comparing aNRP vs aNRP+DHOPE were conducted across different healthcare systems with different mandatory donor stand-off time. This study aims to assess the additional effects of DHOPE following NRP versus NRP alone within a single center.

### Methods

A retrospective analysis was conducted on DCD III and V donors over 50 years of age, classified as ECD, from the



aNRP project in the Netherlands between October 2018 and May 2023. Outcomes were analyzed for one year patient and graft survival, anastomotic strictures (AS), non-anastomotic strictures (NAS) and total out of body time.

### Results

A total of 32 patients were analyzed, with 17 receiving NRP alone and 15 receiving both NRP+DHOPE. Outcomes were not significant across both groups. Graft survival was 100% for the NRP group compared to 93 % for the NRP+DHOPE group. Patient survival was identical at 100% for both groups. AS rates were 12% for NRP and 13% for NRP+DHOPE, while NAS occurred in 0% of NRP and 7% of NRP+DHOPE. Total out of body time and cold ischemia time was 347 and 320 minutes in the NRP group versus 468 and 311 minutes in the NRP+DHOPE group.

### Conclusions

This study demonstrates that the addition of DHOPE after aNRP does not provide significant benefits in terms of graft and patient survival, AS and NAS. Given the comparable outcomes between the two approaches, aNRP alone seems sufficient, reducing costs associated with application of dual perfusion techniques.

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# Normothermic Machine Perfusion Versus Hypothermic Machine Perfusion In Deceased Donor Kidney Transplantation: A Single-Center Randomized Controlled Trial

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### Background

Currently, hypothermic machine perfusion (HMP) is the gold standard for preservation of deceased donor kidneys. However, for extended criteria donor kidney grafts (ECD-DBD) and kidney grafts that are donated after circulatory death (DCD), the risk of delayed graft function (DGF) and primary non-function (PNF) remains high and these grafts are more often discarded. Normothermic machine perfusion (NMP) has emerged as an alternative method of preservation, during which cellular repair processes can initiate during normothermia, without influx of recipient immune cells. The aim of this trial is to compare outcomes of kidney grafts that were preserved with additional end-ischemic NMP to HMP alone.

### Methods

This is a single-centre, open-label, randomized controlled trial. Patients who received a ECD-DBD or DCD kidney were randomized to receive a kidney that was either preserved on HMP with two hours of end-ischemic NMP (intervention group) or HMP alone (control group). Primary outcome was the incidence of DGF. Secondary outcomes were the incidence of (PNF), biopsy-proven acute rejection (BPAR) and graft and patient survival (APOLLO trial, NCT04882254).

### Results

A total of 80 recipients were enrolled, of which 41 received a kidney that was preserved on HMP and NMP and 39 received a graft that was preserved on HMP alone. DGF occurred in 22/38 (58%) patients in the NMP group compared to 19/37 (51%) patients in the HMP group (OR: 1.38, 95% CI: 0.56-3.40, p=0.49). PNF occurred in three patients in the NMP group and two patients in the HMP group (OR: 1.46, 95% CI: 0.23-9.25, p=0.69). There was no difference in episodes of BPAR (NMP: 28% vs HMP



16%,  $p=0.282$ ). There was no difference in death-censored graft ( $p=0.607$ ) and patient survival ( $p=0.623$ ) at one year after transplantation.

### Conclusions

The addition of two hours end-ischemic NMP does not improve early graft outcomes in ECD-DBD and DCD kidney transplantation compared to HMP alone. However, this trial does prove that two hours of end-ischemic NMP is feasible and safe, offering future opportunities for quality assessment or graft repair.

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# Clinical Outcomes Of Abdominal Normothermic Regional Perfusion Versus Sequential Hypo- And Normothermic Machine Perfusion: A Single Center Comparison.

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### Background

To address the shortage of donor livers, extended criteria donors (ECD), including those donated after circulatory death (DCD), are increasingly used. However,

DCD livers are at higher risk of primary non-function and biliary complications due to extended donor warm ischemia. There are two main perfusion techniques to assess liver function: in-situ abdominal normothermic regional perfusion (aNRP) or ex-situ normothermic machine perfusion, in our center combined with dual hypothermic oxygenated perfusion and controlled oxygenated rewarming (DHOPE-COR-NMP; DCN). Due to differences in legislation and practice, most centers have access to only one technique, making multi-center comparisons challenging. This study presents a single center comparison of aNRP and DCN to evaluate the clinical outcomes of transplanted livers.

### Methods

Liver grafts from ECD-DCD donors between October 2018 and the end of June 2023 are included. aNRP was performed when the donor was located in the Western region, otherwise DCN was performed. The primary outcome was death-censored graft survival. Secondary outcomes included acceptance rate, patient survival and posttransplant biliary complications.

### Results

In total, 26 DCN and 43 aNRP procedures were performed, which resulted in 19 (73%) and 32 (74%) liver transplantations, respectively. At one year, death-censored graft survival and overall patient survival rates were 100% and 90% for DCN and both 100% in aNRP (not significant). One year cumulative incidences of non-anastomotic strictures, anastomotic strictures, and bile leakage were 11%, 16% and 6% in DCN and 3%, 22% and 9% in aNRP. Clavien grade of 3 or higher complications were observed in 12% of DCN and 15% of aNRP. These differences were not statistically significant.

### Conclusions

The results in this homogenous cohort confirm that both aNRP and DCN allow safe transplantation of ECD-DCD livers with excellent death-censored graft survival and patient survival. The risk of posttransplant biliary complications in both cohorts was not different. Especially regarding non-anastomotic stricture formation results were better compared to results achieved in historical controls without machine perfusion.

# Viability Assessment Of Donor Livers Over 2 Kilo From Extended Criteria Donors Using Normothermic Machine Perfusion.

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## Background

Sequential dual hypothermic oxygenated, controlled oxygenated rewarming and normothermic machine perfusion (DHOPE-COR-NMP) has been implemented for assessing the viability of extended criteria donor (ECD) livers. Steatotic livers are considered ECD livers due to a higher risk of post-transplant complications. Steatosis and other donor factors, such as gender, length and weight, influence liver size and weight. The aim of this study was to assess the viability of higher weight donor livers during DHOPE-COR-NMP and investigate the correlation between liver viability and the grade of steatosis.

## Methods

Livers  $\geq 2000$  grams prior to perfusion ( $n=7$ ), that underwent DHOPE-COR-NMP were 1:2 time-matched with 14 controls  $< 2000$  grams. Outcome parameters included viability assessment of hepatocellular and cholangiocellular function at 150 minutes of NMP and utilization rate. Vascular resistance corrected for liver weight (mmHg/mL/min/100g) of the hepatic artery (HA) and portal vein (PV) were calculated. Steatosis was graded based on liver biopsies taken prior to perfusion. Presented are median values and range.

## Results

Liver weight was significantly different between groups (2470 (2160-3090) vs. 1340 (1150-1680),  $p < 0.0001$ ). The utilization rate was significantly lower in livers  $\geq 2000$  grams (1/7; 14% vs. 13/14; 93%,  $p = 0.0009$ ). Two heavy livers were declined based on hepatocellular function, three on cholangiocellular function and one on both. Vascular resistance (mmHg/mL/min/100g) was significantly higher in livers  $\geq 2000$  grams for both the HA (3.99 (1.55-5.09) vs. 1.49 (0.87-6.60),  $p = 0.0056$ ) and the PV (0.20 (0.12-0.29) vs. 0.10 (0.07-0.14),  $p = 0.0001$ ). Six of the heavy livers had a steatosis grade of  $< 5\%$ , and one liver showed 15% steatosis. In the control group, three livers had an increased steatosis grade, with levels of 10%, 15%, and 20% in individual livers.

## Conclusions

In conclusion, performing DHOPE-COR-NMP for ECD livers  $\geq 2000$  grams results in a low acceptance rate of only 14%, questioning the deployment of expensive machine perfusion resources for this category. These livers demonstrated an increased vascular resistance, which could not be attributed to the steatosis grade, but may serve as a target for pharmacotherapy.

# Organ Donation After Euthanasia In The Netherlands, Where Are We Now? (Original in Dutch)

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## Background

Organ donation after euthanasia (ODE) is possible for patients with hopeless suffering (somatic or psychological), for whom the euthanasia request has been granted and who wish to donate their organs. Patients with contraindications to donation are excluded. Since 2001, euthanasia has been legal in the Netherlands provided that the conditions of the Euthanasia Act (1) are met. Since 2001, euthanasia has been performed approximately 106,000 times (2). The first ODE in the Netherlands took place in 2012 (3) in a patient suffering from a neurodegenerative disorder. Since then, both the number of requests for euthanasia and ODE have gradually increased. From 2012 it is possible to donate lungs, liver, pancreas and kidneys. Since 2021, heart donation has been possible using the “heart-in-a-box” method, which has increased the organ potential. The purpose of this abstract is to provide insight into the background of the ODE procedures.

## Methods

The figures regarding organ donation after euthanasia and transplantation were used based on data from the NTS.

## Results

Since 1-1-2012 to 1-11-2024, 3457 (3) organ donations have taken place in the Netherlands, 150 (4.3%) of which were ODE procedures. Although the average share of the ODE compared to post-mortem organ donation over these years is 4.7%, we see a proportion of 8.2% in the year 2023 and 9.7% in the year 2024. Of these 150 ODEs, 69 (46%) were men and 81 (54%) were women. 73 (48.6%) cases were based on somatic suffering and 77 (51.4%) on the basis of psychological suffering. Since 2018, there has been an increase in ODE due to psychological suffering (4). Of these 150 ODEs, 32 (21.3%) hearts, 98 (65.3%) lungs, 98 (65.3%) livers, 26 (17.3%) pancreas and 265 (88.3%) kidneys were transplanted.

## Conclusions

Since 2012, we have seen a gradual increase in the number of ODE patients, with a significant increase in 2023 and 2024. In addition, since 2018 there has been a shift from somatic to psychological underlying suffering. The results show that the ODE patient category is a valuable addition to the existing donor potential.

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# From An Opt-In Consent System To An Active Donor Registration: Effects On Family Consent Rates For Organ Donation

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## Background

In July 2020, the Netherlands transitioned its deceased organ donation consent system from an opt-in model to an active donor registration (ADR) system. The primary goal of the new donor act was to raise public awareness on organ donation and consequently increase the number of organ donors. This study evaluates the effectiveness of this new act in increasing the family consent rate for organ donation.

## Methods

National data on deceased patients in intensive care units (ICUs), collected by the Dutch Transplant Foundation (NTS) via NovaNORD, were used to analyse family consent rates for organ donation. A quantitative analysis of 1,178 “Quality Standard Donation” evaluation forms, collected from ICUs between January 2021 and February 2024, was conducted to provide insights into families’ refusal motives.

## Results

After implementation of the new donor act, 14 million Dutch residents were registered: 34% “Yes,” 31% “No,” 24% “No objection,” and 11% “Decision by next of kin.”

For potential donors with a “Yes” registration, family consent for organ donation was given in 86% of the cases in 2021 and remained relatively stable at 86% through 2024.





When “No objection” was registered, family consent was obtained in 47% of the cases in 2021 and 45% in 2024. When “Decision by next of kin” was required, family agreement rates dropped from 46% in 2021 to 28% in 2024. The overall consent rate was 60% in 2021 and 59% in 2024, compared to 42% in 2019 under the opt-in system.<sup>1</sup>

### Conclusions

Since the implementation of the new donor act, the overall consent rate has remained steady at 60%, which is higher than the rate observed in 2019 under the opt-in system. While the consent rate is encouraging, families frequently override the donor’s registered wishes in cases of a “Yes” or “No objection”, often using their own rather than the patients’ perspectives. Honoring the donor’s wishes continues to be a challenge in practice and requires further attention.

1. Dutch Transplant Foundation. Annual report 2019. Leiden, The Netherlands 2020.

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# Carboxyhemoglobin And Smoking Status In Kidney Transplant Recipients

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### Background

Smoking is a risk factor for graft failure and death in kidney transplant recipients (KTRs). Nicotine addiction complicates quitting and self-reported smoking status is

unreliable. Urinary cotinine is the gold standard for identifying active smokers but is costly, infrequently measured, and prone to false positivity in nicotine patches or gum users. We aimed to investigate carboxyhemoglobin (COHb) as a potential biomarker for assessing smoking in KTRs.

### Methods

Smoking status was determined by a questionnaire. Urinary cotinine was measured with the Enzyme Multiplied Immunoassay Technique (lower limit of quantification (LLQ) 100 µg/L), and plasma COHb was obtained from blood gas analysis. The receiver operating characteristic (ROC) curve analysis was used to evaluate the diagnostic performance of the COHb.

### Results

Of 404 KTRs (mean age 56 ± 13 years, 43% female, median time post-transplant 89 months [Interquartile range (IQR) 36-157]), 15.1% had urinary cotinine levels above the LLQ, and the median COHb level was 0.92% [IQR 0.82-1.14]. Urinary cotinine and COHb levels varied significantly by smoking status based on questionnaire responses: non-smokers, ex-smokers, active smokers, and those with unknown status (P<0.001). Among 107 self-reported non-smokers, 1.6% (3 individuals) had cotinine levels above the LLQ (median cotinine 395 µg/L [IQR 305-921], COHb 0.92% [IQR 0.72-1.11]); of 153 ex-smokers, 12.4% (19) had cotinine levels above the LLQ (median cotinine 564 µg/L [IQR 388-829], COHb 0.92% [IQR 0.82-1.11]); of 36 active smokers, 88.9% (32) had cotinine levels above the LLQ (median cotinine 705 µg/L [IQR 484-994], COHb 2.27% [IQR 1.21-3.84]); and of 28 with unknown status, 25% (7) had cotinine levels above the LLQ (median cotinine 952 µg/L [IQR 766-1433], COHb 0.96% [IQR 0.82-1.36]). A significant correlation was observed between urinary cotinine and COHb (Spearman ρ=0.60; P<0.001), with both markers showing comparable area under the curve (AUC) values for detecting smoking exposure (urinary cotinine AUC=0.92, COHb AUC=0.87, p-value between 2 ROC curves=0.10). Using the Youden index, an optimal COHb cut-off of 1.5% was identified, yielding a specificity of 94% and sensitivity of 72%.

### Conclusions

Carboxyhemoglobin, which is more accessible than urinary cotinine, is just as effective in identifying smoking in KTRs.



## Training For Organ Donation Coordinators In The Netherlands; A New Development. (Original in Dutch)

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### Background

A training course for organ donation coordinators (ODC) has been developed on behalf of the Dutch Federation for University Hospitals (NFU) and ODC-NL. The aim was to develop national training for new ODCs that guarantees competence, expertise and uniform working methods.

### Methods

A project group and sounding group were set up. The expertise of various involved bodies was used to develop the training: ODCs, educationalists, donation intensivists, transplant physicians and the Dutch Transplantation Foundation (NTS). The project group first developed final objectives for the training, linked to the required skills, knowledge sources and CanMeds competencies. The training structure was subsequently developed and the required training products were determined. The learning objectives were then described, after which the project group members developed the various training products, in close collaboration with experts. Evaluation and testing instruments have also been developed for

the development of expertise and uniform assessment of the new ODCs. The sounding board reviewed and provided advice. Finally, all products are placed in an online learning management system (LMS).

### Results

The training has a clear structure: The ODC goes through the training from Phase 0 (introduction) via Phase 1 (ICU phase), Phase 2 (care for relatives) to Phase 3 (OR phase). The training products are offered within the LMS in various forms: text, recorded presentation, film, photos, animations, e-learning and scientific articles. To monitor progress, test moments and aptitude tests are included, as well as fixed evaluation moments. From January 2025, the first new ODCs will be trained according to this training.

### Conclusions

With the development of training for the ODCs, the function of the ODC has been further professionalized. As a project group, we are proud to present the training. The first evaluation will take place after the first new ODCs have been incorporated.

## Borders, Bodies And Organs: Preliminary Findings Of A Qualitative Fieldwork Study About Migration And Kidney Sales In Countries Across The Euro-Mediterranean Border.

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## Background

Europe's exclusionary migration governance is intensifying the vulnerabilities of migrants. Sporadic global reports reveal migrants selling or being solicited for kidney sales during their journeys. Yet, this interlinkage(s) between migration and transplantation remains understudied. My PhD research has two aims: to explore the experiences of migrants regarding kidney sales, and to examine the experiences and perspectives of medical professionals with migration-related kidney sales. The first results of this project are presented here.

## Methods

Since 2023, I have conducted multi-sited ethnographic fieldwork across the Netherlands, Greece, Bulgaria, and Italy, spending up to four months in each location. This work includes conversations, interviews, and non-participant observation at asylum centers, NGOs, hospitals, and border regions. So far, I've spoken with over 60 migrants, 12 of whom shared experiences related to kidney sales and organ theft. Additionally, 17 medical professionals have shared insights concerning organ trade and migration.

## Results

Initial findings reveal that migrants experience their journey to and within Europe as fraught with peril, uncertainty, and abuse. Contrastingly, transplant professionals emphasize Europe's commitment to ethics, arguing that strict regulations ensure fair access to organs, preventing any organ trading. Yet, preliminary results reveal that narratives about kidney sales and organ theft circulate in both groups, within and outside of Europe. Migrants speak of receiving lucrative offers by brokers for their kidneys and of friends of friends having sold a kidney. They also see suspicious scars on other migrants' bodies and speculate that migrants are kidnapped for their organs. Medical professionals indicate that organ trade primarily occurs outside of Europe but recount receiving anonymous offers for kidneys and discreet inquiries from patients wanting to buy organs abroad.

## Conclusions

The migration realm and the transplant community are 2 distinct worlds, yet, what binds them are stories and risks of organ trade. While it is too soon to separate fact from fiction among the reported narratives, findings indicate

that alertness is warranted given the lack of knowledge, understanding, and awareness about this issue. Given the social harms co-produced by global organ scarcity and Europe's restrictive migration governance, dialogue about this topic is needed among medical professionals.

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# Health-Related Quality Of Life In Living Kidney Donors Participating In Kidney Exchange Programs

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## Background

Kidney exchange programs (KEP) have revolutionized living donor kidney transplantation (LDKT) by enabling transplants for patients with HLA or ABO incompatible donors. However, the implications for donors participating in KEP, particularly regarding postoperative health-related quality of life (HRQoL), are not well elucidated. This study compares the HRQoL of donors participating in KEP with donors donating directly (non-KEP).

## Methods

The study included 724 donors, with 121 in the KEP group and 603 in the non-KEP group. Outcomes were assessed using the mental component summary (MCS), physical component summary (PCS), EQ-5D-3L, MVI-20



score, and self-rated pain level. We used a mixed-effects regression model to assess differences between KEP and non-KEP over time, accounting for repeated measures within subjects.

### Results

There was a significant temporary decline in both the MCS and PCS post-donation; however, these outcomes returned to pre-donation levels after an interval of two months. Donors participating in the KEP had higher PCS and MCS 1-year post-donation. Comparable results were observed in the self-assessed HRQoL using the EQ-5D-3L instrument, as well as in the fatigue scores measured by the MVI-20.

### Conclusions

We found that participation in KEP does not adversely affect donors' short- or long-term mental and physical HRQoL outcomes and that LDKT donors have HRQoL of pre-donation levels soon after donation. These insights are reassuring, indicating that donors participating in KEP can expect HRQoL comparable to those who do not. This reinforces the viability of KEP as a safe option for expanding LDKT and findings can inform patient and donor education.

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## Organ Donor Potential After Extracorporeal Cardiopulmonary Resuscitation For Out-Of-Hospital Cardiac Arrest – A Post-Hoc Analysis Of The INCEPTION-trial

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## Background

Extracorporeal cardiopulmonary resuscitation (ECPR) is a potentially life-saving intervention in refractory out-of-hospital cardiac arrest (OHCA). ECPR enables ICU admission to patients who otherwise would have died at the emergency department (ED). Still, many of them die, frequently after withdrawal of life-sustaining therapies. The additional time provided by ECPR allows for the assessment of organ donor suitability. The aim of this study was to evaluate the impact of ECPR on the number of potential organ donors after refractory OHCA.

## Methods

We performed a post-hoc analysis of the multicenter INCEPTION trial, which randomized 134 OHCA patients between conventional CPR (CCPR) and ECPR. Detailed patient reports—including liver and kidney function on the day of death, resuscitation details, and medical history—were presented to transplant physicians to determine the acceptability of the liver and kidneys for organ donation. In addition to the intention to treat analysis, we performed an “as-treated” analysis, which was limited to patients arriving without return of spontaneous circulation (ROSC) at the ED.

## Results

Out of 70 patients randomized to ECPR and 64 to CCPR, potential organ donors were identified in 13 (19%) and

4 (6%) patients, respectively ( $\chi^2$  test,  $p=0.060$ ). In the as-treated analysis of patients arriving without ROSC at the ED, 14 out of 55 (26%) treated with ECPR were potential donors, compared to 0 out of 59 treated with CCPR ( $p<0.001$ ). This included 5 (9%) potential kidney donors and 14 (26%) potential liver donors.

## Conclusions

Although ECPR is currently used with life-saving intentions, it may simultaneously increase the number of potential organ donors following cardiac arrest.

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# Attitudes And Acceptance Among Liver Transplant Recipients For Self-Measuring With Home-Monitoring (LASER-study)

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## Background

Liver transplant recipients (LTRs) require lifelong monitoring, with frequent monitoring in their first year after transplantation. Aftercare consists of frequent vital measurements, in-clinic consultations, lifestyle and medication

adjustments. This requires substantial investment from both health care professionals and LTR. A home-monitoring system was introduced as part of standard aftercare with focus on self-measuring. However, little is known about attitudes and acceptance for this new technology among LTRs. LTRs perspectives might not align with the health care professionals vision towards self-measuring. our objective was to investigate the patients' perspectives (attitudes and experiences) prior to initiation of home-monitoring and to assess the level of patient activation during the first year after liver transplantation.

### Methods

This prospective cohort study included all consecutive LTRs between the 1<sup>st</sup> of June 2022 until the 31<sup>st</sup> of May 2023. Data from the baseline measurement was analyzed for this study. LTRs did not participate if there was a language barrier or technical capability, or if they did not give informed consent. LTR were recruited during hospital admission after transplantation, prior to the introduction of the home-monitoring system. Participants were sent an online questionnaire based on Unified Theory of acceptance and use of Technology (UTAUT-33) and Patient Activation Measure (PAM-13) that could be answered using a 5-point Likert scale (0=strongly disagree, 4=strongly agree). Socio-demographic and medical data were obtained from LTRs/participants medical records.

### Results

In total, 51 participants were included, of which 25 (49%) were female and median age was 56 years (IQR 43-65). 44 participants (86%) completed the baseline questionnaire. UTAUT-33 was divided into 6 domains: Expected load ( $M=2.79\pm 0.39$ ), Facilitating conditions ( $M=3.08\pm 0.49$ ), Social influence ( $M=2.00\pm 0.41$ ), Fear ( $M=1.28\pm 0.39$ ), Data Security ( $M=1.5\pm 0.24$ ), Self-Efficacy ( $M=2.02\pm 0.29$ ), Behavioral intention to use ( $M=3.14\pm 0.47$ ), and Informed & engaged ( $M=2.29\pm 0.44$ ). Median PAM-13-T-score was 48.6 (IQR 43.1-59.8). LTRs found on average 2 measurements per day acceptable, ranging from 1 to 4 times a day.

### Conclusions

Prior to use LTRs felt well-informed and expressed willingness to use self-measuring for home-monitoring. We demonstrated high trust and low fears for using home-monitoring. Prospective data collection is ongoing and will assess how perspectives influence the compliance to home-monitoring over time.

# Increase Of Epicardial Fat Over Time After Heart Or Lung Transplantation

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### Background

Immunosuppression, while essential post-transplant, can also contribute to complications. Steroids and calcineurin inhibitors can contribute to metabolic syndrome since they increase rates of obesity and diabetes, hypertension and renal insufficiency. Interestingly, an increase in epicardial fat (EF) is associated with metabolic syndrome as well. Therefore, we performed a pilot study to measure EF.

### Methods

We included heart (HTx) or lung (LTx) transplantation patients with CT scans shortly after transplantation and one year later. After anonymization and randomization, all scans were assessed for EF at 3 different places to semi-quantitatively score the amount of EF (minimum(1), normal(2) or maximum(3)). As such, overall score ranged from 3(minimal EF present) to 12(maximum EF present). The difference in EF was calculated. For each patient, data regarding steroid usage, rejection episodes, body mass index(BMI) and kidney function(CKD-EPI eGFR) was extracted from the electronic patient database(EPD).

### Results

We included 18 HTx patients (4 females, 22%), with a median age of 58[IQR40-61] at transplant. Baseline CTs



and follow-up CTs were acquired 31[IQR14-49] and 390[IQR374-491] days post-transplant. EF increased in 11 patients(61%) from 4[IQR3-4] at baseline to 5[IQR4-6] at one year post-transplant( $p=0.002$ ) and remained stable in 7(39%). Four patients experienced one rejection episode. Steroid dosage decreased from 15[IQR10-30] mg to 5[IQR2.5-10] mg daily ( $p<0.001$ ).

We included 26 LTx patients (11 females, 42%), with a median age of 59[IQR44-64] at transplant. Baseline CTs and follow-up CTs were acquired 18[IQR6-25] and 426[IQR378-490] days post-transplant. EF increased in 14 patients(54%) from 4[IQR3-6] at baseline to 5[IQR4-7] at one year post-transplant( $p<0.001$ ) and remained stable in 12(46%). BMI increased from 23(22-25CI95%) kg/m<sup>2</sup> to 26(24-28CI95%) kg/m<sup>2</sup>, ( $p=0.002$ ). eGFR decreased from 91[IQR 54-105] ml/min to 38[IQR28-58] ml/min, ( $p<0.001$ ). Steroid dosage decreased from 17.5[IQR15-30] mg to 10[IQR10-10] mg daily, ( $p<0.001$ ). Two LTx patients(8%) had rejection before baseline; 15(58%) experienced rejection ( $p=0.001$ ) with 8(53%) having one rejection, 3(20%) two, and 4(27%) three.

### Conclusions

This pilot shows an increase in EF among thoracic transplant patients over one year. Further research with a larger cohort is needed to assess the influence of immunosuppressive therapy and rejection episodes on EF over time and if this influences organ function.

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# The Impact Of Donor And Recipient Sex Combination On Long-Term Outcomes Following Living Donor Kidney Transplantation: A Retrospective Dual-Center Cohort Study

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### Background

The impact of donor and recipient sex on living donor kidney transplantation remains debated. This study investigates the impact of donor-recipient sex combinations on long-term transplant outcomes.

### Methods

A dual-center retrospective study was conducted to identify patients who underwent living donor kidney transplantation from January 2010 to December 2020. Transplantations were categorized into four donor-recipient sex combinations: male-to-male (MDMR,  $n=476$ ), female-to-male (FDMR,  $n=767$ ), male-to-female (MDFR,  $n=463$ ), and female-to-female (FDFR,  $n=372$ ). The primary outcome was death-censored graft survival. The secondary outcomes were patient survival, delayed graft function, acute rejection and graft function.





## Results

There were no significant differences in 10-year death-censored graft survival (MDMR vs FDMR vs MDFR vs FDFR: 63.8% vs 61.7% vs 64.6% vs 61.9%,  $p=0.55$ ) and patient survival rates (72.9% vs 70.9% vs 74.5% vs 73.8%,  $p=0.38$ ) among the sex combinations. The incidence of delayed graft function (8.2% vs 6.1% vs 6.0% vs 5.1%,  $p=0.29$ ) and acute rejection (15.5% vs 16.4% vs 16.4% vs 18.3%,  $p=0.76$ ) was comparable across the groups. Within the same recipient sex, those receiving kidneys from male donors exhibited significantly higher eGFR throughout follow-up compared to recipients of female donor kidneys.

## Conclusions

Donor-recipient sex combinations did not significantly affect long-term graft or patient survival in living donor kidney transplantation. However, kidneys from male donors, potentially due to a higher nephron count, were associated with better renal function compared to those from female donors.

## Background

Kidney transplant recipients (KTR) with high-normal plasma lead concentrations have a higher risk of graft failure (GF). Clinically, chelation therapy using meso-2,3-dimercaptosuccinic acid (DMSA) removes lead. Despite the proposal that chelation therapy can prevent GF through lead removal, evidence is lacking. To guide clinical decisions, we conducted an early economic evaluation, aiming to explore the (economic) feasibility of screening for and implementing chelation therapy with oral DMSA for high-normal plasma lead concentrations in KTR (i.e., the intervention) compared to standard care.

## Methods

A Markov model simulated the life course of 10,000 KTR in the Netherlands from a societal perspective. Transition probabilities were estimated using a Dutch KTR cohort. Costs and utilities were sourced from publications and public data. Model robustness was investigated through deterministic and probabilistic sensitivity analyses. Various administration strategies were tested. Five-year costs were calculated from a healthcare payer's perspective. The value of information was assessed.

## Results

The intervention was cost-saving and improved health, leading to a dominant incremental cost-effectiveness ratio. The result was most sensitive to transition probabilities (led by GF, followed by death with functioning graft and death with graft failure). The probability of the intervention being cost-effective was 60%. Chelation strategies did not affect the result. The intervention applied to the Dutch KTR population could save €27 million in the initial five years. Further research is desirable if the cost of obtaining perfect information on GF survival is approximately below €4,000/KTR (all uncertainties under €5,000/KTR).

## Conclusions

The cost-effectiveness of the intervention is robust, except when considering the uncertainties around (graft) survival probabilities in KTR. The proposal of applying chelation therapy in the new aforesaid setting holds significant potential. However, trials that systematically assess the efficacy, administration strategies, and impacts on survival are crucial in updating the current evaluation and informing policies.

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# Early Economic Evaluation Of Chelation Therapy In Kidney Transplant Recipients With High-Normal Lead

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## Donors With Post-Donation eGFR (Dip) Below 35 mL/Min/1.73M<sup>2</sup>

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### Background

Living kidney donation may carry a risk of renal function deterioration after donation.

### Methods

Between 1981 and 2019, 2212 individuals underwent donor nephrectomy in our center. In the present study pre- and post-donation characteristics of donors with an (incidental) post-donation eGFR <35 mL/min/1.73m<sup>2</sup> were compared to all other living donors (controls).

### Results

eGFR data were available from 2207 donors. In 107 donors (4.8%) eGFR had ever been <35 mL/min/1.73m<sup>2</sup>. Lower kidney function pre-donation, higher age and time since donation were risk factors for eGFR <35 mL/min/1.73m<sup>2</sup> in multivariable binary logistic regression analysis.

Three groups could be distinguished:

1. Group 1 donors (n=69; 3.1%) had moderate, though stable eGFR (35-50 mL/min/1.73m<sup>2</sup>) with an occasional dip <35 mL/min/1.73m<sup>2</sup>. None needed kidney replacement therapy (KRT), 14 (20%) died.
2. Group 2 donors (n=11; 0.5%) had progressive kidney function deterioration since donation. In retrospect,

five probably had familial kidney disease, three of them needed KRT, none died. The other six had diverse and unforeseen causes of deterioration, none needed KRT, two (18%) died.

3. Group 3 donors (27, 1.2%) had long-term stable kidney function, that eventually declined due to new-onset severe cardiovascular disease, malignancies or diabetes mellitus, two needed KRT, 15 (56%) died.
4. In the control group (n=2100; 95.2%), none needed KRT.
5. Median eGFR (IQR) at donation: Controls: 94 (84-104); Group 1: 69 (62-75); Group 2: 97 (68-103); Group 3: 78 mL/min/1.73m<sup>2</sup> (63-94). Group 1 and 3 differed significantly from controls (Mann-Whitney, p<0.001; p<0.001).
6. Median age (IQR) at donation: Controls: 51 years (40-60); Group 1: 66 (61-77); Group 2: 52 (45-66); Group 3: 62 years (52-74). Group 1 and 3 differed significantly from controls (Mann-Whitney, p<0.001; p<0.001).
7. Median age (IQR) at last follow-up: Group 1: 78 (73-83); Group 2: 65 (56-81); Group 3: 79 years (71-87). Group 2 significantly differed from groups 1 and 3 (Mann-Whitney, p=0.012; p=0.007).

### Conclusions

Five donors probably had familial kidney disease. Currently, genetic testing could rule out donation. Kidney function decline to an eGFR <35 mL/min/1.73m<sup>2</sup> after kidney donation occurs in 4.8% of all living donors, primarily at high age, but it led to KRT in only 0.2%.

## Donation Experiences And Unmet Care Needs Among Living Kidney Donors: A Literature Review.

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## Background

Half of all kidney transplantations in the Netherlands are performed with a living kidney donor (LKD). Although the vast majority of LKDs are satisfied with (after)care, dissatisfaction is sometimes reported in clinical practice. It is not clear to care professionals why these donors are unsatisfied. The aim of this literature review was to provide insight in donation experiences and potential unmet care needs among living kidney donors in the first year after donation in order to inform intervention development.

## Methods

The literature review was conducted by searching two databases: PubMed and Cochrane.

Inclusion criteria were living kidney donors, articles published after 2014, written in the English or Dutch language. Exclusion criteria were not addressing topics of interest, pre-donation or focus on recipients. A total of 84 articles were screened but did not satisfy the criteria. This resulted in including 11 articles, thematically analyzed after.

## Results

Most experiences during and after kidney donation were positive.

Negative experiences were reported when donors were insecure about their own health, mostly among medically complex LKDs. Other negative experiences were related to unrealistic expectations before donation, causing disappointment after donation. In four studies LKDs expressed feeling anxious, frightened and distressed after donation. In three studies a negative impact on the donor-recipient relationship and donor's financial status was reported.

Three main unmet care needs were identified: the need for improved education pre-donation; a more holistic approach to donor aftercare; and access to psychological support.

Only two studies explore interventions to promote outcomes after donation. One where LKDs received

cognitive behavioral therapy. Donation-related emotions, social problems and physical limitations were discussed. This had a positive effect on the HRQoL of LKDs. The second implemented a digital platform where LKDs shared experiences, which helped processing emotions.

## Conclusions

Risk factors predicting a reduced HRQoL or negative experiences after donation have been explored. Research on how to signal these risk factors using an intervention is yet to be done. LKDs were satisfied with the use of an intervention in earlier studies. Care improvements could be made in educating and coaching LKDs, using a holistic and multidisciplinary approach including psychological support.

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# First Results Of The Pilot CT-scans: The Impact Of Chest And Abdominal CT-scans In DBD And DCD-organ Donor Screening In The Netherlands

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## Background

Chest and abdominal CT-scan could be valuable in DBD- and DCD donor screening. Compared to the currently mandatory chest radiograph and abdominal ultrasound, CT scans provide more detailed information on aberrant vascular anatomy and organ quality. This study aimed to assess the impact of chest and abdominal CT-scan in deceased organ donor screening.

## Methods

A nation-wide prospective cohort study was conducted, including all deceased organ donors in The Netherlands between July 1<sup>st</sup>, 2022 – April 30<sup>th</sup>, 2024, comparing donors who underwent an abdominal ultrasound and chest X-ray (control group) versus those who received chest and abdominal CT-scan (referred to as 'pilot group'). Outcome measurements were the incidence of procurement related injuries to abdominal organs and the incidence and pathology of suspicious lesions found during procurement. The Chi-square test was used to assess differences in procurement related injury.

## Results

Between July 2022 and April 2024, 717 potential organ donors were reported, with 331 donors receiving a CT-scan according to the new scan protocol. In total, 1065 kidneys, 459 livers and 135 pancreases were procured. In the pilot group the incidence of procurement related injury in kidney grafts was significantly lower compared to the control group (16% vs 23%,  $p < 0.01$ ) and the extraction time was shorter by 3 minutes (36 minutes vs 39 minutes,  $p < 0.01$ ). There was no significant difference in the incidence of procurement-related injury for liver and pancreas grafts. However, the hepatectomy time was 2 minutes shorter in the pilot group as compared to the control group (31 minutes versus 33 minutes,  $p = 0.03$ ), while pancreas extraction time was not significantly different. During screening, in 20 donors a suspected lesion (6%) were found in the pilot group versus four (1%) in the control group. During procurement, suspected lesions were identified in 2 donors (0.6%) in the pilot group and in 7 donors (1.8%) in the control group.

## Conclusions

CT scanning appears to reduce both procurement-related injury rates and extraction time for kidney and liver procurement. Additionally, the number of suspected lesions found during procurement was lower in patients with a CT scan in the screening phase. Further analyses on transplant outcome will follow.

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# Reprogramming Innate Immune Memory Using Tacrolimus-Loaded Nanobiologics Promotes Organ Transplant Acceptance

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## Background

Tacrolimus is a highly effective drug for preventing allograft rejection, but its long-term use is associated with substantial side effects. While tacrolimus is primarily recognized for its immunosuppressive effects on T cells, we recently uncovered its influence on innate immune memory. This is a metabolically and epigenetically regulated program controlling the inflammatory reactivity



of innate immune cells, and our findings highlight its critical role in organ transplant survival. Here, we investigated the effects of myeloid-directed tacrolimus-loaded nanobiologics (Tac-NBs) on innate immune memory *in vitro*, and their potential as an induction therapy to improve graft survival in a heart transplant mouse model.

### Methods

Human peripheral blood mononuclear cells (PBMCs) were stimulated for 24 hours with innate immune memory inducer heat-killed *Candida albicans* (HKCA), in presence or absence of Tac-NBs. After five resting days, cells were restimulated with lipopolysaccharide or Pam3CSK4, and interleukin-6 (IL-6) and tumor necrosis factor (TNF) production was assessed using ELISA. Transcriptomic and metabolic effects of Tac-NBs on innate immune cells were investigated by RNA-sequencing and Seahorse technology, 24 hours or six days post-treatment respectively. To assess the effects of Tac-NBs on graft survival, C57BL/6J mice heterotopically transplanted with BALB/c hearts received Tac-NBs induction therapy without subsequent immunosuppressive maintenance therapy.

### Results

Tac-NBs suppressed HKCA-induced IL-6 and TNF production upon restimulation in PBMCs. Transcriptomic

analysis and metabolic profiling revealed that Tac-NBs reversed HKCA-induced regulation of genes involved in oxidative phosphorylation and interferon responses, and inhibited HKCA-induced metabolic activity. In the heart transplant mouse model, Tac-NBs induction treatment resulted into improved graft survival compared to untreated controls (median 75 days vs 8 days) and resulted in long term graft acceptance (> 100 days) in 62.5% of the mice when combined with a single dose of CTLA4 Ig induction treatment.

### Conclusions

Myeloid-directed Tac-NBs suppress cellular metabolism, cytokine memory responses and inflammatory gene transcription in human monocytes *in vitro*. In a heart transplant mouse model, Tac-NBs markedly extend allograft survival and, in combination with CTLA4-Ig, achieve long-term graft acceptance without the need for maintenance immunosuppressive therapy. These findings demonstrate that short-term tacrolimus-induced reprogramming of innate immune cells offers a promising approach to promoting durable graft acceptance.



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