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Normothermic Liver Machine Perfusion at a Large European Center

Real-world Outcomes following 238 Applications

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Objective: To report outcomes from routine clinical practice of liver transplantation (LT) following normothermic liver machine perfusion (NLMP) and compare to LT after static cold storage (SCS).

Background: NLMP is emerging as a clinical routine in LT and has recently received renewed attention; however, outcomes outside of clinical trials are lacking.

Methods: All adult LT between February 2018 and January 2023 were included. A comprehensive viability assessment was applied during NLMP. Outcomes were compared between NLMP and SCS recipients, as well as benchmark and non-benchmark cases.

Results: Of the 332 LT included, 174 underwent NLMP and 158 were transplanted after SCS. Sixty-seven organs were accepted and transplanted only under the premise of NLMP. One-year graft survival for SCS and NLMP recipients was 83.8% versus 81.3% and 93.4% for benchmark cases in the overall cohort. Total preservation time had no influence on graft survival in the NLMP group but was associated with inferior 1-year graft survival in the SCS group. NLMP usage increased significantly over the duration of the study period, as did the median total preservation time. With increasing NLMP use and longer preservation times, nighttime surgery decreased significantly from 41.9% to 4.2%.

Conclusions: Prolonged preservation times ease logistics and enable daytime surgery. The possibility of NLMP offers to expand LT without negatively affecting outcomes.

Keywords: graft preservation time, graft utilization, liver transplantation, nighttime surgery, normothermic machine perfusion

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Since publication of the first human normothermic liver machine perfusion (NLMP) trial in 2016,[1] retrospective single and dual-center studies, as well as multicenter prospective randomized controlled trials (RCTs), have supported the benefit of this technology.[2–6] Preservation of liver grafts using NLMP can offer several advantages compared with static cold storage (SCS),[7,8] including reduced rates of early allograft dysfunction (EAD) as well as increased utilization rates.

Since FDA approval in 2021, NLMP has garnered growing interest.[9] Our clinical NLMP program was initiated on February 1, 2018.[10] The goal was to adopt the technology in a cautious and integrative way and to translate the technical advancements into a measurable clinical benefit. Considering the reality of the allocation system in the Eurotransplant Network as well as the

financial and logistic limitations for transportation, we opted for a back-to-base approach, which is the current reality for many programs. While organ perfusion and device-to-donor transportation services are emerging in the United States, the early adoption of liver NLMP in Europe, as well as many U.S. centers, was a back-to-base application. One of the limitations of this approach is that the study conditions were different and that the findings from the RCTs, which used a device-to-donor approach, are not immediately transferrable to the back-to-base use case.

Hence, our intention was to establish the feasibility of this use case and its implementation in a multidisciplinary working space before establishing the efficacy of NLMP in a real-world setting.[10]

Herein, we now report on our five-year real-world experience with NLMP, comparing outcomes between the conventional procedure of applying SCS and liver transplantation (LT) versus expanding the donor profile, moving LT to daytime hours, and transplanting patients with a higher surgical risk profile through NLMP use.

METHODS

Study Endpoints

The study endpoints were 1-year graft survival, preservation times, NLMP utilization rate, logistical aspects (such as nighttime surgery), incidence of posttransplant (post-Tx) complications such as primary non-function (PNF), EAD, rejection episodes, biliary and arterial complications at 1 year as well as risk factors and their influence on 1-year graft loss and patient death. Endpoints were, in addition, analyzed according to the benchmark definition by Muller et al[11] to account for expected differences in outcomes based on the underlying donor-recipient risk profiles.

Study Population and Study Design

This is a retrospective, observational cohort study of all consecutive adult patients who underwent LT between February 1, 2018 and January 31, 2023. On February 1, 2018, the NLMP program was initiated at our center. We followed a back-to-base, end-ischemic approach using the OrganOx Metra device. NLMP was available throughout the study period without interruption. Based on the need for NLMP,[10] grafts underwent NLMP or SCS. Patient data were extracted from electronic health records, pseudonymized, and collected in a prospectively maintained, auditable institutional database.[12] The study was conducted in accordance with the Declaration of Helsinki and Istanbul, and approved by the Institutional Review Board of the Medical University of Innsbruck (EK 1168/2024). The results were reported according to the strengthening the reporting of observational studies in epidemiology guidelines.[13] Adopting the concept of a liberal organ acceptance policy in the context of the Eurotransplant Network organ allocation and exchange regulations requires careful reflection and cautious consideration of the equality and balance in the organ distribution system. In case an organ was deemed unsuitable for transplantation following NLMP, it was offered to Eurotransplant for reallocation.

Definitions

Benchmark cases were defined according to Muller et al,[11] to be considered a benchmark case, the following donor and recipient characteristics needed to be fulfilled: Model for End-stage Liver Disease (MELD) score ≤ 20, balance of risk (BAR) score ≤ 9, absence of acute liver failure, absence of mechanical ventilation support before LT, absence of portal vein thrombosis, absence of previous major abdominal surgery (HPB or extensive colorectal surgery), a full-size graft from a donation after brain death donor for primary LT [ie, split liver grafts, donation after circulatory determination of death (DCD) grafts, and retransplantations are excluded]. Extended criteria donors (ECDs) were defined according to the Eurotransplant Manual, Chapter 9: The Donor.[14]

Surgical Technique and Normothermic Liver Machine Perfusion Setup

At our center, the standard surgical technique is a cava-replacing approach, without routinely using veno-venous bypass, as previously described.[15] NLMP and viability assessment were performed according to our institutional protocol:[10] Maintenance of physiological pH values without sodium bicarbonate supplementation after 2 hours of NLMP, as well as a rapid decrease and maintenance of lactate values at physiological levels, are considered key indicators of good organ function.[16] Further to this, exceptionally high aspartate transaminase (AST), alanine transaminase, and lactate dehydrogenase levels, as well as a sharp incline of these parameters, are considered warning signals. Other values, such as bile output and biliary pH, glucose, and bicarbonate, are indicators of biliary viability and function.[17] For DCD grafts bile production was considered a must criterion. IL-6 levels, while not part of the viability assessment per se, are analyzed and recorded, serving as a predictor for reperfusion syndrome.[18]

Outcome Assessment

Graft loss was defined as patient death or liver retransplantation. PNF was defined as peak AST ≥ 3000 IU/L plus at least one of the following criteria: INR ≥ 2.5, serum lactate ≥ 4 mmol/L, and total bilirubin ≥ 10 mg/dL (values measured on postoperative day 3, biliary obstruction being excluded).[19,20] EAD was defined according to the Olthoff criteria.[21]

Rejection episodes were diagnosed and classified as previously described.[15] Biliary complications were classified as leaks, anastomotic stenosis, non-anastomotic stenosis, and cholangitis. Pathologies affecting the macroscopic donor bile ducts (non-anastomotic stenosis, biliary cast syndrome, and bile duct necrosis with intrahepatic leakage and biloma formation) in the absence of thrombosis, severe stenosis of the hepatic artery or recurrent disease (ie, primary sclerosing cholangitis) were classified as post-Tx cholangiopathy.[22]

The BAR score incorporates 6 variables [MELD score, donor age, recipient age, cold ischemia time (CIT), transplantation, and the need for life support] available at the time of organ acceptance and ranges from 0 to 27 points. BAR score values have been calculated according to the publication by Dutkowski et al[23] using the online BAR score calculator (https://www.assessurgery.com/bar-score/bar-score-calculator/). Postoperative complications were graded according to the Clavien-Dindo classification system.[24] Complications were further quantified using the Comprehensive Complication Index at hospital discharge and 1 year after transplantation.[25,26]

Statistical Analysis

For descriptive analyses, categorical variables were summarized with the help of absolute numbers and relative (percentages) frequencies. Continuous variables were summarized with means and SD or medians and interquartile range as appropriate. Comparative analysis of categorical variables was conducted using the χ^2 or Fisher exact test (if one or more cells had an expected count of < 5). The Mann-Whitney U and Kruskal-Wallis test were used to compare continuous, not normally distributed variables. Univariate and multivariate binary logistic regression analyses were performed for selected study endpoints, starting with a univariate analysis of each variable. Any variable with a univariate P value < 0.1 was selected as a candidate for the multivariate regression model. Kaplan-Meier survival curves and the log-rank test were used to analyze and compare graft and patient survival. Potential associations between continuous variables were investigated with the help of bivariate correlation analysis using the Spearman correlation coefficient. Receiver operating characteristic curves were plotted, and areas under the curve were analyzed to evaluate the performance of binary classifiers. All effects with a P value < 0.05 were considered statistically significant. Missing values were not imputed. Statistical analysis was conducted with SPSS (IBM SPSS Statistics for Mac, Version 29.0.0.0: IBM Corp.).

RESULTS

Recipient, Donor, and Preservation Characteristics

The study cohort consisted of 174 adult LT recipients in the NLMP group and 158 adult LT recipients in the SCS group (overall N = 332). Indications for LT and recipient demographics can be found in Table 1 and Supplemental Table S1 (Supplemental Digital Content Table S1, http://links.lww.com/SLA/F384; benchmark vs non-benchmark stratified according to NLMP vs SCS). The median recipient age was higher in the NLMP group compared with the SCS group [NLMP 60.0 years (53.0–66.3) vs SCS 58.5 (50.0–64.0), $P = 0.047$]. The proportion of standard risk, benchmark cases was significantly lower in the NLMP group [NLMP 36.2% (63 out of 174) vs SCS 48.7% (77 out of 158), $P = 0.021$]. Donors were older in the NLMP group [NLMP 57.0 years (44.8–67.0) vs SCS 52.5 (40.0–60.0), $P = 0.006$] and ECD [NLMP 83.9% (146 out of 174) vs SCS 62.7% (99 out of 158), $P < 0.001$], as well as DCD rates [NMLP 19.5% (34 out of 174) vs SCS 1.3% (2 out of 158), $P < 0.001$], were higher in the NLMP group. The CIT was significantly shorter in the NLMP group compared with the SCS group [NLMP 6.3 hours (5.3–7.5) vs SCS 7.8 (6.2–9.3), $P < 0.001$] and the total preservation time was significantly longer in the NLMP group [NLMP 22.3 hours (18.0–26.8) vs SCS 7.8 (6.2–9.4), $P < 0.001$].

Indications for Normothermic Liver Machine Perfusion and Utilization Rate

In most cases the indication for NLMP use was not driven by a single factor rather than a combination of multiple factors (donor and recipient factors and logistic aspects). NLMP use permitted us to accept 67 additional liver grafts which we would not have accepted before the introduction of NLMP at our center per center policy. These included DCD and other ECD grafts with additional risk factors, such as advanced age, steatosis, or prolonged ischemia times, livers from donors with suspected malignancy where NLMP provided additional time for histopathologic workup as well as liver grafts from septic donors where NLMP served as a platform to administer targeted anti-infective treatment and monitoring of the treatment response before LT.[27]

Overall, these liver grafts "not accepted without the possibility for NLMP" (n = 67) had a significantly higher Eurotransplant Donor Risk Index [ET-DRI; 2.13 (1.67–2.55) vs 1.70 (1.30–1.95), $P < 0.001$] compared with livers that we would have accepted regardless of NLMP availability. A detailed analysis of the additional liver grafts we were able to accept due to the possibility of NLMP can be found in Supplemental Table S2 (Supplemental Digital Content Table S2, http://links.lww.com/SLA/F384) and Supplemental Table S3 (Supplemental Digital Content Table S3, http://links.lww.com/SLA/F384).

During the study period, we observed an increase in DCD graft usage from 8.1% to 15.3% ($P = 0.302$; Fig. 1). Likewise, the median ET-DRI also increased from 1.61 to 1.75 ($P = 0.210$). The graft utilization rate was 73% (174 LTs out of 238 normothermic perfusions). Reasons for graft discard are listed in Supplemental Table S4 (Supplemental Digital Content Table S4, http://links.lww.com/SLA/F384). A flow chart depicting the fate of all liver grafts offered to our center during the study period can be found in Supplemental Figure S1 (Supplemental Digital Content Fig. S1, http://links.lww.com/SLA/F384).

Preservation Times and Logistical Aspects

The proportion of NLMP grew from 24.3% in the first year to 69.4% in the fifth year ($P < 0.001$; Table 2). At the same time, the median NLMP time increased from 9.4 hours to 17.4 hours ($P = 0.003$) and the median total preservation time increased from 17.1 hours to 22.7 hours ($P < 0.001$; Fig. 2). Importantly, neither NLMP time, CIT, nor total preservation time had any negative influence on graft survival in the NLMP group, whereas in the SCS group, the total preservation time was found to be an independent predictor of 1-year graft loss (Table 4). With the increased use of NLMP and the increased preservation time, nighttime surgery (surgery starts from 8 PM to 8 AM) became increasingly rare, dropping from 41.9% to 4.2% ($P < 0.001$; Table 2).

Complications After Liver Transplantation Following Normothermic Liver Machine Perfusion and Static Cold Storage

The overall incidence of post-Tx complications was similar between the NLMP and SCS groups (Table 3; Supplemental Digital Content Table S5, http://links.lww.com/SLA/F384 benchmark vs non-benchmark outcomes stratified according to NLMP vs SCS). Notably, no PNF occurred in the NLMP group [NLMP 0% (0 out of 174) vs SCS 2.5% (4 out 158), $P = 0.050$]. The NLMP group exhibited a slightly lower, although not significant, EAD rate compared with the SCS group [NLMP 29.9% (52 out of 174) vs SCS 36.1% (57 out of 158), $P = 0.230$]. Risk factors for EAD can be found in Supplemental Table S6 (Supplemental Digital Content Table S6, http://links.lww.com/SLA/F384). Biopsy-proven rejection was lower in the NLMP group compared with the SCS group [NLMP 4.0% (7 out of 174) vs 8.2% (13 out of 158), $P = 0.108$]. The incidence of biliary complications was similar between

TABLE 1. Recipient, Donor, and Preservation Characteristics

	All (N = 332)	NLMP (n = 174)	SCS (n = 158)	*P*	Benchmark (n = 140)	Non-benchmark (n = 192)	*P*
Recipient							
Age (yr)	60.0 (52.0–65.0)	60.0 (53.0–66.3)	58.5 (50.0–64.0)	**0.047**	59.0 (52.0–64.0)	60.0 (53.0–65.0)	0.734
Sex	—	—	—	0.537	—	—	0.583
Female	85 (25.6)	47 (27.0)	38 (24.1)	—	38 (27.1)	47 (24.5)	—
Male	247 (74.4)	127 (73.0)	120 (75.9)	—	102 (72.9)	145 (75.5)	—
BMI (kg/m^2)	25.6 (22.6–28.5)	25.5 (22.0–29.0)	25.7 (22.6–28.0)	0.894	26.0 (22.8–29.0)	25.4 (22.4–28.3)	0.283
Lab-MELD score	15.0 (10.0–20.0)	14.0 (10.0–19.3)	15.0 (10.8–20.0)	0.533	12.0 (9.3–15.0)	18.0 (12.0–24.0)	**< 0.001**
BAR score	5.0 (4.0–10.0)	5.0 (4.0–10.0)	6.5 (3.0–10.0)	0.434	4.0 (3.0–5.0)	9.0 (5.0–12.0)	**< 0.001**
Indication							
MASLD	65 (19.6)	36 (20.7)	29 (18.4)	0.592	33 (23.6)	32 (16.7)	0.117
ALD	52 (15.7)	23 (13.2)	29 (18.4)	0.198	26 (18.6)	26 (13.5)	0.213
metALD	18 (5.4)	12 (6.9)	6 (3.8)	0.213	5 (3.6)	13 (6.8)	0.204
HBV	15 (4.5)	8 (4.6)	7 (4.4)	0.942	11 (7.9)	4 (2.1)	**0.012**
HCV	25 (7.5)	16 (9.2)	9 (5.7)	0.228	10 (7.1)	15 (7.8)	0.819
HCC	103 (31.0)	54 (31.0)	49 (31.0)	0.928	54 (38.6)	49 (25.5)	**0.011**
ALF	30 (9.0)	12 (6.9)	18 (11.4)	0.154	0	30 (15.6)	**< 0.001**
Retransplantation	35 (10.5)	21 (12.1)	14 (8.9)	0.342	0	35 (18.2)	**< 0.001**
Life support	15 (4.5)	6 (3.4)	9 (5.7)	0.325	0	15 (7.8)	**< 0.001**
Mechanical ventilation	12 (3.6)	5 (2.9)	7 (4.4)	0.448	0	12 (6.3)	**0.003**
Portal vein thrombosis	26 (7.8)	18 (10.3)	8 (5.1)	0.074	0	26 (13.5)	**< 0.001**
Benchmark case	140 (42.2)	63 (36.2)	77 (48.7)	**0.021**	—	—	—
Multiorgan transplant	14 (4.2)	7 (4.0)	7 (4.4)	0.854	3 (2.1)	11 (5.7)	0.108
Median follow-up (mo)	23 (11.3–39.0)	19 (10.0–36.0)	27 (12.0–45.3)	**0.009**	26.5 (14.0–42.3)	18.0 (6.0–36.0)	**0.002**
Donor							
Age	55.0 (42.0–65.0)	57.0 (44.8–67.0)	52.5 (40.0–60.0)	**0.006**	57.5 (46.0–68.8)	53.0 (40.0–62.0)	**0.004**
Sex	—	—	—	0.640	—	—	0.147
Female	141 (42.5)	76 (43.7)	65 (41.1)	—	53 (37.9)	88 (45.8)	—
Male	191 (57.5)	98 (56.3)	93 (58.9)	—	87 (62.1)	104 (54.2)	—
BMI (kg/m^2)	26.0 (23.0–29.0)	26.0 (23.0–29.0)	26.0 (24.0–29.0)	0.829	26.0 (24.0–29.0)	26.0 (23.0–28.0)	0.074
COD	—	—	—	**0.006**	—	—	0.230
CVA	184 (55.4)	93 (53.4)	91 (57.6)	—	88 (62.9)	96 (50.0)	—
Circulatory	26 (7.8)	20 (11.5)	6 (3.8)	—	9 (6.4)	17 (8.9)	—
Trauma	72 (21.7)	29 (16.7)	43 (27.2)	—	25 (17.9)	47 (24.5)	—
Hypoxia	23 (6.9)	13 (7.5)	10 (6.3)	—	9 (6.4)	14 (7.3)	—
Other	27 (8.1)	19 (10.9)	8 (5.1)	—	9 (6.4)	18 (9.4)	—
ECD*	245 (73.8)	146 (83.9)	99 (62.7)	**< 0.001**	104 (74.3)	141 (73.4)	0.862
ECD criteria ≥ 2	121 (36.4)	82 (47.1)	39 (24.7)	**< 0.001**	42 (30.0)	79 (41.1)	**0.037**
DCD	36 (10.8)	34 (19.5)	2 (1.3)	**< 0.001**	0	36 (18.8)	**< 0.001**
ET-DRI	1.68 (1.39–2.01)	1.81 (1.49–2.25)	1.54 (1.33–1.83)	**< 0.001**	1.67 (1.32–1.93)	1.70 (1.41–2.14)	0.087
Preservation details							
fWIT (min)	23.0 (18.0–26.0)	23.0 (18.5–26.5)	21.5 (18.0 -)	0.807	—	23.0 (18.0–26.0)	—
CIT (h)	6.8 (5.5–8.3)	6.3 (5.3–7.5)	7.8 (6.2–9.3)	**< 0.001**	6.7 (5.3–8.2)	6.9 (5.5–8.4)	0.329
NLMP time (h)	16.2 (11.4–20.7)	16.2 (11.4–20.7)	—	—	14.7 (11.0–21.0)	17.0 (11.6–20.6)	0.393
Total preservation time (h)	14.2 (7.9–22.7)	22.3 (18.0–26.8)	7.8 (6.2–9.4)	**< 0.001**	10.7 (6.8–19.6)	16.2 (8.3–23.8)	**0.002**
Total operating time (h)	5.7 (4.8–7.0)	5.8 (4.9–7.2)	5.5 (4.6–6.7)	**0.027**	5.5 (4.5–6.5)	5.9 (4.9–7.5)	**0.002**
Nighttime surgery†	69 (20.8)	13 (7.5)	56 (35.4)	**< 0.001**	35 (25.0)	34 (17.7)	0.106

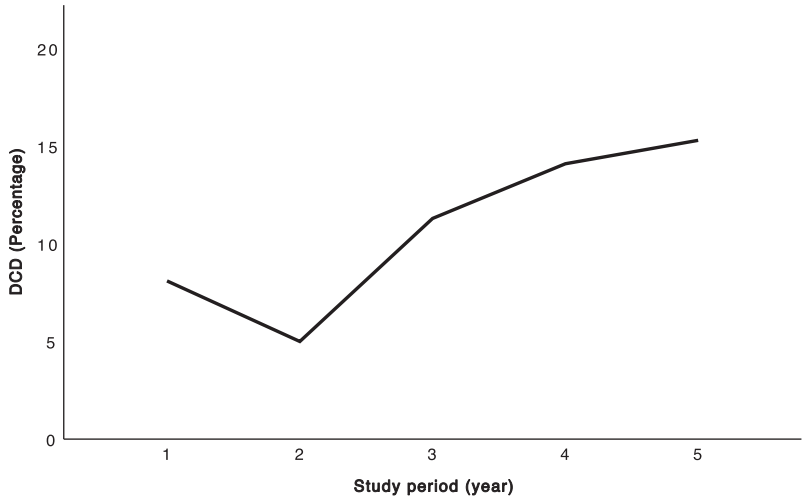
Bold values indicate significant *P* values.

*ECD criteria: Donor age > 65 years, ICU stay with ventilation > 7 days, BMI > 30 kg/m^2, steatotic liver > 40%, serum sodium > 165 mmol/L, alanine transaminase > 105 U/L, AST > 90 U/L, serum bilirubin > 3 mg/dL, donation after cardiocirculatory death.

†Surgery starts from 8 PM to 8 AM.

Values are presented as medians or absolute numbers with interquartile ranges and percentages in parentheses.

ALD indicates alcohol-associated liver disease; ALF, acute liver failure; COD, cause of death; CVA, cardiovascular accident; fWIT, functional warm ischemia time; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; ICU, intensive care unit; MASLD, metabolic dysfunction-associated steatotic liver disease; metALD, metabolic dysfunction-associated liver disease.



Study period (year)	DCD (percentage)
1	8.1
2	5.0
3	11.3
4	14.1
5	15.3

FIGURE 1. The proportion of DCD grafts transplanted increased over the duration of the study period.

groups [NLMP 42.0% (73 out of 174) vs SCS 36.7% (58 out of 158), $P = 0.329$]. There was a tendency for higher post-Tx cholangiopathy rates in the NLMP group compared with the SCS group [NLMP 9.8% (17 out of 174) vs SCS 5.7% (9 out of 158), $P = 0.168$]. This was attributed to a higher proportion of DCD grafts in the NLMP group (34 of 36 DCD grafts in the NLMP group). DCD was found to be a strong independent predictor of post-Tx cholangiopathy (Supplemental Digital Content Table S7, http://links.lww.com/SLA/F384). Arterial complications, reintervention rates within 30 days, unplanned readmission rates within 30 days, as well as intensive care unit (ICU) length of stay, overall length of stay, and overall complications at discharge and at 1 year, were similar between groups (Table 3).

Graft and Patient Survival Analysis

Kaplan-Meier estimates that for 1 and 3-year graft survival rates were similar for NLMP and SCS (Fig. 3A). Survival rates were significantly better for benchmark cases compared with non-benchmark cases (Fig. 3B; Supplemental Digital Content Fig. S2, http://links.lww.com/SLA/F384 benchmark vs non-benchmark survival outcomes stratified according to NLMP vs SCS). In the overall cohort, the BAR score, ET-DRI, reintervention within 30 days, and arterial complications were independent predictors of graft loss at 1 year (Table 4). Receiver operating characteristic curve analysis showed an area under the curve of 0.672 (95% CI: 0.592–0.753, $P < 0.001$) for the BAR score compared with 0.634 (0.554–0.714, $P = 0.002$) for the ET-DRI for 1-year graft loss. The optimal BAR score cutoff, based on the maximum Youden index, was determined to be 10 points (< 10 points vs ≥ 10 points).

TABLE 2. NLMP Use and Nighttime Surgery

Study Year	NLMP Use; n (%)	Nighttime Surgery; n (%)*
1	18/74 (24.3)	31/74 (41.9)
2	38/60 (63.3)	14/60 (23.3)
3	32/62 (51.6)	11/62 (17.7)
4	36/64 (56.3)	10/64 (14.5)
5	50/72 (69.4)	3/72 (4.2)

*Surgery starts time between 8 PM and 8 AM. Concurrent with the increase in NLMP usage from 24.3% to 69.4% ($P < 0.001$), a significant decrease in nighttime surgery from 41.9% to 4.2.% ($P < 0.001$) was observed.

DISCUSSION

The present study reports real-world outcomes of a large European single-center cohort comparing the outcomes of NLMP to those of SCS. We aimed to address the current uncertainty regarding the clinical benefit of NLMP when used in a real-world, back-to-base setting. The true clinical benefits of NLMP as a 24/7 service at a transplant center remain to be more clearly defined. Key criteria for successful implementation of NLMP that are often underestimated in this context are the organizational structure, the procedural aspects, the multidisciplinary character, and the infrastructure requirements in this setting. Accordingly, our first readout of the program was an assessment of safety and feasibility.[10] Building on the early experience, we herein focus on the effectiveness of NLMP in a real-world setting. Our results suggest that NLMP allows us to safely prolong total preservation times without negatively affecting outcomes. Graft survival, as well as the incidence of post-Tx complications, were similar between both groups despite significantly longer total preservation times in the NLMP cohort. To the best of our knowledge, the median total preservation time as well as median NLMP time reported in this study are the longest recorded in any of the normothermic machine perfusion studies published to date. Importantly, these extended total preservation times did not negatively impact graft survival in the NLMP group, whereas in the SCS group, prolonged total preservation time was found to be an independent predictor of graft failure at 1 year. Our findings are similar to those of Hefler et al,[2] who found no significant differences in post-Tx outcomes when comparing NLMP to SCS in a North American liver transplant cohort despite significantly longer total preservation times in the NLMP group. This difference persisted even after matching for lab-MELD, donor risk index, donor and recipient age as well as donor type. While Hefler and colleagues performed propensity score matching to adjust for baseline risk differences, Wehrle and colleagues

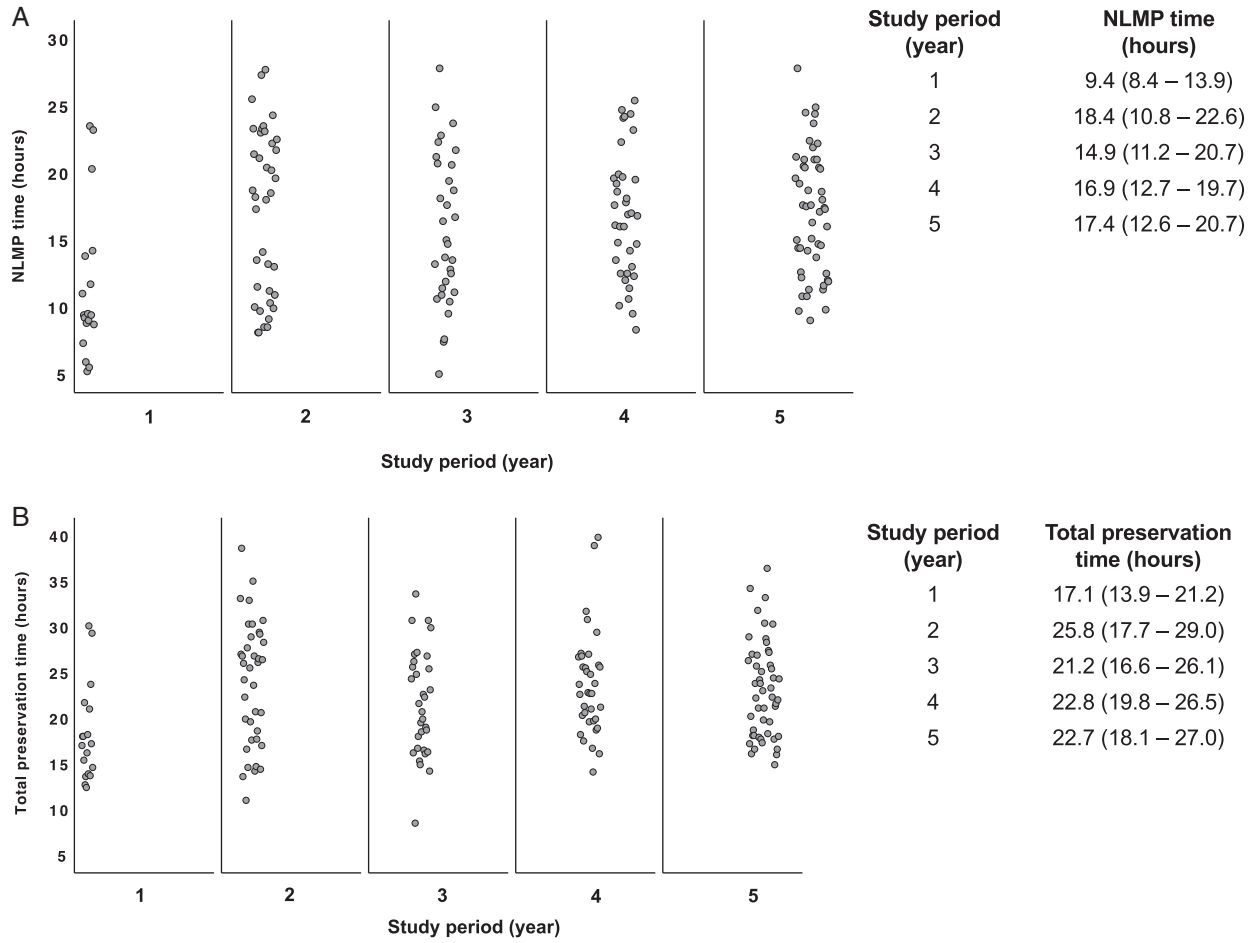


FIGURE 2. The development of NLMP (A) and total preservation time (B) over the duration of the study period is depicted. Median NLMP and total preservation times for each study year with IQR in parentheses are shown. IQR indicates interquartile range.

undertook a different approach, matching SCS recipients to NLMP recipients 2:1 based on the BAR score.[4] The BAR score has previously been shown to have the best predictive capability out of all predictive scores available before LT,[28] and was found to be an independent predictor of graft survival in our study. Both NLMP and SCS recipients exhibited similar BAR scores at baseline, even without performing statistical matching. This is in line with our program's philosophy of conscientious donor-recipient matching to avoid high-risk combinations. Thus, instead of performing statistical matching, we compared outcomes for benchmark and non-benchmark cases, aiming to reflect real-world transplant scenarios and capture the "real-world experience" more accurately. Benchmarking in surgery has recently been introduced for numerous surgical procedures, including LT.[11,29–32] Benchmarking allows for outcome comparison across different centers, and reporting the percentage of benchmark cases in a liver transplant cohort allows to estimate the amount of risk a center is taking on. We have shown that survival outcomes for both NLMP and SCS, as well as benchmark cases, were excellent and well within the published references. As expected, outcomes for non-benchmark cases were worse compared with benchmark cases, however, non-benchmark outcomes were similar in the NLMP and SCS group. Naturally, overall outcomes will depend on the proportion of benchmark cases in the overall cohort. In our setting, NLMP resulted in a lower number of standard risk benchmark cases in the NLMP group compared with the SCS group. In other words, higher-risk non-benchmark cases were shifted towards the NLMP group. One factor driving this development is the fact that it has become the center policy to put all DCD grafts on the pump for viability assessment. Another contributing factor to this development is the tendency to shift complex recipients towards NLMP.

In the present study, the CIT was significantly shorter in the NLMP cohort compared with the SCS cohort, which contrasts with the results of 2 North American studies that also employed a back-to-base approach.[2,4] This observation is most likely related to our streamlined workflow. Since the first description of our NLMP workflow,[10] we have made some modifications to simplify NLMP setup. The OrganOx Metra is now set up in the transplant ICU by the ICU nursing staff, while the liver graft is benched in the operating room (OR) in anticipation of NLMP. Once the liver has been prepared and is ready to commence NLMP, the OrganOx Metra is transferred to the OR where NLMP is initiated. As soon as NLMP is started, the clock on the CIT stops,

TABLE 3. Clinical Outcomes and Complications

	All (N = 332)	NLMP (n = 174)	SCS (n = 158)	*P*	Benchmark (n = 140)	Non-benchmark (n = 192)	*P*
PNF	4 (1.2)	0	4 (2.5)	0.050	1 (0.7)	3 (1.6)	0.641
EAD	109 (32.8)	52 (29.9)	57 (36.1)	0.230	47 (33.6)	62 (32.2)	0.806
Rejection*	20 (6.0)	7 (4.0)	13 (8.2)	0.108	11 (7.9)	9 (4.7)	0.231
Biliary complications*	131 (39.5)	73 (42.0)	58 (36.7)	0.329	52 (37.1)	79 (41.1)	0.461
Bile duct leaks	39 (11.7)	20 (11.5)	19 (12.0)	0.881	15 (10.7)	24 (12.5)	0.618
AS	70 (21.1)	41 (23.6)	29 (18.4)	0.245	27 (19.3)	43 (22.4)	0.493
NAS	33 (9.9)	19 (10.9)	14 (8.9)	0.531	13 (9.3)	20 (10.4)	0.734
Post-Tx cholangiopathy	26 (7.8)	17 (9.8)	9 (5.7)	0.168	10 (7.1)	16 (8.3)	0.690
Cholangitis	41 (12.3)	19 (10.9)	22 (13.9)	0.406	17 (12.1)	24 (12.5)	0.922
Arterial complications*	26 (7.8)	14 (8.0)	12 (7.6)	0.879	6 (4.3)	20 (10.4)	**0.040**
Stenosis	12 (3.6)	8 (4.6)	4 (2.5)	0.314	3 (2.1)	9 (4.7)	0.220
Thrombosis	13 (3.9)	5 (2.9)	8 (5.1)	0.304	3 (2.1)	10 (5.2)	0.155
Jump graft occlusion	1 (0.3)	1 (0.6)	0	1.000	0	1 (0.5)	1.000
CCI							
At discharge	48.1 (29.6–70.1)	50.9 (30.8–71.7)	46.1 (29.6–66.1)	0.177	38.2 (24.7–58.6)	55.8 (36.5–75.9)	**< 0.001**
12 mo	71.2 (48.9–99.0)	71.4 (50.6–99.0)	70.7 (45.3–95.1)	0.205	58.4 (39.2–86.6)	79.0 (56.3–99.0)	**< 0.001**
Reintervention							
Reintervention ≤ 30 d	147 (44.3)	80 (46.0)	67 (42.4)	0.513	51 (36.4)	96 (50.0)	**0.014**
Readmission ≤ 30 d	23 (6.9)	12 (6.9)	11 (7.0)	0.981	11 (7.9)	12 (6.3)	0.569
ICU stay (d)	5.0 (3.0–9.0)	5.0 (3.0–9.5)	4.0. (3.0–9.0)	0.118	4.0 (3.0–6.0)	5.0 (4.0–12.0)	**< 0.001**
Hospital stay (d)	21.0 (15.3–30.0)	21.0 (16.0–33.3)	19.0 (15.0–29.0)	0.057	18.0 (14.0–24.8)	22.0 (16.0–38.5)	**< 0.001**

Bold values indicate significant *P* values.
*Within 1 year.
NLMP versus SCS, benchmark versus non-benchmark.
Values are presented as medians or absolute numbers with interquartile ranges and percentages in parentheses.
AS indicates anastomotic stricture; CCI, Comprehensive Complication Index; NAS, non-anastomotic stenosis.

regardless of any unforeseeable events that might happen during anesthesia induction or the recipient hepatectomy. Especially for complex recipients such as those with portal vein thrombosis, previous major abdominal surgeries, as well as for redo LTs (ie non-benchmark cases), not having to worry about the CIT while performing a potentially complex hepatectomy is a luxury to have. Since CIT is one of the most important modifiable risk factors in transplantation,[23,33] keeping the median CIT to 6 hours was one of the added benefits of NLMP for our program. The shorter CIT in the NLMP group allowed us to keep the BAR score similarly low compared with the SCS group despite a significantly higher donor and recipient age in the NLMP group.

Furthermore, the logistical aspects afforded by "stopping the clock" on the CIT through the application of NLMP are profound and underappreciated in our perception. With the increasing usage of NLMP and increasing NLMP times over the duration of the study period, we saw a significant decrease in nighttime procedures. With the help of NLMP, LT was essentially converted into a scheduled daytime procedure. Furthermore, complex parallel procedures such as simultaneous adult and pediatric split LT were avoided because of the availability of NLMP.[17] Having the luxury of performing LT under controlled conditions during the daytime without significant time constraints also facilitates teaching and education in the OR as well as the overall well-being of the surgical, anesthesia, and OR staff. With physician burnout and work-life balance becoming increasingly important aspects in medicine and surgery especially,[34–36] moving transplant surgery out of the night might help with surgeon attrition and OR workforce retention. The literature indicates that reducing nighttime operating hours leads to lower levels of burnout and depression among physicians, ultimately improving their overall well-being.[37] Moreover, discard rates and nonusage rates of liver grafts have been shown to be higher during the nighttime or on weekends.[38] NLMP may help to take human factors, such as fatigue or other lifestyle aspects out of the equation, as it essentially avoids nighttime transplantation and allows more flexibility, which could help mitigate increased discard and nonusage rates during untimely hours.

Recently, Brüggenwirth et al[39,40] have demonstrated that not only NLMP, but also prolonged hypothermic oxygenated machine perfusion (HOPE) and dual HOPE (DHOPE) may allow to improve transplant logistics and move liver transplant surgery out of the night. In an investigator-initiated, single-center prospective trial comparing conventional DHOPE (1–2 hours) with prolonged DHOPE (8 hours) safety and feasibility of the prolonged approach was established.[40] In this study,[40] prolonged DHOPE also facilitated daytime LT. However, with limited data available and data from RCTs lacking, prolonged DHOPE is still at an early stage. Overall, the transformation of LT from an urgent to a semielective procedure not only enhances the efficiency and effectiveness of the transplant operation but also promotes a healthier, more sustainable work environment for medical professionals. Still, as pointed out by a recent study from Li et al,[41] there are obstacles that need to be overcome. In their study, Li and colleagues found that, while the majority of European and U.S. liver transplant centers have adopted NLMP, 41% of all centers that have implemented NLMP still performed more than 50% of their LT during nighttime or on weekends.[41] This is in stark contrast to our experience where nighttime LT decreased from 42% to 4% since implementing NLMP into the clinical routine.

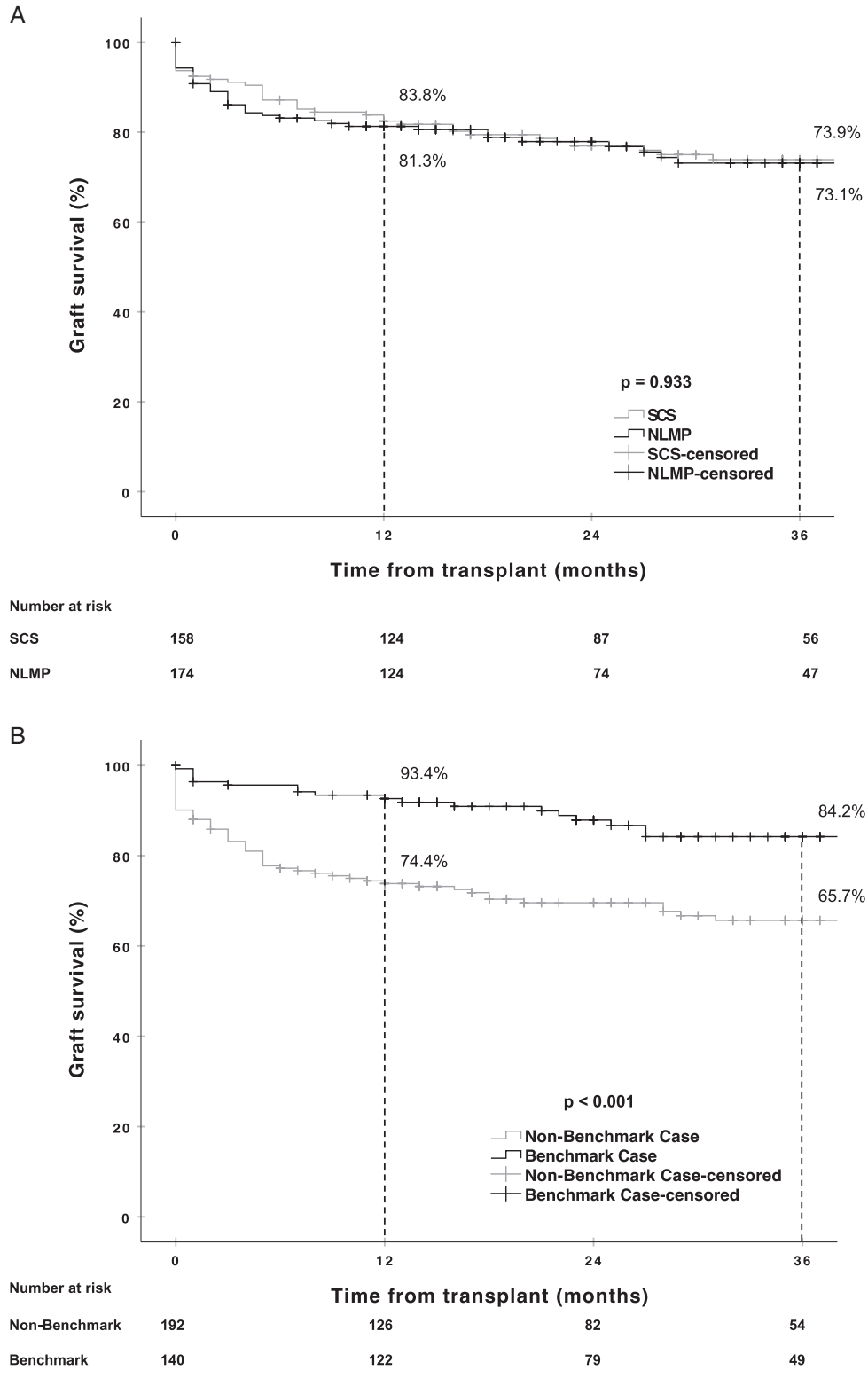


FIGURE 3. Kaplan-Meier survival curves showing 1 and 3-year graft survival for NLMP versus SCS (A) and benchmark versus non-benchmark cases (B).

Moving forward, combining different machine perfusion approaches, such as standard or prolonged DHOPE and NLMP, in an effort to best utilize the individual advantages of each technology will most likely maximize the overall benefit for both patients and health care providers.

In our setting, NLMP not only allowed us to keep the CIT to a minimum while extending total preservation times thereby easing logistics, but also served as a platform for viability assessment. With the ongoing shortage of suitable donor organs and the increasing use of ECD organs, viability

TABLE 4. Risk Factors for 1-year Graft Loss—Binary Logistic Regression Analysis

	Univariate		Multivariate*	
	OR 95% CI	*P*	OR 95% CI	*P*
Overall				
Non-benchmark case	4.586 (2.161–9.731)	**< 0.001**	—	—
Recipient age	1.004 (0.980–1.029)	0.722	—	—
Lab-MELD	1.062 (1.026–1.099)	**< 0.001**	—	—
BAR score	1.156 (1.085–1.232)	**< 0.001**	1.234 (1.049–1.453)	**0.011**
Donor age	1.011 (0.993–1.030)	0.230	—	—
ECD	0.937 (0.488–1.796)	0.844	—	—
DCD	2.145 (0.968–4.752)	0.060	—	—
ET-DRI	2.636 (1.559–4.458)	**< 0.001**	2.939 (1.410–6.127)	**0.004**
CIT (h)	1.136 (1.009–1.279)	**0.036**	—	—
Total preservation time (h)	1.034 (1.001–1.068)	**0.043**	—	—
EAD	1.327 (0.728–2.417)	0.356	—	—
LOS ICU	—	—	—	—
LOS hospital	—	—	—	—
Reintervention within 30 d	3.814 (2.031–7.162)	**< 0.001**	3.626 (1.760–7.471)	**< 0.001**
Arterial complication	6.286 (2.728–14.486)	**< 0.001**	5.390 (2.046–14.198)	**< 0.001**
Post-Tx-cholangiopathy	1.219 (0.439–3.385)	0.704	—	—
NLMP				
Non-benchmark case	4.976 (1.657–14.941)	**0.004**	—	—
Recipient age	1.014 (0.980–1.049)	0.425	—	—
Lab-MELD	1.094 (1.040–1.151)	**< 0.001**	—	—
BAR score	1.183 (1.079–1.297)	**< 0.001**	—	—
Donor age	1.020 (0.996–1.045)	0.103	—	—
ECD	0.492 (0.194–1.246)	0.135	—	—
DCD	2.235 (0.939–5.317)	0.069	—	—
ET-DRI	2.568 (1.331–4.953)	**0.005**	3.373 (1.351–8.421)	**0.009**
Accepted without Metra (no)	0.560 (0.259–1.214)	0.142	—	—
CIT (h)	1.050 (0.886–1.244)	0.572	—	—
NLMP time (h)	1.046 (0.975–1.122)	0.210	—	—
Total preservation time (h)	1.045 (0.981–1.114)	0.171	—	—
EAD	1.290 (0.571–2.915)	0.540	—	—
Reintervention within 30 d	3.186 (1.405–7.227)	**0.006**	3.937 (1.454–10.661)	**0.007**
Arterial complication	7.556 (2.407–23.719)	**< 0.001**	7.327 (1.908–28.138)	**0.004**
Post-Tx-cholangiopathy	1.418 (0.430–4.673)	0.566	—	—
SCS				
Non-benchmark case	4.114 (1.444–11.721)	**0.008**	—	—
Recipient age	0.991 (0.957–1.027)	0.611	—	—
Lab-MELD	1.037 (0.987–1.089)	0.149	—	—
BAR score	1.140 (1.042–1.247)	**0.004**	—	—
Donor age	0.994 (0.966–1.024)	0.704	—	—
ECD	1.432 (0.552–3.715)	0.460	—	—
ET-DRI	2.863 (1.040–7.887)	**0.042**	—	—
Total preservation time (h)	1.353 (1.104–1.657)	**0.004**	1.265 (1.002–1.598)	**0.048**
EAD	1.440 (0.587–3.533)	0.425	—	—
Reintervention within 30 d	4.817 (1.782–13.016)	**0.002**	3.599 (1.227–10.551)	**0.020**
Arterial complication	5.079 (1.456–17.715)	**0.011**	—	—
Post-Tx-cholangiopathy	0.722 (0.086–6.057)	0.764	—	—

Bold values are statistically significant $P < 0.05$.

*Variables which remained as significant independent predictors in the multivariate model are displayed. Total preservation time was an independent predictor of 1-year graft loss in the SCS group but not in the NLMP group.

Variables with P value < 0.1 in the univariate analysis were considered for multivariate analysis.

LOS, Length of stay; OR, Odds ratio.

assessment has become an essential tool to safely expand the donor pool. Several groups have now shown that livers that were initially declined based on traditional criteria can be successfully transplanted following machine perfusion and viability assessment.[42–44] The ability to perform viability assessment before making the decision whether to transplant or discard an organ has changed our center's acceptance policy. This change has prompted us to accept higher-risk grafts with higher ET-DRIs without transferring the risk to the recipient. Despite the overall donor risk being significantly higher in the NLMP group compared with the SCS group, no PNF was recorded in the NLMP group. Similarly, Hefler et al[2] also reported no PNF in their NLMP cohort and others have found similar results.[3] This shows that hepatocellular viability assessment during NLMP is reliable and reproducible.

In line with outcomes reported by Hefler et al[2] and findings from a recent U.S. RCT,[45] but contrasting results

from previous RCTs,[5,6] we did not find a significant reduction of EAD in the NLMP group. This observation might have been an issue of limited statistical power as the EAD rate was 30% in the NLMP group versus 36% in the SCS group and 27% versus 39% when comparing benchmark NLMP to benchmark SCS. The relevance of EAD as a binary outcome parameter as defined by Olthoff et al[21] has previously been questioned.[46] Moreover, EAD has not been validated in the context of machine perfusion. Dilution and washout of biomarkers such as AST into the perfusate most likely leads to false low AST levels in the recipient. The Consortium for Organ Preservation in Europe trial has demonstrated that reduced EAD rates are related to reduced peak transaminase levels.[47] Fodor et al[48] have shown that out of the three diagnostic criteria, peak AST levels are the weakest outcome predictor providing further evidence as to why EAD is of limited use as an endpoint in machine perfusion studies. In our study the presence of EAD had no influence on graft survival neither in the overall cohort nor in the NLMP and SCS groups. EAD most likely needs to be redefined and validated in the context of NLMP.[47]

Overall, current hepatocellular viability criteria allow the safe selection of organs for transplantation but may lead to unnecessary high discard rates.[43] The discard rate in our study was 27% and thus similar to the 24% discard rate reported by Watson et al.[49] Discard rates have been shown to differ between the United States and Europe reflecting differences in the organ acceptance process. In the United States, programs apply a more selective approach to organ offers as the retrieval costs are higher, and thus, the decision to decline a liver is more likely to happen at the time of organ offer.[45] In Europe, centers with established NLMP programs may be more likely to defer the decision until after a period of NLMP has allowed for viability assessment. Deferring the final decision to accept or decline a liver to a time when we had a chance to gather more data has been one of the key benefits of NLMP. While our approach may lead to a higher discard rate after NLMP we would argue that fully assessing a liver graft before making the decision whether to decline or not is the more rational approach compared with declining livers at offering before retrieval, as this seems to defeat the purpose of trying to expand the donor pool using NLMP. Ultimately, viability assessment and the identification of reliable parameters remains a work in progress. The decision on whether to transplant or discard an organ may not be as clear-cut as it should be. Rather, the goal should be to develop predictive scores that allow the estimate of post-Tx outcomes for a specific liver graft from a specific donor, with a specific risk profile and specific performance during viability assessment that is transplanted into a specific recipient. This way, calculated risks can be taken, and the decision of whether to transplant or discard an organ can be individualized based on recipient factors and local circumstances such as regional waitlist mortality rates.

Compared with hepatocellular viability assessment, cholangiocellular viability assessment is less well-established and remains an unmet clinical need.[50] NLMP alone, most likely does not result in a decrease in biliary complications and, most importantly, post-Tx cholangiopathy.[42,51,52] The 10% post-Tx cholangiopathy rate in our NLMP cohort is almost identical to the 11% reported by Watson et al[49] in a similar European cohort. Of all RCTs published on this topic, only the OCS Liver Protect trial found a decrease in post-Tx cholangiopathy in the normothermic perfusion arm compared with the SCS arm.[6] All other RCTs did not provide any evidence to suggest that NLMP can reduce the incidence of post-Tx cholangiopathy. None of these RCTs was designed or powered to show a difference in the incidence of post-Tx cholangiopathy.[5,45,53] This is in line with our observations, as DCD graft usage was the most significant independent predictor of post-Tx cholangiopathy, despite the fact that almost all DCD were normothermically perfused before LT. The way forward will most likely be a combination of DHOPE to bioenergetically recondition the mitochondria of the liver graft followed by either controlled rewarming and NLMP or going straight to NLMP. This way, marginal liver grafts can be reconditioned during HOPE and viability can be assessed during NLMP while still maintaining most logistical advantages. Data coming from the Netherlands have demonstrated the huge potential of this approach to safely extend the donor pool, showing very low post-Tx cholangiopathy rates following DHOPE-controlled rewarming-NMP in nationally declined liver grafts.[54]

Having NLMP available at our center allowed us to accept liver grafts that would not have been accepted otherwise. These, in addition, accepted liver grafts include livers from donors with suspected malignancies where NLMP gave us time to perform a thorough histopathologic evaluation, septic or infectious donors where NLMP served as a platform to treat and assess liver grafts,[27,55] as well as DCD and other ECD donors with additional risk factors such as prolonged functional warm ischemia time, advanced age or macrovesicular steatosis. Importantly, these, in addition, accepted grafts had no negative impact on graft survival (Table 4). Of course, this observation needs to be viewed within the context of the local waitlist dynamics. As pointed out above, center policies in terms of organ acceptance will differ based on waitlist mortality rates and organ availability.

The present study has several limitations. First, the retrospective single-center study design warrants external validation of our findings. Second, due to our center policy almost all DCD grafts have been normothermically perfused, limiting comparison of DCD-NLMP to DCD-SCS. For endpoints with low event rates, the statistical power might have been too low to detect significant differences. Another limitation is the fact that the outcomes of grafts discarded after NLMP remain unknown. Ultimately, viability assessment and defining reliable parameters remain a work in progress. Now, that the safety of current hepatocellular viability criteria has been repeatedly demonstrated, it might be time to carefully expand viability criteria to decrease discard rates without compromising outcomes. Strengths of this study include the close follow-up of our transplant recipients, a high level of data completeness, and data granularity stemming from an integrated, auditable medical documentation platform at our institution. The large NLMP cohort, long preservation times, and, compared with other studies, longer median follow-up time, as well as the structured approach, are additional strengths and give substance to this study. Furthermore, reporting outcomes (ie biliary complications, Comprehensive Complication Index, etc) at standardized time points (1 year) while also reporting the proportion of benchmark cases in the overall cohort as well as in the NLMP and SCS groups and comparing outcomes based on benchmark and non-benchmark cases is a unique feature of the present study and in line with recent recommendations on how to report and assess the quality of surgical interventions.[56,57]

CONCLUSIONS

In summary, NLMP has resulted in significantly shorter CIT and significantly longer total preservation times compared with SCS. Prolonged total preservation time was an independent predictor of 1-year graft loss in the SCS but not the NLMP group. Thus, NLMP allows a safe prolongation of the overall preservation time by stopping the clock on the CIT. The extended preservation time provides significant logistical advantages, essentially converting LT into a scheduled daytime procedure, which we believe is an underappreciated aspect of this technology. The possibility to perform viability assessment before transplantation has allowed us to accept liver grafts with a higher ET-DRI without transferring the risk to the recipient as the ability to normothermically perfuse the liver and perform viability assessment before ultimately deciding whether to transplant or discard the organ serves as an additional safety net. Within this context, we would like to emphasize the importance of a close by central laboratory with short transport routes and fast turnaround times.

Furthermore, the decision process becomes more objective as it is more informed and based on more data points compared with the previous process of evaluating donor laboratory values and the macroscopic appearance of the liver graft. Combining the logistical advantages of NLMP with the possibility of assessing organs has allowed us to increase the number of successful LTs at our center. Despite NLMP, DCD graft usage was one of the most independent predictors of post-Tx cholangiopathy highlighting the fact that NLMP alone most likely does not result in lower cholangiopathy rates (at least not in the back-to-base setting) and that cholangiocellular viability assessment remains a work in progress. We would like to emphasize that while NLMP has enabled us to transplant more livers with a higher risk profile, donor-recipient matching (ie, avoiding high-risk donor and recipient combinations) remains a key aspect.

REFERENCES

1. Ravikumar R, Jassem W, Mergental H, et al. Liver transplantation after ex vivo normothermic machine preservation: a phase 1 (first-in-man) clinical trial. *Am J Transplant*. 2016;16:1779–1787.
2. Hefler J, Leon-Izuierdo D, Marfil-Garza BA, et al. Long term outcomes after normothermic machine perfusion in liver transplantation -experience at a single North American centre. *Am J Transplant*. 2023;23:976–986.
3. Yamamoto T, Atthota S, Agarwal D, et al. Impact of portable normothermic machine perfusion for liver transplantation from adult deceased donors. *Ann Surg*. 2023;278:e922–e929.
4. Wehrle CJ, Zhang M, Khalil M, et al. Impact of back-to-base normothermic machine perfusion on complications and costs: a multi-center, real-world risk-matched analysis. *Ann Surg*. 2024;280:300–310.
5. Nasralla D, Coussios CC, Mergental H, et al. A randomized trial of normothermic preservation in liver transplantation. *Nature*. 2018;557:50–56.
6. Markmann JF, Abouljoud MS, Ghobrial RM, et al. Impact of portable normothermic blood-based machine perfusion on outcomes of liver transplant: the OCS liver PROTECT randomized clinical trial. *JAMA Surg*. 2022;157:189–198.
7. Parente A, Tirotta F, Pini A, et al. Machine perfusion techniques for liver transplantation - a meta-analysis of the first seven randomized controlled trials. *J Hepatol*. 2023;79:1201–1213.
8. Tingle SJ, Dobbins JJ, Thompson ER, et al. Machine perfusion in liver transplantation. *Cochrane Database Syst Rev*. 2023;9:Cd014685.
9. Croome KP. Introducing Machine perfusion into routine clinical practice for liver transplantation in the United States: the moment has finally come. *J Clin Med*. 2023;12:Cd014909.
10. Cardini B, Oberhuber R, Fodor M, et al. Clinical implementation of prolonged liver preservation and monitoring through normothermic machine perfusion in liver transplantation. *Transplantation*. 2020;104:1917–1928.
11. Muller X, Marcon F, Sapisochin G, et al. Defining benchmarks in liver transplantation: a multicenter outcome analysis determining best achievable results. *Ann Surg*. 2018;267:419–425.
12. Öfner D. Quality assurance in surgery—a moral obligation. *Eur Surg* 2024;56:110–115.
13. von Elm E, Altman DG, Egger M, et al. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. *Int J Surg*. 2014;12:1495–1499.
14. Eurotransplant Foundation. *Eurotransplant Manual Chapter 9: The Donor*, 4th ed. Eurotransplant Foundation; 2022. Accessed August 12, 2023. https://www.eurotransplant.org/professionals/eurotransplant-manual/
15. Krendl FJ, Fodor M, Buch ML, et al. The BAR score predicts and stratifies outcomes following liver retransplantation: insights from a retrospective cohort study. *Transpl Int*. 2024;37:12104.
16. Hofmann J, Meszaros AT, Butler A, et al. Predictive value of early postoperative lactate (<6 h) during normothermic machine perfusion and outcome after liver transplantation: results from a multicentre study. *Br J Surg*. 2024;111:znae084.
17. Krendl FJ, Cardini B, Laimer G, et al. Normothermic Liver machine perfusion and successful transplantation of split liver grafts: from proof of concept to clinical implementation. *Transplantation*. 2024;108:1410–1416.
18. Mathis S, Weissenbacher A, Putzer G, et al. Interleukin-6 levels during normothermic machine perfusion impact postreperfusion hemodynamics of liver graft recipients: a prospective single-center observational study. *Transplantation*. 2024;108:1166–1171.
19. Eurotransplant Foundation. *Eurotransplant Manual Chapter 5: ET Liver Allocation System*. ELAS; 2023. Accessed August 12, 2023. https://www.eurotransplant.org/professionals/eurotransplant-manual/
20. Hartog H, Hann A, Perera M. Primary nonfunction of the liver allograft. *Transplantation*. 2023;106:117–128.
21. Olthoff KM, Kulik L, Samstein B, et al. Validation of a current definition of early allograft dysfunction in liver transplant recipients and analysis of risk factors. *Liver Transpl*. 2010;16:943–949.
22. de Vries Y, von Meijenfeldt FA, Porte RJ. Post-transplant cholangiopathy: classification, pathogenesis, and preventive strategies. *Biochim Biophys Acta Mol Basis Dis*. 2018;1864(4 pt B):1507–1515.
23. Dutkowski P, Oberkofler CE, Slankamenac K, et al. Are there better guidelines for allocation in liver transplantation? A novel score targeting justice and utility in the model for end-stage liver disease era. *Ann Surg*. 2011;254:745–753.
24. Dindo D, Demartines N, Clavien P-A. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg*. 2004;240:205–213.
25. Slankamenac K, Graf R, Barkun J, et al. The comprehensive complication index: a novel continuous scale to measure surgical morbidity. *Ann Surg*. 2013;258:1–7.
26. Clavien PA, Vetter D, Staiger RD, et al. The Comprehensive Complication Index (CCI): added value and clinical perspectives 3 years "down the line. *Ann Surg*. 2017;265:1045–1050.
27. Krendl FJ, Oberhuber R, Breitkopf R, et al. Normothermic liver machine perfusion as a dynamic platform for assessment and treatment of organs from septic donors. *J Hepatol*. 2023;78:e56–e57.

28. Moosburner S, Wiering L, Roschke NN, et al. Validation of risk scores for allograft failure after liver transplantation in Germany: a retrospective cohort analysis. *Hepatol Commun*. 2023;7:e0012.
29. Schlegel A, van Reeven M, Croome K, et al. A multicentre outcome analysis to define global benchmarks for donation after circulatory death liver transplantation. *J Hepatol*. 2022;76:371–382.
30. Abbassi F, Gero D, Muller X, et al. Novel benchmark values for redo liver transplantation. does the outcome justify the effort? *Ann Surg*. 2022;276:860–867.
31. Mueller M, Breuer E, Mizuno T, et al. Perihilar cholangiocarcinoma - novel benchmark values for surgical and oncological outcomes from 24 expert centers. *Ann Surg*. 2021;274:780–788.
32. Li Z, Rammohan A, Gunasekaran V, et al. Novel benchmark for adult-to-adult living-donor liver transplantation: integrating eastern and western experiences. *Ann Surg*. 2023;278:798–806.
33. Pan ET, Yoeli D, Galvan NTN, et al. Cold ischemia time is an important risk factor for post–liver transplant prolonged length of stay. *Liver Transpl*. 2018;24:762–768.
34. Fleming CA, Augustinus S, Lemmers DHL, et al. Career needs assessment for early career academic surgeons using a modified accelerated Delphi process. *Ann Surg*. 2023;278:655–661.
35. Golisch KB, Sanders JM, Rzhetsky A, et al. Addressing surgeon burnout through a multi-level approach: a national call to action. *Curr Trauma Rep*. 2023;9:28–39.
36. Sinskey JL, Schwartz R, Boscardin CK, et al. Looking across the drape: a novel quality improvement approach to understanding surgeon and anesthesiologist burnout. *Ann Surg*. 2024;280:e2–e7.
37. Lindemann J, Dageforde LA, Brockmeier D, et al. Organ procurement center allows for daytime liver transplantation with less resource utilization: may address burnout, pipeline, and safety for field of transplantation. *Am J Transplant*. 2019;19:1296–1304.
38. Carpenter DJ, Chiles MC, Verna EC, et al. Deceased brain dead donor liver transplantation and utilization in the United States: nighttime and weekend effects. *Transplantation*. 2019;103:1392–1404.
39. Brüggenwirth IMA, Mueller M, Lantinga VA, et al. Prolonged preservation by hypothermic machine perfusion facilitates logistics in liver transplantation: a European observational cohort study. *Am J Transplant*. 2022;22:1842–1851.
40. Brüggenwirth IMA, Lantinga VA, Lascaris B, et al. Prolonged hypothermic machine perfusion enables daytime liver transplantation - an IDEAL stage 2 prospective clinical trial. *EClinicalMedicine*. 2024;68:102411.
41. Li Z, Pfister M, Huwyler F, et al. Revolutionizing liver transplantation transitioning to an elective procedure via ex situ normothermic machine perfusion - a benefit analysis. *Ann Surg*. 2024;280:887–895.
42. Mergental H, Laing RW, Kirkham AJ, et al. Transplantation of discarded livers following viability testing with normothermic machine perfusion. *Nat Commun*. 2020;11:2939.
43. Quintini C, Del Prete L, Simioni A, et al. Transplantation of declined livers after normothermic perfusion. *Surgery*. 2022;171:747–756.
44. van Leeuwen OB, de Vries Y, Fujiyoshi M, et al. Transplantation of high-risk donor livers after ex situ resuscitation and assessment using combined hypo- and normothermic machine perfusion: a prospective clinical trial. *Ann Surg*. 2019;270:906–914.
45. Chapman WC, Barbas AS, D'Alessandro AM, et al. Normothermic machine perfusion of donor livers for transplantation in the United States: a randomized controlled trial. *Ann Surg*. 2023;278:e912–e921.
46. Fodor M, Zoller H, Oberhuber R, et al. The need to update endpoints and outcome analysis in the rapidly changing field of liver transplantation. *Transplantation*. 2021;106:938–949.
47. Martins PN, Rizzari MD, Ghinolfi D, et al. Design, Analysis, and pitfalls of clinical trials using ex situ liver machine perfusion: the international liver transplantation society consensus guidelines. *Transplantation*. 2021;105:796–815.
48. Fodor M, Woerdehoff A, Peter W, et al. Reassessment of relevance and predictive value of parameters indicating early graft dysfunction in liver transplantation: AST is a weak, but bilirubin and inr strong predictors of mortality. *Front Surg*. 2021;8:693288.
49. Watson CJE, Gaurav R, Fear C, et al. Predicting early allograft function after normothermic machine perfusion. *Transplantation*. 2022;106:2391–2398.
50. Watson CJE, Gaurav R, Swift L, et al. Bile chemistry during ex situ normothermic liver perfusion does not always predict cholangiopathy. *Transplantation*. 2024;108:1383–1393.
51. Watson CJE, Kosmoliaptsis V, Pley C, et al. Observations on the ex situ perfusion of livers for transplantation. *Am J Transplant*. 2018;18:2005–2020.
52. Liew B, Nasralla D, Iype S, et al. Liver transplant outcomes after ex vivo machine perfusion: a meta-analysis. *Br J Surg*. 2021;108:1409–1416.
53. Ghinolfi D, Rreka E, De Tata V, et al. Pilot, open, randomized, prospective trial for normothermic machine perfusion evaluation in liver transplantation from older donors. *Liver Transpl*. 2019;25:436–449.
54. van Leeuwen OB, Bodewes SB, Lantinga VA, et al. Sequential hypothermic and normothermic machine perfusion enables safe transplantation of high-risk donor livers. *Am J Transplant*. 2022;22:1658–1670.
55. Krendl FJ, Resch T, Eschertzhuber S, et al. Normothermic liver machine perfusion as a dynamic platform for assessment and treatment of organs from a donor with malaria - expanding the indications. *J Hepatol*. 2024;81:e236–e237.
56. Domenghino A, Walbert C, Birrer DL, et al. Consensus recommendations on how to assess the quality of surgical interventions. *Nat Med*. 2023;29:811–822.
57. de Goeij FHC, Wehrle CJ, Abassi F, et al. Mastering the narrative: precision reporting of risk and outcomes in liver transplantation. *J Hepatol*. 2024;S0168-8278:02713–2.

