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Original Article

Static cold storage compared with normothermic machine perfusion of the liver and effect on ischaemic-type biliary lesions after transplantation: a propensity score-matched study

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Abstract

Background: Given the susceptibility of organs to ischaemic injury, alternative preservation methods to static cold storage (SCS), such as normothermic machine perfusion (NMP) are emerging. The aim of this study was to perform a comparison between NMP and SCS in liver transplantation with particular attention to bile duct lesions.

Methods: The outcomes of 59 consecutive NMP-preserved donor livers were compared in a 1 : 1 propensity score-matched fashion to SCS control livers. Postoperative complications, patient survival, graft survival and bile duct lesions were analysed.

Results: While patients were matched for cold ischaemia time, the total preservation time was significantly longer in the NMP group (21 h *versus* 7 h, $P < 0.001$). Patient and graft survival rates at 1 year were 81 *versus* 82 per cent ($P = 0.347$) and 81 *versus* 79 per cent ($P = 0.784$) in the NMP and SCS groups, respectively. The postoperative complication rate was comparable ($P = 0.086$); 37 per cent NMP *versus* 34 per cent SCS patients had a Clavien-Dindo grade IIIb or above complication. There was no difference in early (30 days or less) (NMP 22 *versus* SCS 19 per cent, $P = 0.647$) and late (more than 30 days) (NMP 27 *versus* SCS 36 per cent, $P = 0.321$) biliary complications. However, NMP-preserved livers developed significantly fewer ischaemic-type bile duct lesions (NMP 3 *versus* SCS 14 per cent, $P = 0.047$).

Conclusion: The use of NMP allowed for a significantly prolonged organ preservation with a lower rate of observed ischaemic-type bile duct lesions.

Introduction

With a persistent shortage of donor livers, the use of extended-criteria donor organs, including donation after circulatory death, continues to rise. Outcomes are more often affected by early graft dysfunction, primary non-function and post-transplant biliary complications necessitating laborious interventions[1–9]. Non-anastomotic intrahepatic strictures represent the most severe form of post-transplant biliary complication. Amongst non-anastomotic intrahepatic strictures, ischaemic-type biliary lesions (ITBL) represent the most detrimental form of manifestation. These lesions are characterized by biliary duct irregularities, strictures, dilatations and intraductal cast formations in the presence of a patent hepatic artery[9,10]. The incidence of ITBL after liver transplantation ranges from 3.9–25 per cent. The clinical presentation is rather non-specific, including abdominal pain, fever and cholestasis[9,10]. Despite several treatment options, approximately 50 per cent of patients with ITBL require retransplantation or die[10–14].

Ex vivo normothermic machine perfusion (NMP) offers the possibility to extend liver preservation and perform viability assessment. This technology holds the potential to limit the injury resulting from static cold storage (SCS) and eventually to reduce organ discard rates[5,7–9]. The impact of this novel preservation method on the incidence of bile duct injuries including ITBL, remains unclear and a matter of debate[5–8]. The aim of this analysis was to investigate the effect of NMP on post-transplant outcomes, including biliary lesions, against a propensity score-matched SCS cohort.

Methods

Study design and endpoints

All patients undergoing NMP and liver transplantation with a minimum follow-up of 3 months were included. The outcomes of 59 consecutive liver transplantations following NMP were retrospectively matched and compared with matched SCS liver graft

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transplantations in a 1 : 1 case approach (*Tables S1, S2* and *Figs S1, S2*). All transplants were performed at the Medical University of Innsbruck between January 2007 and April 2020. Matched control patients were identified by using the propensity score method[15], applying the following criteria: graft type donation after determination of death by neurological criteria (DBD) or determination of death after cardiocirculatory arrest (DCD); donor age; Eurotransplant Donor Risk Index; allocation; donor steatosis; cold ischaemia time; duration of surgery; recipient surgical risk score; recipient Model of End-stage Liver Disease (MELD) score; recipient age; recipient hepatocellular carcinoma; recipient hepatitis C virus (*Table S2*). The study protocol was approved by the institutional medical review board. In reference to a previously described concept[8], NMP was applied for:

- Recipient-related indications: in patients with high-risk profile including surgically complex recipients and a pending Covid-19 test, in order to ease the time pressure and reallocate the organ in case hepatectomy is considered impossible
- Donor-related indications: DCD, extended-criteria donor, steatosis, suspected malignancy, suspected infection
- Logistics: omitting parallel surgeries in cases of multiple organs for transplantation, overlap with other urgent surgeries and avoidance of night-time procedures especially in complex patients[8].

More than one reason may apply. Night-time procedures were avoided, and NMP times of up to 24 hours were routinely accepted. Main indications for use of NMP for 59 transplanted as well as discarded livers are shown in *Fig. S3ab* and *Table S3*. Machine perfusion was performed using a commercially available NMP system (OrganOx *metra*®, Oxford, UK), in a back-to-base approach[16]. The details of the centre protocol are published elsewhere[8,16]. The decision to transplant or discard an organ was based on perfusate parameters as previously outlined by the study group and others[8,16]. Specifically, rapid lactate clearance to physiological values within 4 hours, as well as maintenance of physiological pH without need of sodium bicarbonate supplementation after 4 hours of NMP were considered as key indicators for good graft function. In contrast, exceptionally high lactate dehydrogenase, aspartate aminotransferase and alanine aminotransferase values in the perfusate and/or rapid increase were considered as risk factors[8]. In order to address the donor organ quality as a factor specifically, a subgroup analysis was performed including only livers subjected to NMP due to donor-related indications.

The primary endpoints were patient and graft survival at 30, 90 and 365 days. Secondary endpoints included early allograft dysfunction[17], vascular and biliary complications and duration of hospital stay.

Classification and assessment of ITBL

Bile duct imaging following liver transplantation was assessed by magnetic resonance cholangiopancreatography (MRCP) performed either per protocol at 6 months and then annually, and/or in response to graft dysfunction as indicated by elevated serum liver function parameters or clinical evidence of graft-related deterioration. Hence, patients without clinical or laboratory evidence of biliary injury also underwent radiological assessment. Further to the MRCPs performed per protocol, all imaging studies of the biliary tree (MRCP, endoscopic retrograde cholangiopancreatography (ERCP), percutaneous transhepatic cholangiographic drainage, cholangiography via the biliary drain), were re-reviewed by a single radiologist (B.H.) blinded to the clinical information.

Since no uniformly applied classification for ITBL is available, the most robust established criteria[10–12,14,18,19] were adopted with minor modifications in order to optimize capture and grading of the injury, and also reproducibility of the readout (*Fig. 1*, *Table S4*). ITBL was defined as stricture, dilatation or irregularity of the intra- or extrahepatic bile ducts of the liver graft with or without biliary cast formation in the absence of hepatic artery stenosis or thrombosis[10–12,14,18,19]. Ductal dilatation was considered when the duct was greater than 8 mm (extrahepatic ducts) in diameter or enlarged compared with its central portion (intrahepatic ducts). Stricture was defined as ductal narrowing of a short or long segment with proximal dilatation (*Fig. 1*). Severity scoring was based on number of lesions including degree of narrowing, prestenotic dilatation, mucosal irregularity and extensiveness of the lesions per area. Localization of biliary lesions at the time of initial presentation was categorized according to predefined criteria on the basis of the region and side of the liver[10–12,14,18,19]. In addition, the location of the lesions was categorized as left-sided, right-sided or bilateral. The severity of biliary lesions was categorized on the basis of an arbitrary severity index in which lesions were scored per area as mild (1–2), moderate (3–4) or severe (5–6) (*Fig. 1*, *Table S4*).

Statistical analysis

Statistical analyses were performed using R© 2016 statistical software (Team RC, Foundation for Statistical Computing, Vienna, Austria)[20].

Data were presented as proportions (per cent), medians and interquartile ranges. Propensity score-matched control patients were identified using a generalized linear logistic regression model. The number of NMP patients determined the sample size in the control group. A 1 : 1 optimal pair matching was performed with the goal of minimizing the absolute pairwise distances in the matched sample[15]. Matching was conducted using the R package MatchIt version 4.1.0[15,20]. The differences between the groups were quantified using two-tailed *P* values. A univariable analysis to compare the NMP and SCS control groups was performed. Comparative analysis of clinical outcomes in the NMP and SCS group was conducted using the χ^2 and Fisher's exact test for categorical variables and Mann–Whitney *U* test for continuous variables. Ordinal variables were treated as continuous variables. Mann–Whitney *U* tests were approximated by using the t or F distributions. Patient and graft survival rates were compared using the Kaplan–Meier method and the log rank test. Two-tailed $P < 0.050$ was considered significant throughout the entire analysis.

Results

Donor, preservation and recipient characteristics

Some 59 SCS patients were matched 1 : 1 with NMP patients. Indications for transplantation and recipient demographic data are shown in *Table 1*. Median patient MELD was 15 in the NMP group *versus* 17 in the SCS group ($P = 0.487$). Median recipient age was 63.4 years in the NMP group *versus* 60.6 years in the SCS group ($P = 0.260$). Nine (16 per cent) grafts in the NMP group and four (7 per cent) grafts in the SCS group were from DCD donors (Maastricht category III), the remaining grafts were from DBD donors ($P = 0.133$). Median donor age was 57 years in the NMP group *versus* 56 years in the SCS control group ($P = 0.808$) and median Eurotransplant Donor Risk Index was 1.9 in the NMP group *versus* 1.8 in the SCS controls ($P = 0.733$). A detailed

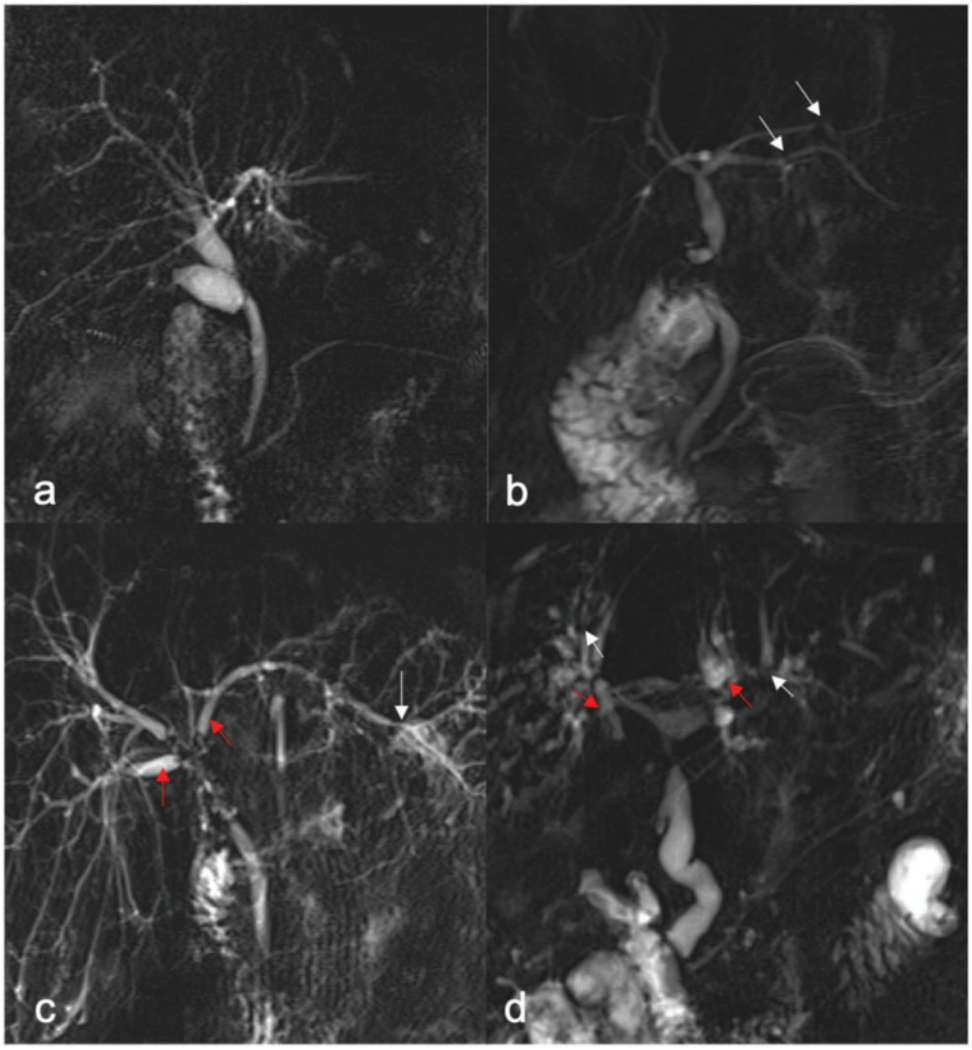

Fig. 1 Magnetic resonance cholangiopancreatography for evaluation of ischaemic-type biliary lesions after liver transplantation.

a Regular cholangiogram without strictures or ductal dilatation. **b** Signs of a mild ischaemic-type biliary lesion. **c** Signs of a moderate ischaemic-type biliary lesion. **d** Signs of a severe ischaemic-type biliary lesion. Strictures and ductal dilatations are indicated by white and red arrows respectively. The applied classification refers to established criteria[10–12,14,18,19] with minor modifications.

summary and comparison of donor characteristics and operative data between SCS and NMP grafts is provided in *Table 2*.

During the study period, a total of 75 livers were preserved via NMP. Sixteen were discarded due to insufficient organ quality. The total preservation time was significantly longer in NMP than SCS livers (21 hours *versus* 7 hours, $P < 0.001$) while cold ischaemia time was equal. Median anastomosis time was significantly shorter in the SCS group compared with the NMP group (42 minutes in the SCS *versus* 50 minutes in the NMP group; $P < 0.001$) (*Table 2*), possibly impacting on the result in favour of SCS.

Patient survival, graft survival, duration of stay

The 30-, 90-, and 365-days patient survival rate was 97, 89 and 81 per cent in the NMP group *versus* 98, 93 and 82 per cent in the SCS group respectively ($P = 0.347$, *Fig. 2a*). Graft survival rates in the NMP and SCS groups at 30, 90 and 365 days were 95, 89 and 81 per cent *versus* 95, 91 and 79 per cent, respectively ($P = 0.784$, *Fig. 2a*). No primary non-function was recorded in the two groups. Compared with the SCS group, the NMP cohort showed a similar rate of early allograft dysfunction (34 *versus* 32 per cent, $P = 0.794$). Reoperation rates and severe adverse events were similar in the two groups ($P = 0.086$). Clavien-Dindo complications grade IIIb or above occurred in 37 per cent (NMP) *versus* 34 per cent (SCS). Except for arterial thrombosis (NMP 0 per cent (0 of 59 patients) *versus* SCS 7 per cent (4 of 59), $P = 0.042$), a similar rate of vascular complications was recorded between the two groups. Of the four patients with arterial thrombosis in the SCS group, two patients died before retransplantation, one was successfully retransplanted and one maintained stable disease. Median duration of hospital stay was significantly shorter in the NMP compared with the SCS group (17 *versus* 23 days, $P = 0.006$) (*Table 3*)

The analysis of ITBL patients revealed that patient and graft survival did not differ significantly between the NMP and SCS groups ($P = 0.550$, $P = 0.314$ respectively). A more detailed analysis of ITBL patients is shown in *Fig. 2b*.

For an isolated assessment of livers marginally suitable for transplantation, a subgroup analysis was carried out for all livers subjected to NMP due to donor-predominant indications. The recipient and donor characteristics are displayed in *Table S5* and *S6*. The total preservation time differed significantly between both groups (24 hours in the NMP *versus* 7 hours in the SCS group, $P < 0.001$). The duration of hospital stay was significantly shorter

Table 1: Recipient characteristics in the matched cohort

Characteristic	SCS ($n = 59$)†	NMP ($n = 59$)†	P‡
Recipient age (years)*	60.6 (10.5)	63.4 (12.7)	0.260
BMI (kg/m^2)*	25.30 (5.15)	25.40 (4.70)	0.653
Recipient sex			0.306
Male	48 (81)	52 (88)	
Female	11 (19)	7 (12)	
MELD score*	17 (10)	15 of 58 (12)	0.487
Indication for liver transplantation			
Alcoholic steatohepatitis	12 (20)	14 (24)	0.657
Non-alcoholic steatohepatitis	6 (10)	9 (15)	0.407
Primary non-function	1 (2)	.	0.315
Polycystic liver disease	2 (3)	.	0.154
Budd Chiari syndrome	.	2 (3)	0.154
Primary biliary cirrhosis	3 (5)	1 (2)	0.309
Primary sclerosing cholangitis	.	3 (5)	0.079
Cryptogenic liver cirrhosis	5 (8)	3 (5)	0.464
Hepatitis virus infection	3 (5)	3 (5)	1.000
Cholangitic abscess formation	9 (15)	6 (10)	0.407
Alpha 1-antitrypsin deficiency	1 (2)	3 (5)	0.309
Acute liver failure	7 (12)	7 (12)	1.000
Tumour	21 (36)	20 (34)	0.847
Tumour entity			
Hepatocellular carcinoma	17 (29)	19 (32)	0.689
Cholangiocellular carcinoma	3 of 51 (6)	.	
Liver metastases of colon malignancy	.	1 of 56 (2)	
Other	1 of 51 (2)	.	
Tumour treatment	17 of 52 (33)	16 of 57 (28)	0.600
Transarterial chemoembolization	9 of 52 (17)	9 of 57 (16)	0.831
Radiofrequency ablation	9 of 52 (17)	8 of 57 (14)	0.638
CHILD score			0.291
A	13 of 49 (27)	12 of 45 (27)	
B	29 of 49 (59)	21 of 45 (47)	
C	7 of 49 (14)	12 of 45 (27)	
ABO blood group			0.099
A	27 of 58 (47)	28 (47)	
B	6 of 58 (10)	13 (22)	
O	19 of 58 (33)	17 (29)	
AB	6 of 58 (10)	1 (2)	
Hepatitis C virus			0.414
Negative	55 (93)	56 of 58 (97)	
Positive	4 (7)	2 of 58 (3)	
Encephalopathy	13 (22)	11 (19)	0.647
Cirrhosis	46 (78)	50 (85)	0.344
Surgical Risk Score			0.923
None	.	1 (2)	
Low	24 (41)	25 (42)	
Middle	17 (29)	11 (19)	
High	18 (31)	22 (37)	
Portal vein open			0.763
Yes	52 (88)	46 of 56 (82)	
Partial obstruction of portal vein trunk	3 (5)	3 of 56 (5)	
Complete obstruction of portal vein trunk	2 (3)	4 of 56 (7)	
Thrombosis right or left portal branch	2 (3)	3 of 56 (5)	

Values in parentheses are percentages unless indicated otherwise. *values are median (i.q.r.). †Where patient numbers are not the total in the group, this is stated. SCS, static cold storage; NMP, normothermic machine perfusion; MELD, Model of End-stage Liver Disease. ‡χ^2 and Fisher's exact test for categorical variables and Mann–Whitney *U* test for continuous variables. Dot (.) signifies zero.

in the NMP group (24 days in the SCS *versus* 16 days in the NMP group, $P = 0.003$). Four patients with arterial thrombosis were recorded in the SCS group *versus* none in the NMP cohort ($P = 0.040$). Patient and graft survival did not differ significantly ($P = 0.942$, $P = 0.586$ respectively, *Table S8*). Details regarding donor, operative data, recipient data, complications and survival are reported in *Tables S5–S8*.

Biliary complications

There was no significant difference in the overall rate of total biliary complications (NMP 30 of 59 patients *versus* SCS 29 of 59, $P = 0.854$). This was also true when stratified into early (30 days or less) *versus* late (more than 30 days) biliary complications ($P = 0.647$, $P = 0.321$, respectively). Bile duct leaks occurred in 17 per cent (NMP 10 of 59 patients) *versus* 19 per cent (SCS 11 of 59),

Table 2 Donor characteristics and operative data in the matched cohort

Characteristic	SCS ($n = 59$)†	NMP ($n = 59$)†	P‡
Donor age (years)*	56.0 (16.5)	57.0 (22.0)	0.808
Donor sex			0.266
Male	36 (61)	30 (51)	
Female	23 (39)	29 (49)	
Donor BMI (kg/m^2)*	25.50 (4.45)	26.60 (4.30)	0.161
Donor height (m)*	1.7 (0.1)	1.7 (0.2)	0.172
Donor weight (kg)*	78.0 (18.0)	80.0 (20.0)	0.996
Steatosis			0.639
None	33 (56)	28 of 58 (48)	
Mild	20 (34)	27 of 58 (47)	
Medium	4 (7)	3 of 58 (5)	
Severe	2 (3)	.	
Eurotransplant Donor Risk Index*	1.78 (0.51)	1.85 (0.72) ($n = 58$)	0.733
Donor artery anatomy			0.922
Normal	43 (73)	42 of 57 (74)	
Variance	16 (27)	15 of 57 (26)	
Donation after cardiac death	4 (7)	9 of 58 (16)	0.133
Partial/split liver	.	1 (2)	0.315
Allocation			0.836
Local	8 (14)	10 of 57 (18)	
Regional	33 (56)	30 of 57 (53)	
National	18 (31)	17 of 57 (30)	
Cause of death			0.121
Trauma	8 (14)	13 of 57 (23)	
Anoxia	9 (15)	14 of 57 (25)	
Cardiovascular event	39 (66)	25 of 57 (44)	
Other	3 (5)	5 of 57 (9)	
Intensive care unit duration of stay (days)*	3 (4)	4 (4) ($n = 57$)	0.638
Sodium (U/l)*	148 (10) ($n = 58$)	145 (12) ($n = 53$)	0.616
Latest GGT*	35 (70)	64 (94) ($n = 56$)	0.067
Simultaneous transplant			0.776
No	54 of 54 (100)	57 of 57 (100)	
Liver–kidney	.	.	
Heart–liver	.	.	
Multiorgan	.	.	
Surgery duration (min)*	366 (126)	388 (130) ($n = 57$)	0.479
Mass clamping lig. hepatoduodenale	.	2 (4) ($n = 57$)	0.147
Anastomosis time (min)*	42 (11)	50 (10) ($n = 57$)	<0.001
Cold ischaemia time (h)*	7 (3)	6 (2) ($n = 57$)	0.055
Total preservation time (h)*	7 (3)	21 (12) ($n = 58$)	<0.001

Values in parentheses are percentages unless indicated otherwise; *values are median (i.q.r.). †Where patient numbers are not the total in the group, this is stated. SCS, static cold storage; NMP, normothermic machine perfusion; GGT, gamma-glutamyl transferase. ‡χ^2 and Fisher's exact test for categorical variables and Mann–Whitney *U* test for continuous variables. Dot (.) signifies zero

($P = 0.810$), anastomotic strictures in 36 per cent (NMP 21 of 59 patients) *versus* 39 per cent (SCS 23 of 59), ($P = 0.703$) and non-anastomotic intrahepatic strictures in 8 per cent (NMP 5 of 59 patients) *versus* 17 per cent (SCS 10 of 59) ($P = 0.167$) of patients. Livers undergoing NMP developed significantly lower rates of ITBL compared with SCS livers (NMP 3 per cent (2 of 59 patients) *versus* SCS 14 per cent (8 of 59), $P = 0.047$) (*Table 3*). Two patients were retransplanted and one patient died due to cholangiosepsis, all belonging to the SCS group. One mild, one moderate and six severe ITBL lesions occurred in the SCS group. In contrast, two mild lesions were found in the NMP cohort. When patients with bile cast syndrome were stratified into extra- and intrahepatic casts, three of eight patients in the SCS group developed extrahepatic and two of eight intrahepatic casts. The two patients in the NMP group displaying ITBL did not have bile cast syndrome. A detailed description of the donor, recipient and operative profile of patients developing ITBL in both groups is shown in *Tables S9* and *S10*.

Discussion

The current study compares NMP with conventional SCS in human liver transplantation in a 1 : 1 matched design. From this experience, it is concluded that a significant prolongation of liver preservation is technically feasible, albeit associated with procedural efforts such as training and coordination of a

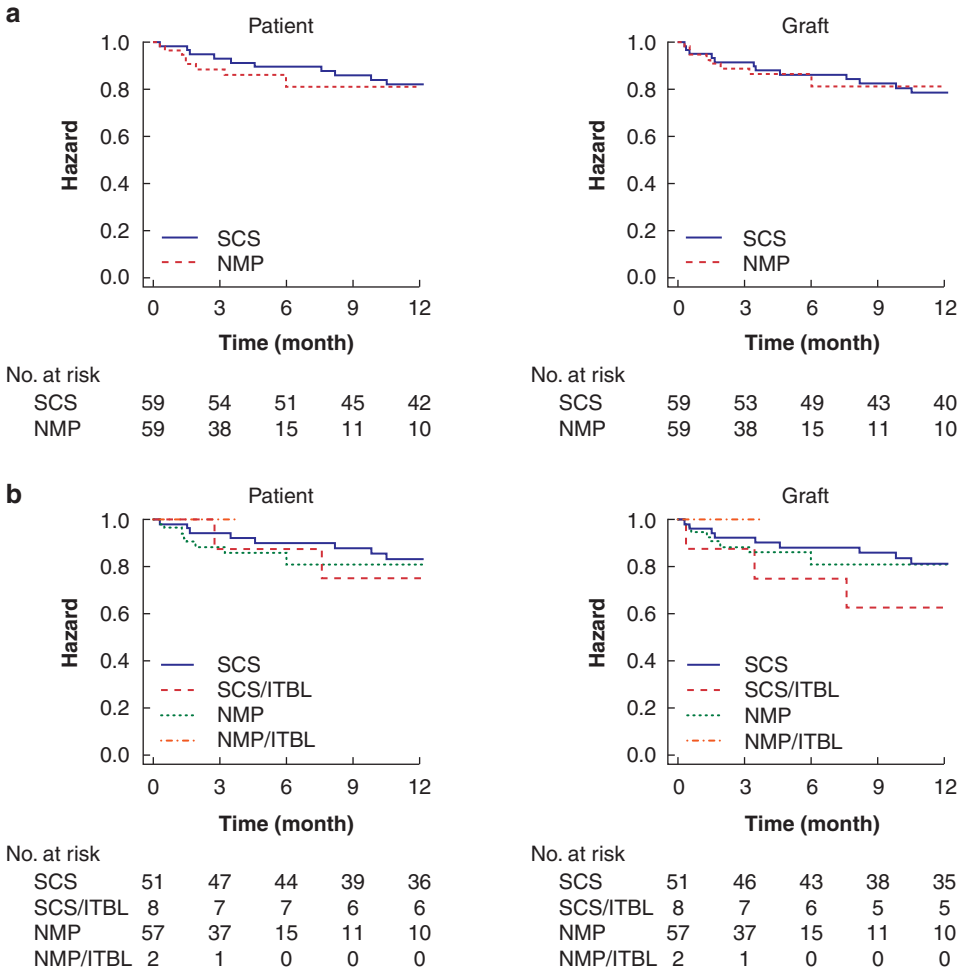

Fig. 2 a Patient and graft survival of normothermic machine perfusion and static cold storage groups in days. b Patient and graft survival of normothermic machine perfusion and static cold storage groups highlighting patients with ischaemic-type bile duct lesions. SCS, static cold storage; NMP, normothermic machine perfusion; ITBL, ischaemic-type bile duct lesions

multidisciplinary team in order to establish NMP as a safe routine. The study displays favourable results of liver transplantation following NMP, particularly in reference to a reduced rate of ITBL, in that 14 per cent of patients in the SCS and 3 per cent in the NMP group developed ITBL. In accordance with previous analyses[4,16,21], no statistical differences in patient or graft survival between NMP and SCS were found (*Fig. 2a,b*).

The supplementation of vasodilators during NMP is thought to contribute to the preservation of peribiliary vascular microcirculation and to avoid accumulation of toxic substances[16]. While reduced early allograft dysfunction rates and shorter hospital stays for NMP have been demonstrated in previous studies[16,22], the impact on the biliary complication rate is less clear[16,21–25]. In a prospective RCT, the early allograft dysfunction rate was 10.1 and 29.9 per cent in the NMP and SCS groups, respectively[16]. Case-control studies reported early allograft dysfunction rates of 27.6 per cent following NMP *versus* 42.5 per cent after SCS[21]. While the primary non-function rate in clinical practice ranges from 5–8 per cent[17], primary non-function was not seen in this trial.

The benefit of NMP with regard to logistics, the burden of night-time procedures and personnel is significant[16]. The relevance of tripling the preservation time is underestimated in the current discussion. It allows for meaningful consequences and planning, as well as careful reflection on organ utilization. While the effect on healthcare workers' lifestyle was not the priority of the study, the knock-on effect of the technology is palpable in the authors' experience.

The most important finding of the study was a significantly lower incidence of ITBL in the NMP group, suggesting a potential advantage of NMP in avoiding bile duct damage. In the RCT[16], the ITBL rate was 7.7 per cent (7 of 91 patients) after NMP *versus* 9.5 per cent (8 of 84) after SCS. In one case-controlled study, no ITBL were reported in the NMP group *versus* 4 of 27 patients in the SCS group[21]. In another case series (22 patients), the ITBL rate was 18.2 per cent. Two studies comparing different NMP modalities reported an ITBL rate of 2.7 per cent[21]. The incidence of biliary complications might be driven by the ambition to detect alterations of the bile duct prior to the eventual appearance of clinical symptoms. For the radiological categorization of ITBL, an existing definition[18,19], further adapted in order to optimize capture and grading of the injury, was applied. There is a clear need for standardization of the assessment, and the grading herein applied offers a suitable and reproducible classification. The incidence of symptomatic ITBL was 20 per cent (2 of 10 patients) in this cohort and the lesions qualifying for ITBL are mild in some patients. The lower incidence in the NMP group possibly results from an optimal assessment of liver viability and function before transplantation. Although shorter hospital stays are largely attributed to patient and concurrent disease-related factors, cost savings through this and lesser ERCP rates are relevant to healthcare economics (*Tables S11* and *S12*).

Table 3 Clinical outcomes and complications

Outcome	SCS ($n = 59$)†	NMP ($n = 59$)†	P‡
Duration of stay (days)*	23 (21)	17 (12)	0.006
Clavien Dindo classification			0.086
I	3 (5)	.	
II	22 (37)	15 of 57 (26)	
IIIa	.	5 of 57 (9)	
IIIb	12 (20)	12 of 57 (21)	
IVa	17 (29)	18 of 57 (32)	
V	5 (8)	7 of 57 (12)	
Early allograft dysfunction	20 of 58 (34)	19 (32)	0.794
Vascular complications	9 (15)	8 (14)	0.793
Arterial complications	5 (8)	6 (10)	0.752
Arterial dissection	1 (2)	1 (2)	1.000
Arterial thrombosis	4 (7)	.	0.042
Arterial stenosis	2 of 58 (3)	3 (5)	0.662
Portal vein stenosis	1 (2)	1 (2)	1.000
Venous thrombosis	5 (8)	3 (5)	0.464
Reoperation	21 (36)	24 (41)	0.570
Reoperation≤30 days	20 (34)	24 (41)	0.446
Haematoma	13 (22)	13 (22)	1.000
Acute kidney failure	8 (14)	5 (8)	0.378
Bile duct complications	29 (49)	30 (51)	0.854
Bile duct complications≤30 days	11 (19)	13 (22)	0.647
Bile duct complications>30 days	21 (36)	16 (27)	0.321
Bile duct leak	11 (19)	10 (17)	0.810
Anastomotic strictures	23 (39)	21 (36)	0.703
Non-anastomotic strictures	10 (17)	5 (8)	0.167
ITBL	8 (14)	2 (3)	0.047
ITBL grade			n.a.
Mild	1 of 8 (12)	2 of 2 (100)	
Moderate	1 of 8 (12)	.	
Severe	6 of 8 (75)	.	
Intrahepatic cast	3 of 25 (12)	0 of 17	0.138
Extrahepatic cast	6 of 25 (24)	0 of 17	0.029
Cholangitis	11 (19)	4 (7)	0.053

Values in parentheses are percentages unless indicated otherwise; *values are median (i.q.r.). †Where patient numbers are not the total in the group, this is stated. SCS, static cold storage; NMP, normothermic machine perfusion. ITBL, ischaemic-type biliary lesions. ‡χ^2 and Fisher's exact test for categorical variables and Mann–Whitney *U* test for continuous variables. Dot (.) signifies zero.

Three mechanisms are thought to be involved in the development of ITBL: ischaemia reperfusion injury, bile salts and immune-mediated mechanisms[9]. Potential risk factors for ITBL were detected previously and include logistical aspects such as cold and warm ischaemia time[9]. Further to the warm ischaemia time, the cold ischaemia time causes injury to the biliary epithelium and damage to the peribiliary arterioles[23–30]. Recently, novel and promising strategies for treatment of cholangiopathies have been investigated[31]. Cholangiocyte organoid application in human livers undergoing *ex vivo* NMP resulted in repair of intrahepatic bile ducts[31].

Limitations of the present study included a retrospective design and a 1-year follow-up period. A possible bias concerning the selection of participants beyond the data displayed in the demographics is recognized. It is also acknowledged that the small sample size of ITBL in both groups and the bias related to the relative novelty of the technology enhance the risk of a bias of era. While this study provides encouraging evidence, any potential beneficial effect of NMP against ischaemic cholangiopathy needs to be further investigated[21,27]. Since requirement for treatment was not included in the ITBL definition, a radiological difference in the early stage may have limited immediate clinical significance. Early ITBL detection in asymptomatic patients, however, should result in close monitoring. The limited number of livers from DCD may explain the relatively low ITBL rate. Larger studies with higher DCD rates are obligatory to confirm these results. The development of parameters predicting the ITBL rate during the *ex vivo* phase remains a priority to direct decision making. The inclusion of SCS patients going back to 2007 means that not all patients were submitted to MRCP per protocol. Finally, a limiting factor of the matching approach is related to the ambition to include all NMP patients from the beginning of the trial. Despite an optimized matching process, residual confounders cannot be ruled out.

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Supplementary material

Supplementary material is available at *BJS* online

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