From Patients to Providers: Assessing Impact of Normothermic Machine Perfusion on Liver Transplant Practices in the US

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BACKGROUND: Normothermic machine perfusion (NMP) of livers allows for the expansion of the donor pool and minimization of posttransplant complications. Results to date have focused on both donor and recipient outcomes, but there remains potential for NMP to also impact transplant providers.

STUDY DESIGN: Using United Network for Organ Sharing Standard Transplant Analysis file data, adult deceased donors who underwent transplantation between January 1, 2016, and December 31, 2022, were identified. Transplanted livers were divided by preservation methods (static cold storage [SCS] and NMP) and case time (day-reperfusion 8 AM to 6 PM). Patient factors, transplant characteristics, and short-term outcomes were analyzed between Mahalanobis-metric-matched groups.

RESULTS: NMP livers represented 742 (1.4%) of 52,132 transplants. NMP donors were more marginal with higher Donor Risk Index scores (1.78 ± 0.50 NMP vs 1.49 ± 0.38 SCS, $p < 0.001$) and donation after cardiac death frequency (36.9% vs 8.4%, $p < 0.001$). NMP recipients more often had model for end-stage liver disease (MELD) exception status (29.9% vs 23.4%, $p < 0.001$), lower laboratory MELD scores (20.7 ± 9.7 vs 24.3 ± 10.9, $p < 0.001$), and had been waitlisted longer (111.5 [21.0 to 307.0] vs 60.0 [9.0 to 245.0] days, $p < 0.001$). One-year graft survival (90.2% vs 91.6%, $p = 0.505$) was similar between groups, whereas length of stay was lower for NMP recipients (8.0 [6.0 to 14.0] vs 10.0 [6.0 to 16.0], $p = 0.017$) after adjusting for confounders. Notably, peak case volume occurred at 11 AM with NMP livers (vs 9 PM with SCS). Overall, a higher proportion of transplants was performed during daytime hours with NMP (51.5% vs 43.0%, $p < 0.001$).

CONCLUSIONS: NMP results in increased use of marginal allografts, which facilitated transplantation in lower laboratory MELD recipients who have been waitlisted longer and often have exception points. Importantly, NMP also appeared to shift peak caseloads from nighttime to daytime, which may have significant effects on the quality of life for the entire liver transplant team. (J Am Coll Surg 2024;238:844–852. © 2024 by the American College of Surgeons. Published by Wolters Kluwer Health, Inc. All rights reserved.)

Drs Wang and Shubin contributed equally to this work.

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Abbreviations and Acronyms

DCD	=	donation after cardiac death
DRI	=	Donor Risk Index
HR	=	hazard ratio
MELD	=	model for end-stage liver disease
NMP	=	normothermic machine perfusion
SCS	=	static cold storage
STAR	=	Standard Transplant Analysis
UNOS	=	United Network for Organ Sharing

Normothermic machine perfusion (NMP) has evolved the practice of liver transplantation. During NMP, an allograft is placed on an ex vivo machine that provides oxygenated perfusion at physiologic temperature.[1-4] Two devices in the US—the OrganOx Metra (OrganOx Ltd; Oxford, UK) and TransMedics OCS (TransMedics Inc; Andover, MA)—have completed randomized clinical trials and received FDA approval in 2021 (Fig. 1).[1,4] Studies for liver perseveration with NMP to date have primarily focused on donor and recipient metrics and have assessed its role in decreasing the incidence of ischemia–reperfusion injury contributing to early allograft dysfunction,[1,5,6] postreperfusion syndrome,[4] ischemic biliary complications,[1,7] and lower rates of organ discard.[3,8,9]

Currently, there are no studies exploring the potential benefit of NMP for providers, healthcare teams, and transplant centers. Growing evidence has emerged suggesting increasing burnout among abdominal transplant surgeons and fellows in the US.[10,11] In addition to the effects on personal health and professional development, provider burnout has borne consequences for patient care through increased medical errors, increased healthcare costs, strained interpersonal relationships, and poorer clinical outcomes.[12] Indeed, there remains an opportunity for NMP to improve the efficiency of transplantation for the entire liver transplant team.

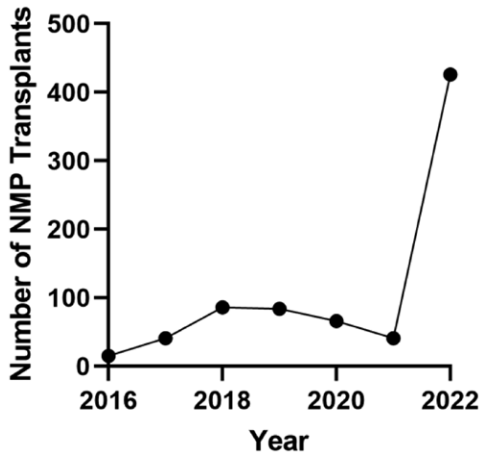

Figure 1. Normothermic machine perfusion (NMP) transplant volume in the US since 2016.

We aimed to evaluate the role of NMP for liver preservation in both patients and providers, hypothesizing increased use of donor organs, improved transplantation outcomes, and a shift of cases from nighttime to daytime with NMP. As NMP allows ex vivo assessment and potential optimization of graft function, we explored differences in donor quality and recipient risk profiles between NMP and traditional static cold storage (SCS) cases to elucidate the technology's role in expanding the liver donor pool.

METHODS

Data source

This study analyzed the United Network for Organ Sharing (UNOS) Standard Transplant Analysis (STAR) files that contain data on all donors, waitlisted candidates, and recipients of solid organ transplantation in the US. Periodic follow-ups (including, but not limited to, graft function and patient mortality) were reported to the Organ Procurement and Transplantation Network by transplant centers. This study was deemed exempt by the IRB of the University of Texas Southwestern Medical Center as all analyzed patient information was de-identified.

Study population

Deceased donor livers from January 1, 2016, to December 31, 2022, were identified using UNOS STAR file data (84,779). This start date was chosen as this was the first time NMP livers were used in the US. Livers from pediatric donors were excluded from analysis (6,572, 7.8%). One hundred seventy-six organs preserved with hypothermic or other (non-normothermic) machine perfusion were excluded (0.2%) from analysis and an additional 335 organs were excluded due to insufficient or mislabeled data entries in the STAR file database (0.4%).

Donor, recipient, and transplant characteristics

To assess donor and recipient characteristics as a function of organ preservation method, transplants were separated into NMP and SCS groups and compared. Transplant case features, including but not limited to, case time of day and total cold ischemia time, were examined. Daytime cases were defined as those with reperfusion time occurring between 8:00 AM and 5:59 PM local time of the transplanting center (nighttime: reperfusion between 6:00 PM and 7:59 AM local time). Reperfusion time was defined as the donor clamp time plus the total storage time (cold ischemic time plus any time placed on pump).

Recipient outcomes

The primary outcomes studied between groups were 1-year graft survival. Secondary outcomes included recipient waitlist time, hospital length of stay, and liver discard rate. The liver discard rate was subanalyzed by the following donor characteristics described by Feng and colleagues[13] as high risk: age, ethnicity, cause of death contributing to brain death, and donation after cardiac death (DCD) status. Discarded livers were defined as those not used for transplant after initial procurement.

Statistical analysis

The statistical analyses were performed using STATA 16/MP4 (StataCorp, College Station, TX), and p values of <0.05 were considered statistically significant. Patient characteristics were described using mean (SD) for normally distributed continuous variables, median [interquartile range] for non-normally distributed continuous variables, and frequencies for categorical variables. Comparison by univariate analyses was made using the chi-square test for categorical variables. For continuous variables, the Shapiro–Francia test was used to determine normality, and statistical significance was determined using the Wilcoxon rank-sum test for non-normal data and a 2-sample *t*-test for normal data. Survival analysis was conducted using the Kaplan–Meier method, and the log-rank test for equality of survivor functions was used to compare overall survival between groups.

Matched outcomes analysis

To assess the impact of preservation method on recipient outcomes, nearest-neighbor Mahalanobis-metric matching (https://www.stata.com/manuals/teteffectsnnmatch.pdf) in a 1:1 manner was used to account for confounding while comparing primary and secondary outcomes among the treatment group (NMP-preserved livers) and control group (SCS-preserved livers). The following clinically relevant patient and transplant characteristics were used as covariates for matching: donor age, donor BMI, Donor Risk Index (DRI) score, DCD donor, donor ethnicity, recipient age, recipient ethnicity, recipient final laboratory model for end-stage liver disease (MELD) score, recipient status at the time of transplant, recipient MELD exception status, and recipient on life support.

RESULTS

We identified 77,696 deceased donor livers offered for donation during the study period, of which 52,132 (67.1%) were transplanted. Seven hundred ninety-one (1.0%) deceased donor livers were placed on NMP, and 742 (93.8%) were eventually transplanted into suitable recipients. Notably, 55.9% (415) of all transplanted NMP cases completed in the US were performed in 2022, after FDA approval (Fig. 1). The median storage time of transplanted NMP livers was significantly longer than that of SCS livers (9.0 [6.8 to 12.2] vs 5.7 [4.6 to 7.0] hours, p < 0.001). Additionally, the median recipient waitlist time was 112 days for livers preserved with NMP (interquartile range 21 to 307 days), compared with 60 days (9 to 245 days) for those preserved in SCS (p < 0.001). The overall discard rate for NMP livers was significantly lower than that of SCS livers (3.8% vs 7.2%, p < 0.001).

Donor and recipient characteristics in NMP cases

Deceased donor liver grafts preserved with NMP were transplanted from donors who were older (46.3 ± 14.0 vs 42.2 ± 15.0 years, p < 0.001), had higher BMIs (29.8 ± 6.9 vs 28.3 ± 6.6 kg/m^2, p < 0.001), and considered overall higher risk by DRI (1.78 ± 0.50 vs 1.49 ± 0.38 DRI, p < 0.001), when compared with liver grafts preserved in SCS (Table 1). Additionally, NMP liver grafts were more often transplanted from DCD donors (36.9% vs 8.4%, p < 0.001). Recipients of NMP livers were significantly older (57.2 ± 11.0 vs 54.5 ± 12.8 years, p < 0.001) and had higher rates of MELD exception status (29.9% vs 23.4%, p < 0.001) and lower laboratory MELD scores at the time of transplant (20.7 ± 9.7 vs 24.3 ± 10.9, p < 0.001), compared with their SCS counterparts.

Outcomes between organ preservation methods

Despite the use of more marginal deceased donors, 1-year graft survival was not significantly different between recipients of liver grafts with either preservation method during the study period (89.3% vs 91.5%, p = 0.103). Notably, NMP preservation resulted in a 2-day shorter median length of stay for the primary transplantation hospitalization (8.0 [6.0 to 14.0] vs 10.0 [7.0 to 17.0], p < 0.001). Cox regression models comparing 1-year graft survival of NMP and SCS groups, while adjusting for donor and recipient covariates, also found no significant difference in the hazard ratio (HR) for graft failure (HR 1.219, 95% CI 0.802 to 1.851, p = 0.354, **Supplemental Digital Content 1**, Table 1, http://links.lww.com/JACS/A331).

Outcomes from matched NMP and SCS groups

To control for possible confounders and differences in donor and recipient pretransplant risk, Mahalanobis-metric-matched cohorts of NMP- and SCS-preserved livers were prepared (Table 2). The 1-year graft survival was statistically similar between groups (90.2% vs 91.6%,

Table 1. Donor and Recipient Characteristics of Cases Preserved With Normothermic Machine Perfusion and Static Cold Storage

Variable	Static cold storage (N = 51,390)	Normothermic machine perfusion (N = 742)	p Value
Donor age, y, mean (SD)	42.2 (15.0)	46.3 (14.0)	<0.001
Male donor, n (%)	31,244 (60.8)	456 (61.5)	0.720
Donor BMI, kg/m^2, mean (SD)	28.3 (6.6)	29.8 (6.9)	<0.001
Macrovesicular fat, %, mean (SD)	8.8 (11.9)	9.0 (11.5)	0.780
Donor risk index, mean (SD)	1.488 (0.382)	1.781 (0.503)	<0.001
Donation after cardiac death donor, n (%)	4,318 (8.4)	274 (36.9)	<0.001
Donor race and ethnicity, n (%)			0.043
White	32,679 (63.6)	507 (68.3)	
Black	9,200 (17.9)	110 (14.8)	
Hispanic	7,588 (14.8)	96 (12.9)	
Other	1,923 (3.7)	29 (3.9)	
Recipient age, y, mean (SD)	54.5 (12.8)	57.2 (11.0)	<0.001
Male recipient, n (%)	33,316 (64.8)	489 (65.9)	0.540
Recipient BMI, kg/m^2, mean (SD)	28.8 (6.1)	28.9 (5.8)	0.540
Laboratory MELD, mean (SD)	24.3 (10.9)	20.7 (9.7)	<0.001
Recipient status, n (%)			<0.001
Status 1A	1,425 (2.8)	4 (0.5)	
Status 1B	253 (0.5)	0 (0.0)	
Other	49,712 (96.7)	738 (99.5)	
MELD exception, n (%)	11,121 (23.4)	139 (29.9)	0.001
Recipient race and ethnicity, n (%)			<0.001
White	35,948 (70.0)	553 (74.5)	
Black	4,065 (7.9)	33 (4.4)	
Hispanic	8,443 (16.4)	126 (17.0)	
Other	2,934 (5.7)	30 (4.0)	
Recipient waitlist time, d, median [IQR]	60.0 [9.0–245.0]	112.0 [21.0–307.0]	<0.001
Prior abdominal surgery, n (%)	24,815 (49.1)	386 (52.4)	0.073
History of portal vein thrombosis, n (%)	7,170 (14.0)	105 (14.2)	0.910
On life support, n (%)	4,837 (9.4)	33 (4.4)	<0.001
1-y graft survival, events (%)	4,077 (91.5)	56 (89.3)	0.103
Length of stay, d, median [IQR]	10.0 [7.0–17.0]	8.0 [6.0–14.0]	<0.001

IQR, interquartile range; MELD, model for end-stage liver disease.

p = 0.505; Fig. 2), but median length of stay of NMP recipients was shorter compared with that of SCS recipients (8.0 [6.0 to 14.0] vs 10.0 [6.0 to 16.0], p = 0.017). Similarly, Cox regression also found no significant difference in HR for graft failure with NMP vs SCS preservation (HR 1.356, 95% CI 0.692 to 2.659; p = 0.375, **Supplemental Digital Content 2**, Table 2, http://links.lww.com/JACS/A331).

Shift in case load

The peak case load shifted from 9 PM (N = 2,608, 5.1%) with SCS preservation to 11 AM (N = 55, 7.4%) with NMP preservation (Fig. 3). Daytime cases comprised 51.5% (382) with NMP preservation vs 43.0% (22,123) with SCS preservation (p < 0.001). Three hundred (40.4%) grafts preserved with NMP underwent reperfusion the day after initial clamping at procurement, compared with 12,288 (23.9%) grafts preserved with SCS (p < 0.001). Notably, 31.3% (232) of all NMP cases during the study period were performed with a reperfusion time between 8 AM and 12 PM.

Available donor pool augmented by NMP

In total, 76,905 SCS and 791 NMP deceased donor livers were offered for transplantation during the study period, and 5,531 (7.2%) and 30 (3.8%) livers were discarded after procurement, respectively (Fig. 4). The

Table 2. Matching Covariates and Outcomes from Mahalanobis-Metric-Matched Cohorts of Transplanted Static Cold Storage and Normothermic Machine Perfusion Livers

Variable	Static cold storage (N = 457)	Normothermic machine perfusion (N = 462)	p Value
Donor age, y, mean (SD)	46.0 (14.0)	48.1 (14.1)	0.026
Male donor, n (%)	285 (62.4)	284 (61.5)	0.780
Donor BMI, kg/m^2, mean (SD)	29.8 (6.8)	29.9 (6.9)	0.770
Macrovesicular fat, %, mean (SD)	9.4 (12.2)	9.1 (11.1)	0.790
Donor risk index, mean (SD)	1.702 (0.461)	1.714 (0.470)	0.690
Donation after cardiac death donor, n (%)	136 (29.8)	138 (29.9)	0.970
Donor race and ethnicity, n (%)			0.980
White	313 (68.5)	314 (68.0)	
Black	70 (15.3)	73 (15.8)	
Hispanic	62 (13.6)	61 (13.2)	
Other	12 (2.6)	14 (3.0)	
Recipient age, y, mean (SD)	57.4 (10.4)	57.4 (10.7)	0.990
Male recipient, n (%)	319 (69.8)	313 (67.7)	0.500
Recipient BMI, kg/m^2, mean (SD)	29.3 (5.6)	29.0 (5.7)	0.390
Laboratory MELD, mean (SD)	20.1 (9.7)	20.1 (9.9)	0.970
Recipient status, n (%)			0.990
Status 1A	2 (0.4)	2 (0.4)	
Other	455 (99.6)	460 (99.6)	
MELD exception, n (%)	138 (30.2)	137 (29.7)	0.860
Recipient race and ethnicity, n (%)			0.750
White	363 (79.4)	366 (79.2)	
Black	16 (3.5)	18 (3.9)	
Hispanic	67 (14.7)	62 (13.4)	
Other	11 (2.4)	16 (3.5)	
Recipient waitlist time, d, median [IQR]	116.0 [21.0–293.0]	152.0 [33.0–352.0]	0.033
History of abdominal surgery, n (%)	245 (54.4)	234 (51.1)	0.310
History of portal vein thrombosis, n (%)	76 (16.6)	73 (15.8)	0.730
On life support, n (%)	20 (4.4)	20 (4.3)	0.970
1-y graft survival, events (%)	37 (91.6)	41 (90.2)	0.505
Length of stay, d, median [IQR]	10.0 [6.0–16.0]	8.0 [6.0–14.0]	0.017

IQR, interquartile range; MELD, model for end-stage liver disease.

most common reasons for discard of NMP-preserved livers were poor allograft function (9, 30%), "other" (7, 23.3%), and an inability to locate a suitable recipient (4, 13.3%). In contrast, the most common reasons for discard of SCS livers were biopsy findings (1,902, 34.4%), "other" (1,461, 26.4%), and prolonged warm ischemic time (467, 8.4%). Poor allograft function comprised the primary reason for 3.6% (N = 198) of discarded SCS livers.

Among higher risk donors, as defined by the DRI,[13] SCS-preserved livers demonstrated significantly higher rates of discard vs those preserved with NMP: nearly 2-fold in DCD donors, greater than 2-fold in donors with cerebrovascular accident causing brain death, and greater than 3-fold in donors older than 60 years (Table 3).

DISCUSSION

We present the largest retrospective analysis worldwide examining NMP preservation for liver transplantation. Given the substantial growth in the usage of NMP, understanding practice patterns and outcomes is imperative. These data support earlier publications that NMP reduces allograft discards[3] and add that NMP is used for higher risk donors in older, lower laboratory MELD recipients. Discarded grafts preserved with NMP were most commonly turned down for poor allograft function, consistent

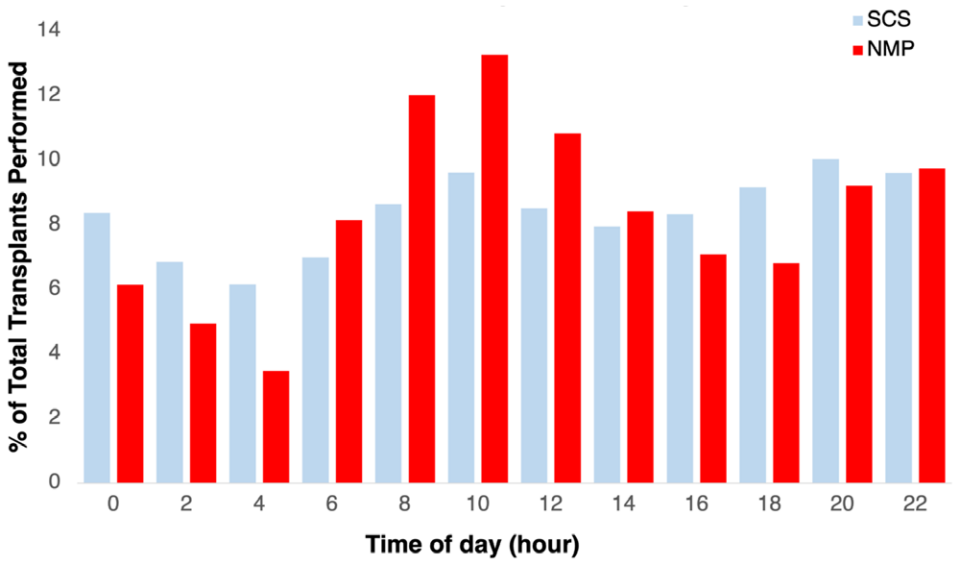

Figure 2. Comparison of short-term liver graft survival by the preservation method among Mahalanobis-metric-matched groups. NMP, normothermic machine perfusion; SCS, static cold storage.

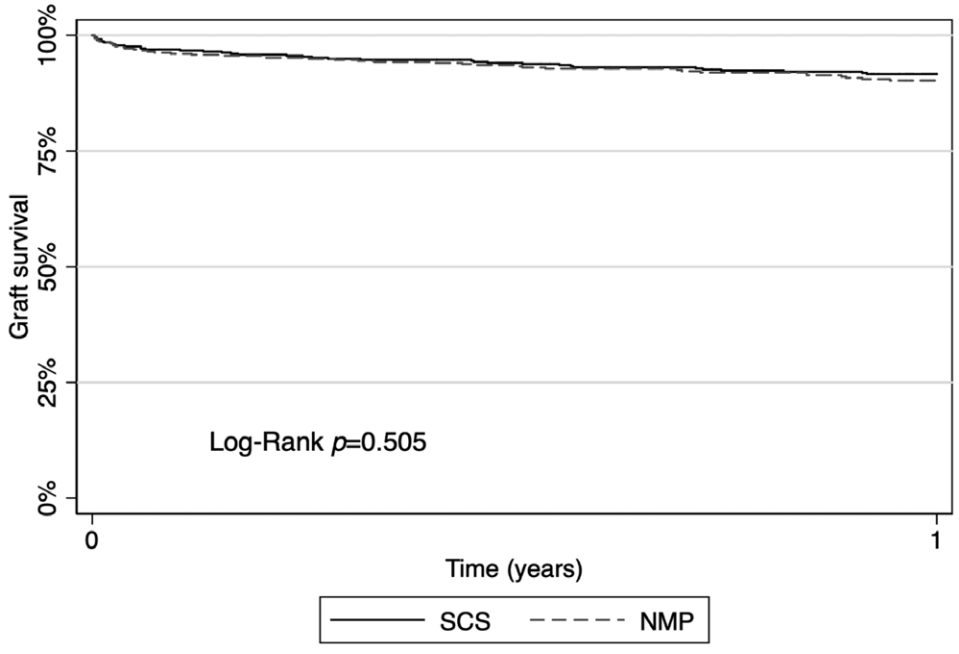

Figure 3. Case volume during the day between static cold storage (SCS) and normothermic machine perfusion (NMP) preservation.

with the premise of NMP as a tool for graft assessment. Importantly, NMP was associated with an increase in daytime cases. The ability to have greater control over operating room start times without negatively impacting patient outcomes is important in promoting allograft use, optimizing team-based care, and preventing burnout for members of the transplant team.[11]

In 2020, we were among the first in the US to describe higher rates of organ use with NMP use.[3] Other reports, including single-center and multicenter randomized controlled trials, have corroborated these findings.[1,2,4,5,8,9,14-17] However, these studies have largely been limited by analysis cohort sizes as NMP case volumes were still relatively low during the time at which

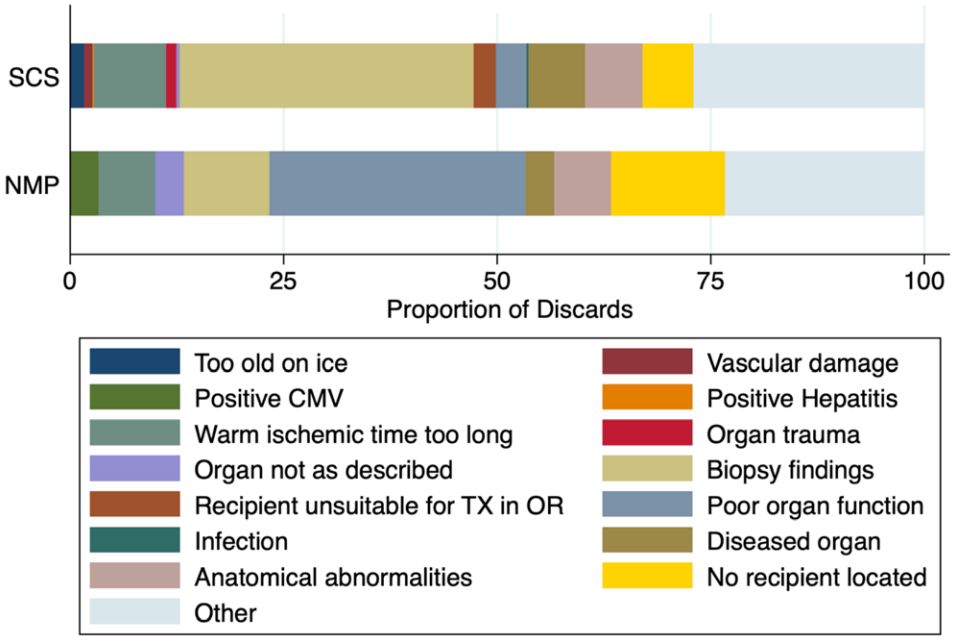

Figure 4. Graft discard reasons for SCS (n = 5,531) and NMP (n = 30) grafts not transplanted after procurement from deceased donor. NMP, normothermic machine perfusion; OR, operating room; SCS, static cold storage; TX, transplantation.

Table 3. Discard Rate Among Subsets of High-Risk Deceased Donors

Variable	Static cold storage, %	Normothermic machine perfusion, %	p Value
Age > 60 y	9.7	2.9	0.006
Black race	5.4	5.2	0.931
Cerebrovascular accident	8.3	3.0	0.002
"Other" causes of brain death	5.0	0.0	0.273
Donation after cardiac death	9.7	5.3	0.009

these reports were published. Herein we report NMP rates of discard of 3.8%, 1-year graft survival of 89.3%, and a reduction in hospital length of stay of 2 days. These findings are consistent with other large-scale retrospective studies of liver transplantation with NMP, which report discard rates ranging from 3.5% to 11.7%, 1-year graft survival rates ranging from 84% to 94%, and reduced hospital length of stays ranging up to 3.6 days.[3,8,18-21]

Although our assessment of NMP on donors and recipients is consistent with the existing literature, it offers additional insight into the effects on providers and transplant teams. Importantly, among the transplant community, there has been increasing focus on rates of provider burnout.[10,11,22] Specifically, Bertges Yost and colleagues,[11] in a national survey of transplant surgeons, demonstrated a burnout rate among abdominal transplant surgeons of 38%. These individuals demonstrated higher levels of emotional exhaustion, depersonalization, and reduced feelings of personal accomplishment.[11] Compared with surgical oncology (28%), head and neck surgery (34%), and pediatric surgery (31%), this figure represents a rate of burnout on the higher end of the spectrum for surgical subspecialties.[23-25] Although institutional, cultural, and professional factors have been shown to contribute to burnout among surgeons in general,[23,25,26] irregular working hours, more frequent on-call responsibilities, and patient complexity are uniquely implicated in promoting burnout among abdominal transplant surgeons.[27] As demonstrated by the national shift in peak case volume from 9 PM to 11 AM, NMP has the potential to address multiple of these associated factors. However, it should be acknowledged that multiple factors such as increased time needed to prepare organ for perfusion, the need for a period to assess allograft function while on perfusion, and other logistical challenges in addition to surgeon discretion could play a

role in the increase in daytime cases. More studies are needed to determine the factors that influence case start times. Although shift of operations to daytime hours can decrease work-related nighttime sleep deprivation and improve team dynamics, indeed, further detailed survey of burnout among members of the transplant team at centers with high and low NMP usage is of great importance to understand the technology's direct effect on provider morale.

Of note, the findings presented in this report may also offer additional insights for value-based care.[28] Although still novel to the field of liver transplantation, value-based care has emerged as an area of focus in various surgical fields.[29] The results from the present cohort demonstrated 2-day shorter median hospital length of stays in cases performed with NMP. As healthcare value has traditionally been defined as outcomes divided by costs, and hospital length of stay is directly associated with costs, the benefits of NMP technology on healthcare value delivery is promising but requires further study accounting for costs associated with NMP, as well as potential for decreasing known complications that correlate with increased healthcare use (eg early allograft dysfunction and biliary strictures).[30] Cost data remain limited, with literature reported costs ranging between $15,000 and $50,000 per procurement dependent on device and pricing constructs.[31,32] This should be considered in conjunction with any associated potential savings. Additionally, center-specific practice variations, technology vendor differences, and economies of scale will alter individual costs. Future work to evaluate the value added with additional costs materialized from NMP is of great importance.

As this was a retrospective study from a large registry database, several limitations should be mentioned. Primarily, the UNOS dataset does not capture center-specific criteria for graft acceptance, evaluation, and usage. We were unable to control for all possible pre-, intra-, and postoperative factors that may have confounded the outcomes presented in this report. Matched pair analysis with Mahalanobis-metric matching was used to mitigate this possibility, although may only partially account for confounders. Variations over time, including UNOS allocation policy changes and the COVID-19 pandemic, are additional sources of possible confounding; however, our matched pair analysis did not include a time component (eg surgery year) due to the few NMP transplants that occurred in the early years after introduction of the technology.

Finally, this report is based on best available publicly reported data, and further studies are warranted. In particular, the long-term outcomes of those receiving allografts with prolonged pump time should be closely monitored to prevent previous issues such as biliary strictures from prolonged cold ischemia.[33] Cold ischemia time as currently reported in the UNOS STAR file lumps "true" cold ischemia time and any time on pump into this singular value. For NMP cases, pump time is not currently tracked, and cold ischemia time for these cases may not be truly representative of graft preservation time while in a hypothermic state. Thus, this analysis also serves as a call to establish granular, longitudinal databases with meaningful recipient follow-up data in addition to technology-specific data. Specifically, the STAR file does not capture data such as NMP flow rates, blood and bile laboratory values while under perfusion, and organ pump time. As NMP use has increased and changed the dynamic of liver transplantation (from utilization, to donor and recipient matching, to logistics, and to potential provider benefit), it remains imperative to continually evaluate the impact of adopting this emerging technology.

CONCLUSIONS

NMP preservation before liver transplant has demonstrated noteworthy benefits for both patients and providers. We demonstrate similar recipient outcomes to those of established SCS preservation techniques, a substantial shift in liver transplant cases toward daytime hours, and decreased discard rates. These phenomena occurred in the setting of NMP usage with more marginal organs and transplantation in lower MELD recipients, thus demonstrating the opportunity for expansion of the donor pool for recipients in need.

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