Received: 16 March 2024 | Accepted: 13 May 2024

DOI: 10.1097/LVT.0000000000000412

ORIGINAL ARTICLE

The impact of normothermic machine perfusion and acuity circles on waitlist time, mortality, and cost in liver transplantation: A multicenter experience

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Abstract

Ex situ normothermic machine perfusion (NMP) helps increase the use of extended criteria donor livers. However, the impact of an NMP program on waitlist times and mortality has not been evaluated. Adult patients listed for liver transplant (LT) at 2 academic centers from January 1, 2015, to September 1, 2023, were included (n = 2773) to allow all patients ≥ 6 months follow-up from listing. Routine NMP was implemented on October 14, 2022. Waitlist outcomes were compared from pre-NMP pre-acuity circles (n = 1460), pre-NMP with acuity circles (n = 842), and with NMP (n = 381). Median waitlist time was 79 days (IQR: 20–232 d) at baseline, 49 days (7–182) with acuity circles, and 14 days (5–56) with NMP ($p < 0.001$). The rate of transplant-per-100-person-years improved from 61-per-100-person-years to 99-per-100-person-years with acuity circles and 194-per-100-person-years with NMP ($p < 0.001$). Crude mortality without transplant decreased from 18.3% (n = 268/1460) to 13.3% (n = 112/843), to 6.3% (n = 24/381) ($p < 0.001$) with NMP. The incidence of mortality without LT was 15-per-100-person-years before acuity circles, 19-per-100 with acuity circles, and 9-per-100-person-years after NMP ($p < 0.001$). Median Model for End-Stage Liver Disease at LT was lowest with NMP, but Model for End-Stage Liver Disease at listing was highest in this era ($p < 0.0001$). The median donor risk index of transplanted livers at baseline was 1.54 (1.27–1.82), 1.66 (1.42–2.16) with acuity circles, and 2.06

Abbreviations: CIT, cold ischemia time; DBD, brain-dead donor; DCD, circulatory death donor; DRI, donor risk index; FDA, Food and Drug Administration; LT, liver transplantation; MELD, Model for End-Stage Liver Disease; NMP, normothermic machine perfusion; SCS, static cold storage; UNOS, United Network for Organ Sharing.

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(1.63–2.46) with NMP ($p < 0.001$). Six-month post-LT survival was not different between eras ($p = 0.322$). The total cost of health care while waitlisted was lowest in the NMP era ($53,683 vs. $32,687 vs. $23,688, $p < 0.001$); cost-per-day did not differ between eras ($p = 0.152$). The implementation of a routine NMP program was associated with reduced waitlist time and mortality without compromising short-term survival after liver transplant despite increased use of riskier grafts. Routine NMP use enables better waitlist management with reduced health care costs.

INTRODUCTION

The incidence of end-stage liver disease is 5.2 million cases per year, with the global and US-specific prevalence increasing by almost 75% from 1990 to 2017.[1–3] Liver transplantation (LT) continues to represent the only definitive treatment for end-stage liver disease with long-term survival.[4,5] As such, the annual LT volume continues to increase each year, with over 9200 transplants performed in the United States in 2021.[6] Given the high disease prevalence and the high rate of associated mortality, there continues to be a desperate need to increase access to viable organs for those awaiting transplant.[7] Access to organs, longer waitlist times, and increasing waitlist mortality are complex and multifactorial but generally serve as measures of how well we are getting patients with end-stage disease to their only definitive treatment options.[7–9]

Machine perfusion is one potential strategy for improving both access to organs and outcomes after transplantation. Both types of ex situ machine perfusion, normothermic (NMP) and hypothermic-oxygenated (HOPE), have gained rapid global attention for their profound potential, though only NMP is currently approved for routine use in the United States.[10–17] Frequently cited potential benefits of NMP include possibly increased organ utilization, the reduction of early allograft dysfunction, and the reduction of biliary complications provided the static cold storage (SCS) prior to NMP is not too long.[18,19] An important additional benefit of any perfusion technique appears with improved logistics within the complex landscape of LT.[13,17,20–22]

However, since the approval of the 2 NMP devices in late 2021 (OrganOx metra, TransMedics OCS), no study has yet examined the impact of machine perfusion on waitlist times or mortality in the United States. Our centers implemented a machine perfusion program using the OrganOx Metra in October 2022, and end-ischemic NMP has been integrated as a standard practice with internal guidelines. Thus, we aim to examine the impact of our new machine perfusion program on waitlist outcomes. We hypothesize that both time from listing to transplant and waitlist mortality will be reduced since programmatic integration of NMP.

METHODS

Adult patients (age 18 y or above), who were listed for liver transplant from January 1, 2015, to September 30, 2023, at 2 academic liver transplant centers (Cleveland Clinic, Cleveland, OH and Cleveland Clinic Weston, FL), were included in this retrospective study. An end date of September 30, 2023, was chosen to allow 6 months exposure time for patients in the most recent era. Patients were excluded who were evaluated for transplant but not listed. Patients listed for multiorgan transplants, including heart-liver, lung-liver, or liver-kidney, were included. Patients listed for liver-intestine transplants were excluded. This research was conducted according to ethical principles outlined in the Declaration of Helsinki. The study was approved by the Institutional Review Board. Consent was waived as this was a retrospective study, and no direct contact was made with patients. The OrganOx Metra is Food and Drug Administration (FDA)-approved as the standard of care, and thus no consent is needed for the use of this device.

Patients were identified using the transplant records system Phoenix, which is integrated with our institutional electronic medical records system. Records were reviewed for recipient demographics, including age, sex/gender, race, and body mass index (BMI, kg/m^2). Indication for transplant and history of cancer, particularly HCC, was also reviewed. The date of initiation of a transplant evaluation, date of activation on the waitlist, and date of transplant if applicable were recorded. Patient's current status on waitlist was also recorded, including transplanted, actively waiting, removed due to death, removed due to being too ill, removed due to being too well, or inactive on the list (status 7). Patients with HCC were defined as any patient with HCC regardless of receipt of exception points.

Logistics and implementation of machine perfusion

The implementation of routine ex situ NMP (OrganOx *Metra*) began in both included centers on October 14, 2022. The median waitlist time for all included patients during the study duration was 64 days. Thus, each era was chosen to begin 128 days (×2 the median) before the date of the implemented change. This strategy was chosen because patients waitlisted before the first date of a change may still be waitlisted when the change occurred, thus could have variable and difficult-to-predict effects on their waitlist times. Patients were also divided to account for the United Network for Organ Sharing (UNOS) acuity circle policy, which established the 500-mile circle for liver donation on February 4, 2020.[23,24] Therefore, patients were divided into 3 groups from January 1, 2015, to September 29, 2019 (pre-Acuity Circle era); September 30, 2019, to June 7, 2022 (post-Acuity Circle but before NMP); and beginning June 8, 2022 (the NMP era).

Programmatic guidelines for machine perfusion are listed in Supplemental Figure S1, http://links.lww.com/LVT/A613 but the final decision on if a liver will undergo NMP at our center is made at the discretion of the accepting transplant surgeon. In cases of machine perfusion, liver allografts were perfused using a back-to-base approach. Briefly, the organ is procured as per national standard with cold flush and SCS, followed by transport to the accepting recipient center. After back table preparation, the liver was connected to OrganOx Metra and perfused until the recipient hepatectomy was completed. Both centers typically aim for at least 4 hours of NMP once initiated to confirm liver graft viability. A viability assessment is performed of the liver using perfusate and bile chemistry analysis prior to the decision to transplant the organ.[25] In cases where no machine perfusion is used, the liver is transplanted under SCS.

Since implementing NMP, our center has pushed the limitations of graft risk using this approach. Notably, we accept circulatory death donor (DCDs) up to 70 years of age with functional warm ischemia time $\leq$ 30 minutes (functional warm ischemia time, defined as $SpO_2 < 80\%$ or systolic blood pressure < 80 mm Hg). We further accept up to 30% steatosis of the DCD liver. This represents a liberalized set of criteria from pre-NMP, when we accepted up to 60 years of age, no steatosis, and $\leq$30 minutes fWIT. In brain-dead donor (DBD) grafts, we have no donor age limit. We accept up to 50% steatosis using NMP and viability testing.

Outcomes

The primary outcomes of interest were time from listing to transplant, referred to as waitlist time, and waitlist mortality. For the purposes of this study, the definition of waitlist mortality includes listed patients who died prior to receiving a liver transplant and patients who were removed because of being too ill to receive a liver transplant prior to their death. Mortality and rate of transplant were also reported per 100 patient-years. This calculation is performed according to the Scientific Registry of Transplant Recipients annual report guidelines, with time calculated from the date of listing until the earliest date of death, transplant, removal from the waitlist, or the end of the study period.[6] The time a candidate is inactive on the waitlist is included in the calculation of person-years. Survival outcomes were also examined within a 1-year time frame of listing to account for the shorter follow-up time from the listing date in the machine perfusion era. Additional outcomes included the laboratory Model for End-Stage Liver Disease (MELD) score at listing and at transplant and the number of inpatient admissions a candidate underwent during the waitlist period prior to transplant. While small variations in practice have naturally occurred, there have not been major center-wide changes in our waitlist management, transplant operative technique, immunosuppression, or post-transplant management during the study period that we can identify as likely to impact this outcome. Finally, donor risk index (DRI) is a described and validated tool for the assessment of graft risk.[26] DRI was obtained directly from UNOS data. Patient-level DRI data were available from January 1, 2016, to June 30, 2023.

Direct and total cost data were obtained for all patient encounters from the date of listing to the date of transplant, removal from the waiting list, or death, depending on waitlist outcome. These costs represent costs to the health care system for all patients. Only encounters at the transplant centers in this study were included; costs incurred at outside hospitals could not be obtained. Similarly, only admissions at the transplant centers could be captured in our data set. Our centers began keeping records of "dry runs" in 2019, wherein an organ is procured and ultimately not used, either declined prior to transfer "back-to-base" or returned to the center and not transplanted. Information regarding the volume and costs of these runs is provided. There was not enough data to properly analyze dry runs in the pre-acuity circle era.

Statistical analysis

Descriptive statistics were used to summarize the characteristics of the study population. Continuous variables were represented by mean and SD or median and IQR depending on the distribution of the data. Categorical variables were represented as counts and percentages. Categorical variables were analyzed using chi-square tests or Fisher exact tests as appropriate. Continuous variables were analyzed using *t* tests or Mann-Whitney *U* tests, depending on the distribution of

TABLE 1 Demographic and background information for all included patients both overall and split by listing date before or after the rise of machine perfusion

	Total (n = 2683)	Pre-NMP, pre-acuity circle (n = 1460) January 1, 2015, to June 29, 2019	Pre-NMP acuity circle (n = 842) June 30, 2019, to June 7, 2022	Machine perfusion (n = 381) June 8, 2022, to September 30, 2024	*p*
Recipient risk factors					
Recipient age	59 (49–65)	59 (51–66)	58 (47–65)	58 (48–65)	0.06
Recipient gender, male, n (%)	1651 (61.7)	912 (62.4)	491 (58.2)	248 (65.1)	0.18
Recipient body mass index (kg/m^2)	28 (24–33)	28 (24–33)	28 (24–33)	27 (24–31)	0.22
Lab MELD score at listing	18 (12–25)	17 (11–24)	18 (12–25)	20 (14–26)	**< 0.001**
Lab MELD at transplant	23 (17–30)	24 (18–30)	24 (15–29)	22 (14–31)	**< 0.001**
HCC (yes, no)	605 (21.8%)	379 (26%)	143 (17.0%)	22 (5.7%)	**< 0.001**
Implantation time (mins)	41 (35–48)	42 (35–50)	41 (34–48)	39 (34–44)	**0.01**
Number transplanted	1933 (72.1%)	1097 (71.4%)	580 (68.8%)	256 (67.2%)	**0.03**
Donor risk factors for patients undergoing LT (n = 1984)					
Donor type[a]					
DBD	1581/1933 (81.8%)	940/1097 (86%)	444/580 (77%)	197/256 (77%)	**< 0.001**
DCD, n (%)	167 (8.6%)	73 (6.7%)	53 (9.1%)	41 (16%)	—
LDLT, n (%)	185 (9.6%)	84 (7.7%)	83 (14.3%)	18 (7.0%)	—
Donor age	42 (29–54)	42 (30–54)	44 (30–55)	41 (29–55)	0.91
Donor BMI (kg/m^2)	27 (23–32)	27 (24–32)	27 (23–31)	27 (24–31)	0.29
Cold ischemia time (h)[b]	6.2 (5.1–7.5)	6.2 (5.2–7.5)	5.8 (4.8–7.1)	6.3 (5.1–12.0)	**< 0.001**
Total preservation time (h)[c]	6.5 (5.2–7.7)	6.2 (5.2–7.5)	5.8 (4.8–7.1)	SCS: 6 (5–12) NMP: 16 (12–19)	—

Note: Values refer to the time a patient was listed for transplant unless otherwise specified.
[a]In transplanted patients only (n = 1984).
[b]Cold ischemia time prior to NMP in cases where NMP is used or total time of SCS in other cases.
[c]Total preservation time described as the time from cross-clamp in the donor until "liver out of ice" in the recipient, also known as the time implantation of the liver begins in the recipient.
Bold values are statistically significance *p*-value < 0.05.
Abbreviations: BMI, body mass index; DBD, brain-dead donor; DCD, circulatory death donor; LDLT, living donor liver transplant; LT, liver transplantation; MELD, Model for End-Stage Liver Disease; NMP, normothermic machine perfusion; SCS, static cold storage.

the data. Kaplan-Meier survival analysis was performed to assess the impact of the machine perfusion era on waitlist and overall mortality. Poisson distribution was performed by comparing incidence rates between eras. Cost-per-listed-day was calculated by dividing total waitlist costs by days from listing to transplant, removal, or mortality. Multivariate Cox-Regression analysis was conducted to assess the impact of various factors on both waitlist mortality without LT and on time from listing to transplant. All statistical analyses were performed using IBM SPSS Statistics V. 28.0.

RESULTS

A total of 2683 patients were included. Across all eras, 1933 (72.1%) listed patients received an LT. The median candidate age at listing was 59 years (IQR: 49–65 years). The overall median time from listing to LT in all patients was 64 days (IQR: 13–205 d). The median time from evaluation to listing was 56 days (IQR: 14–115 d), and the median time from evaluation to transplant was 155 days (60–318 d). Among transplanted patients, there was an increase in the utilization of circulatory death donors during the NMP era versus both pre-NMP eras, with or without acuity circles ($p < 0.001$). Median cold ischemia time (CIT) in the entire study was 6.2 hours (5.1–7.5); in cases of NMP, the median CIT before NMP was 6.5 hours (5.5–7.5), and the median total preservation time from donor cross-clamp to liver implantation was 16 hours (12–19) (Table 1). The volume of all transplants and the volume of deceased donor cases are provided, with a clear increase in case volume over the study period

(Figure 1). Since the implementation of the OrganOx Metra NMP program in 2022, the combined centers have utilized the device in a total of 239 cases at the time of data collection. An additional 99 machine perfusion cases were performed on trial (NCT05045794, NCT02515708),[25,27] 25 of which were during the NMP era. Seventeen of these were HOPE perfusions in the Bridge-to-Life trial, 15 of which were in the NMP era. The percentage of cases employing NMP was 0.5% with pre-acuity circles (n = 8), 8.7% (n = 74) with acuity circles, and 69.3% (n = 264) in the NMP era.

During the study period, 354 total grafts were perfused, 18 (5.1%) of which were discarded after viability testing or other concerns during NMP led to belief regarding graft viability. Of these 18, 6 were trial grafts,[25] and 12 were discarded after perfusion with the OrganOx Metra. All 12 of these grafts were accepted with perfusion waivers, in which the cost of the graft is incurred by the organ procurement organization if the graft is not able to be implanted.

Patients were divided into 3 groups: the era before acuity circle implementation (n = 1460), with acuity circles but pre-NMP (n = 842), and NMP (n = 381).The median time from listing to LT was 79 days (IQR: 20 d) before acuity circles, 49 days (IQR: 7–182) with acuity circles, and 14 days (IQR: 5–56 d) with NMP ($p < 0.001$). The rate of transplant per 100-person-years improved significantly with NMP, from 61-per-100-person-years before the acuity circle policy to 99-per-100-person-years with acuity circles, and finally 194-per-100-person-years with NMP ($p < 0.001$) (Table 2). There was also an improved rate of transplant when adjusted for the amount of time on waitlist for patients using time-to-event analysis ($p < 0.001$) (Figure 2A).

The costs of medical care for listed patients were examined next. In the pre-acuity circle era, the median total cost of health care while waitlisted was $53,683 ($17,499–$157,908) versus $32,687 ($9,603–$113,948) in the acuity circle era and just $23,688 ($3,888–$119,390) in the NMP era ($p < 0.001$). There was no difference in the cost of health care per day on the waitlist between eras ($p = 0.15$) (Table 3, Figure 2B)

Overall mortality without transplant decreased from 18.3% (n = 268/1460) before acuity circles to 13.3% (n = 112/843) with acuity circles to 6.3% (n = 24/381, $p < 0.001$) in the NMP era. The incidence of death without LT was 15-per-100-person-years before acuity circles, 19-per-100-person-years during the pre-NMP acuity circle era, and 9-per-100-person-years during the NMP era ($p < 0.001$) (Figure 3A). Among all patients listed for liver transplant, patients listed in the NMP era experienced the greatest 1-year survival from the time of listing using time-to-event analysis ($p < 0.001$) (Figure 3B). Finally, regarding the outcomes of patients after LT, there was an improvement in patient survival up to 6 months following LT in both the acuity circle and NMP eras compared with pre-acuity circles ($p < 0.001$) (Figure 3C). This also correlated to a reduction in graft loss up to 6 months after transplant ($p < 0.001$). Our group recently published extensive 90-day risk-matched outcomes of NMP, noting general improvements in outcomes up to 90 days post-LT with NMP.[29] In the same study, there have been 8 reported cases of graft-related graft loss in NMP treated grafts, resulting from ischemic cholangiopathy (n=4), intra-abdominal sepsis (n=2) and primary non-function (n=2).

The median laboratory MELD score at listing increased during each era and was the highest in the era of machine perfusion (17 vs. 18 vs. 20, $p < 0.001$). The median MELD at transplant was significantly lower during the NMP era (22 points) versus the other 2 eras ($p < 0.001$), yet there was no difference in MELD at LT before (24 points) and after (24 points) implementation of the acuity circles policy ($p = 0.129$) (Figure 4A). The number of admissions per candidate while awaiting LT was reduced from 1.60 to 0.94 after the implementation of the machine perfusion program ($p < 0.001$).

A multivariate analysis using a Cox-proportional hazard model was established evaluating the impact

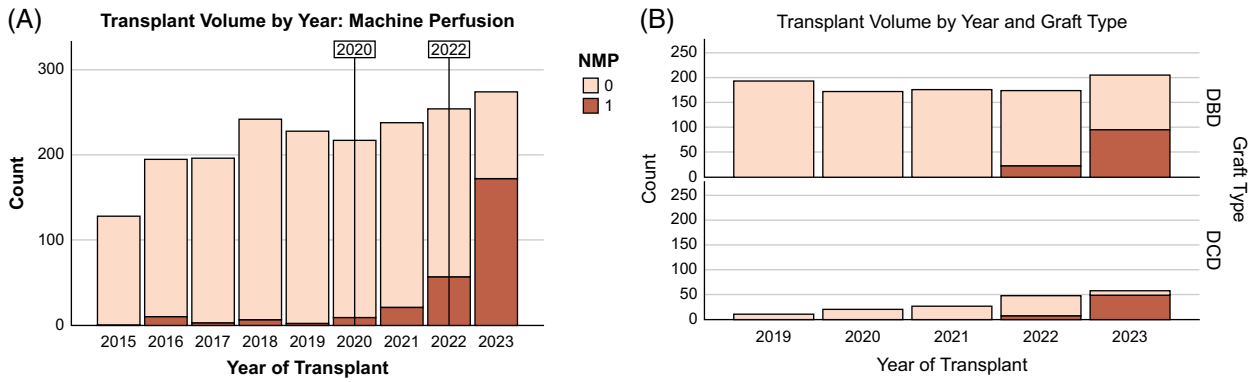

FIGURE 1 Transplant volumes by year. (A) The volume of patients receiving liver transplant by year split by use of machine perfusion (red) versus static cold storage (blue). (B) Snapshot of the volume of deceased donor LT by year from 2019-present showing the rapid increase in the use of NMP in both graft types. Abbreviations: DBD, brain-dead donor; DCD, circulatory death donor; NMP, normothermic machine perfusion.

TABLE 2 Waitlist outcomes by era

	Total	Pre-NMP, pre-acuity circle	Pre-NMP, acuity circle	NMP	*p*
Listed patients (n)	2683	1460	842	381	—
Incidence of transplant per-100-listed-patient-years	77	61	99	194	**< 0.001**
Incidence of waitlist mortality per-100-listed-patient-years	16	15	19	9	**< 0.001**
Incidence of waitlist removal per-100-listed-patient-years	9	5	18	22	**< 0.001**

Note: Outcome for waitlisted patients. Outcomes are reported per-100-listed-patient-years in the format employed in SRTR/OPTN annual reporting to account for differential exposure time.[6,28]

Patients removed for being too well for transplant.

Bold values are statistically significance *p*-value < 0.05.

Abbreviation: NMP, normothermic machine perfusion.

of available factors on the likelihood of a listed patient dying prior to receiving an LT. Being listed after NMP (HR = 0.286 ± 0.149, $p < 0.001$) and during the post-NMP era (HR = 0.573 ± 0.133, $p < 0.001$) were most strongly protective for mortality without LT. Increasing candidate age (HR = 1.031 ± 0.005, $p < 0.001$), higher body mass index (1.024 ± 0.007, $p < 0.001$), and lab MELD (1.040 ± 0.006, $p < 0.001$) at listing were associated with increased mortality before LT (Table 4A). A similar model was also conducted evaluating factors influencing the time from listing to LT in patients who received a transplant using the same input factors against the outcome of days on waitlist, with higher HRs associated with reduced waiting time. Again, the strongest predictors of a short waitlist time were listed during NMP era (HR = 2.146 ± 0.087, $p < 0.001$) or during the acuity circle era (1.489 ± 0.066, $p < 0.001$) (Table 4B).

To understand why waitlist times were affected in this analysis, we investigated our institutional practices with respect to graft-associated risk using the donor risk index (DRI). The median DRI of transplanted livers before acuity circles was 1.54 (IQR: 1.27–1.82) versus 1.66 (1.42–2.16) after acuity circles but before NMP, and 2.06 (1.63–2.46) during the NMP era ($p < 0.001$). This is an increase in median DRI during the NMP era of 34% versus the pre-acuity era and 24% from the acuity circle era (Figure 4B). This analysis was repeated with CIT set to the reference standard (< 8 h) in the calculation of DRI to account for possible conflation of CIT and machine perfusion time in the UNOS data. The adjusted DRI was again significantly greater in the NMP era (1.87, IQR: 1.56–2.29) versus pre-acuity circle (1.45, 1.19–1.71) or acuity circle eras (1.53, 1.18–1.87, $p < 0.001$) (Figure 3C). After equalization of CIT between eras, increases in graft risk measured by DRI originated from an increase in the use of national donors (58.6% vs. 47.0% vs. 13.8%, $p < 0.001$) and an increase in the utilization of DCD grafts (22.5% vs. 16.1% vs. 10.0%). There was no difference in the donor race ($p = 0.13$) and cause of death distribution ($p = 0.54$).

Finally, we report information on the dry runs in which an organ was accepted and procured, but ultimately the organ was not utilized (either the organ was declined during procurement or was placed on pump and failed viability testing). At time of submission, only 9 organs had been placed on pump and failed viability

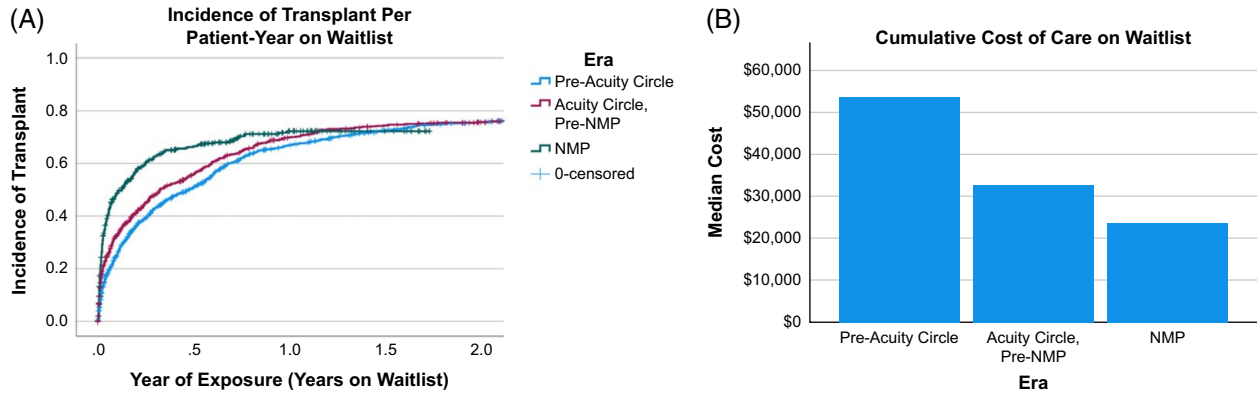

FIGURE 2 Incidence of transplant and cost of health care while waitlisted. (A) Incidence of transplant per listed-patient-years by era demonstrating an increased incidence of successful transplant in the post-acuity circle, machine perfusion era ($p < 0.001$). (B) The cumulative cost of medical care for patients listed for transplant, showing significant cost savings in the NMP and acuity circle eras ($p < 0.001$). There was no difference in cost per day on waitlist ($p = 0.152$). Abbreviation: NMP, normothermic machine perfusion.

TABLE 3 Waitlist times and cost of health care while waitlisted in patients receiving liver transplantation

	Evaluation to waitlist	Waitlist to transplant	Evaluation to transplant
Pre-machine perfusion, pre-acuity circle	57 (IQR 24–112)	79 (20–232)	169 (68–332)
Post-acuity circle, pre-machine perfusion	55 (23–118)	49 (7–182)	135 (41–304)
Machine perfusion	58 (19–110)	14 (5–56)	79 (25–158)
p	0.90	**< 0.001**	**< 0.001**
Costs			
	Direct cost while waitlisted	Total cost while waitlisted	
Pre-machine perfusion, pre-acuity circle	$10,793 ($3612–$33,459)	$53,683 ($17,499–$157,908)	—
Post-acuity circle, pre-machine perfusion	$7732 ($2045–$25,050)	$32,687 ($9603–$113,948)	—
Machine perfusion	$4530 ($752–$26,198)	$23,688 ($3888–$119,390)	—
p	**< 0.001**	**< 0.001**	—

Note: Median time in days from evaluation to waitlist activation, waitlist to transplant, and total time from evaluation and transplant divided into 3 eras, Before September 29, 2019 (pre-acuity circle), September 30, 2019, to June 7, 2022 (post-acuity circle, pre-machine perfusion), and after June 8, 2022 (machine perfusion). Bold values are statistically significance *p*-value < 0.05.

testing, a utilization rate of 96.4% (n = 239/248) once organs were placed on the NMP device. Dry runs occurred 40 times in 2019 (DBD = 16, DCD = 24), 65 times in 2020 (DBD = 18, DCD = 47), 41 times in 2021 (DBD = 17, DCD = 24), 47 times in 2022 (DBD = 15, DCD = 32), and 99 times in 2023 (DBD = 20, DCD = 79). There was a greater number of dry runs-per-month in the NMP era (9.9 vs. 3.54). The total cost of dry runs was $651,477 in the NMP era (n = 123) and $905,041 in the acuity circle era (n = 124). The cost-per-run was significantly reduced in the NMP era ($1775, IQR: $500–$7 998) versus the pre-NMP era ($6773, IQR: $3000–$10,103, $p < 0.001$). Before NMP, the median nautical miles traveled per dry run where the plane was dispatched was 319 (IQR: 235–646) versus 512 (288–723) with NMP. However, in the NMP era, 64 cases (52.0%) were conducted with local procurement, where the plane was not sent, which would account for

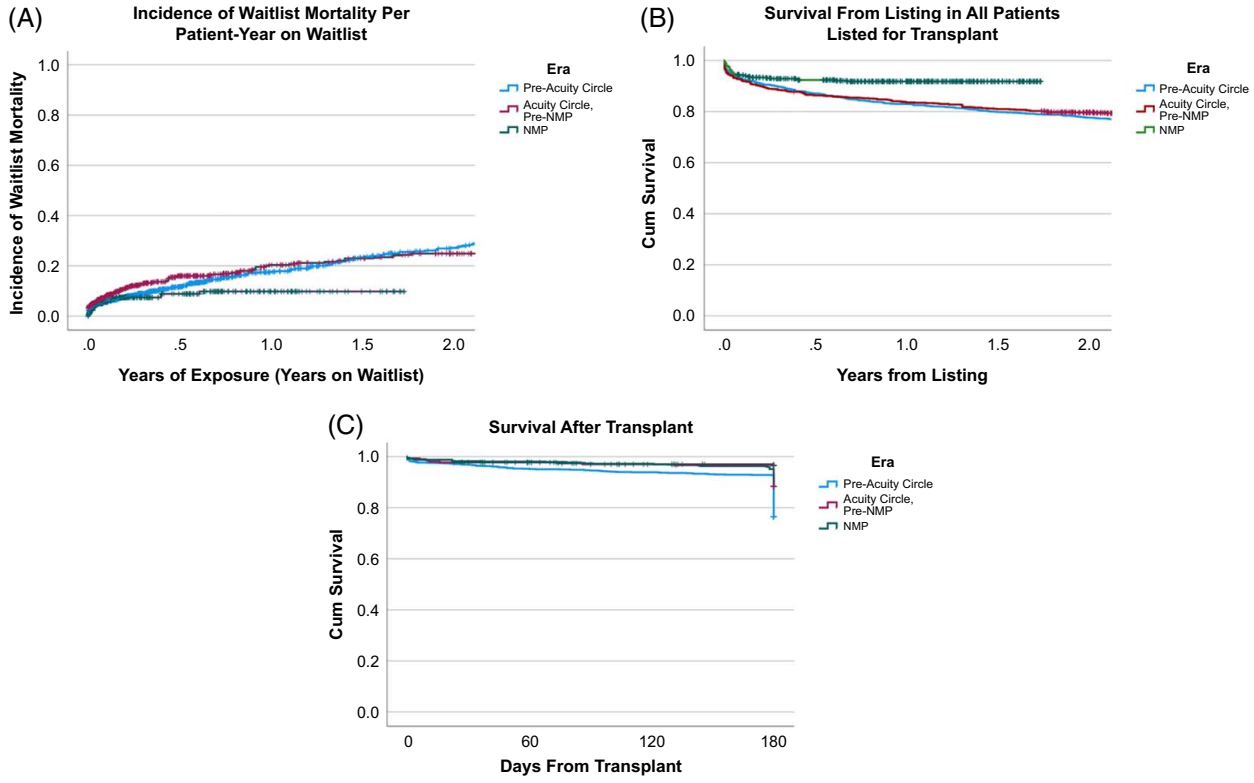

FIGURE 3 Survival in patients listed for liver transplant by era. (A) Incidence of waitlist mortality per listed patient-years, showing a significant reduction in the incidence of waitlist mortality per exposure time in the NMP era (green, $p < 0.001$). (B) Survival up to 1 year from listing in all patients listed split by listing pre-acuity circles (blue), with acuity circles but pre-NMP (red) or with NMP (green). Survival is most improved in the NMP era ($p < 0.001$). (C) Survival up to 6 months after transplant in those receiving transplant. There was an improvement in post-liver transplantation survival in both the NMP and acuity circle eras ($p < 0.001$). Abbreviation: NMP, normothermic machine perfusion.

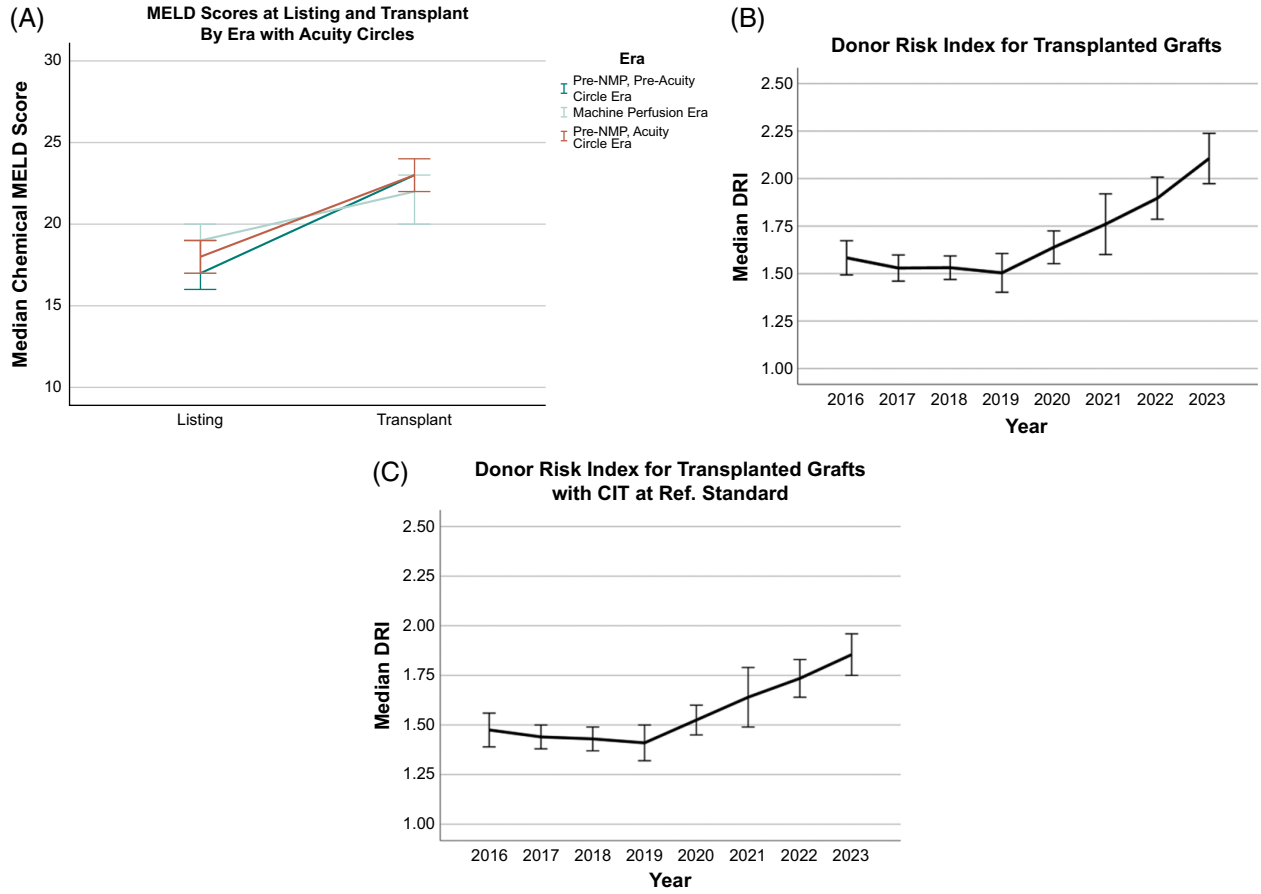

FIGURE 4 Recipient MELD and graft risk by era. (A) MELD scores compared across three eras, including the acuity circle era. The median chemical MELD at listing increased from the pre-NMP, pre-acuity circle era to the acuity circle era, to the highest value in the NMP era ($p < 0.001$). Despite this, the MELD at transplant was significantly lower in the NMP era versus either of the other two ($p < 0.001$). (B) Median DRI with IQR is demonstrated for each year of transplantation for which data from the United Network for Organ Sharing was available (January 1, 2016 to June 1, 2023), demonstrating a significant increase in DRI during the study period. (C) Median DRI with IQR with CIT adjusted for all cases to represent the reference standard/minimum, accounting for the CIT being improperly recorded to include NMP in United Network for Organ Sharing databases. Despite this adjustment, we find a significant increase in DRI during the study period. Abbreviations: CIT, cold ischemia time; DRI, donor risk index; MELD, Model for End-Stage Liver Disease; NMP, normothermic machine perfusion.

a travel distance of 0 miles. This happened only 29 times (23.3%) in the pre-NMP era. When those cases were treated as a travel distance of 0 miles, the median actual distance traveled was just 0 miles (0–337) in the NMP era versus 236 miles (0–570) pre-NMP ($p < 0.001$). This is thus a significant reduction in actual travel distance with NMP.

DISCUSSION

This study is, to our knowledge, the first to investigate the impact of a machine perfusion program on waitlist outcomes in patients listed for LT in the United States and the first to do so in multicenter fashion. A significant reduction in waitlist mortality and time to transplant was observed since the integration of machine perfusion across the entire program using incidence-per-listed-year and time-to-event analyses to limit bias introduced by differential exposure time. These effects were not limited to cases in which NMP was not employed, but rather felt program wide; this approach was chosen as the decision to use NMP can be arbitrary at the time of transplant, thus we sought to evaluate the impact of programmatic use of NMP on waitlist management. We further demonstrate that patients are being transplanted at lower lab MELD scores despite being listed at higher scores. This indicates that our patients are receiving liver transplant in a timelier fashion during the modern era, which includes both 500-mile acuity circles and NMP technology. The reduced waitlist times may be related to an increase in transplant volume due to an ability to utilize riskier grafts, as demonstrated by the rapid increase in DRI with NMP seen in Figure 4. Finally, reduced waiting times across both included centers did lead to a reduction in the cost of medical care for patients awaiting transplant, demonstrating an area where the added cost of machine perfusion can be offset by improved patient outcomes.

The recent rise of machine perfusion has led to a rapid change in the practice of liver transplant surgery in

TABLE 4 Multivariate analyses of factors affecting waitlist mortality and time

Factor	Hazard ratio ± 95% CI	p
A. Factors predicting waitlist mortality		
Increasing age at listing	1.031 ± 0.005	< **0.001**
Increasing body mass index (kg/m^{2+})	1.024 ± 0.007	**0.004**
Black race	1.111 ± 0.199	0.62
Asian Race	1.207 ± 0.505	0.99
Multiracial	0.510 ± 0.460	0.13
Male sex	0.786 ± 0.102	**0.03**
HCC	0.370 ± 0.129	< **0.001**
Underlying steatotic liver disease (SLD)[a]	0.825 ± 0.119	0.13
Listing post-NMP	0.286 ± 0.149	< **0.001**
Listing pre-NMP, post-acuity circle	0.573 ± 0.133	< **0.001**
Increasing lab MELD at Listing	1.040 ± 0.006	< **0.001**
B. Factors predicting time on waitlist before LT		
Increasing age at listing	1.005 ± 0.002	**0.01**
Increasing body mass index (kg/m^{2+})	1.008 ± 0.004	0.05
Black race	1.011 ± 0.096	0.91
Asian race	1.318 ± 0.245	0.26
Multiracial	0.873 ± 0.139	0.33
Male sex	1.122 ± 0.051	**0.03**
HCC	1.090 ± 0.054	0.10
Underlying steatotic liver disease (SLD)[a]	0.890 ± 0.058	**0.04**
Listing post-NMP	2.146 ± 0.0.087	< **0.001**
Listing pre-NMP, post-acuity circle	1.489 ± 0.066	< **0.001**
Increasing lab MELD at listing	1.104 ± 0.004	< **0.001**

Note: A. Cox-proportional hazard model for predictors of likelihood of a patient experiencing mortality after being waitlisted without receiving a liver transplant. B. Cox-proportional hazard model for predictors of waitlist time until transplant. Bold values are statistically significance p-value < 0.05.

[a]Steatotic liver disease has replaced nonalcoholic steatohepatitis in the new AASLD guidelines, and thus SLD encompasses this cohort.[30]

Abbreviations: LT, liver transplantation; MELD, Model for End-Stage Liver Disease; NMP, normothermic machine perfusion; SLD, steatotic liver disease.

the United States. There are currently 2 devices that are FDA approved for clinical use: the OCS liver system (TransMedics, approved September 28, 2021) and the OrganOx metra (approved December 9, 2021), the latter of which is used by both centers in this study.[21] Both products are NMP-specific devices. One of the potential clinical impacts of these devices is to increase access to organs for patients on the waiting list, many of whom suffer for months or even years awaiting transplant.[11,13] This may relate, in part, to be secondary to an improved ability to use otherwise nonviable organs, as investigated in multiple prospective trials, though this has not yet been definitively proven[10,25] However, no study to date has examined the impact of NMP on patients awaiting organs, who would arguably represent the primary benefactors of increased organ utilization. We demonstrate significant improvements in waitlist times and incidence of transplant per listed patient-year after implementation of an NMP program, as well as a reduction in the incidence of death without LT. These findings are upheld when accounting for differential exposure time using time-censored analyses. Barshes et al[31] have previously shown that using extended criteria donors can reduce waitlist mortality, which supports our findings of improved waitlist outcomes in the machine perfusion era and tracks with our findings of a higher percentage of DCD donors in the NMP era. As demonstrated by the nearly 25% increase in DRI, NMP is allowing the use of much riskier grafts. Post-transplant survival was not compromised, indicating that the use of riskier grafts is not immediately associated with worse post-LT outcomes and that the benefits felt by waitlisted patients are not being offset by detriments after transplant. Finally, patients were transplanted earlier in the disease process, as measured by lower lab MELD at transplantation, despite having higher lab MELD scores at listing in the machine perfusion era.

It is critical to note that this study was not limited to cases employing NMP, and NMP is not used in all cases in the included programs. However, frequent use of NMP may benefit patients program wide rather than on a strict case-by-case basis, as NMP appears to have accelerated the timeline to transplant across the entire program. While NMP has been previously theorized to be cost prohibitive,[32–35] we demonstrate that establishing an NMP program can lead to significant cost savings in listed patients. Previous work by our group has demonstrated that while NMP is associated with increased costs of organ acquisition/preservation in the amount of ~$35k, it is associated with improvement in selected post-LT outcomes, which leads to an equalization of costs in the 90 days after transplant despite the initial increase in cost.[29] This study also found reductions in intensive care unit length of stay, postoperative need for dialysis, and reoperation in the NMP cohort, which helps explain how the up-front cost of NMP can be offset by improvements in post-LT outcomes. This study further finds cost savings in the pre-LT period, adding to the places where improvements in patient outcomes may also be associated with lower costs of medical care. Dry runs represent another potential cost. We note that there is a significant increase in the rate of dry runs in the NMP era, which we hypothesize is secondary to our ongoing acceptance of increased risk, including increased utilization of DCD grafts. However, we do also note the cost-per-run is decreased in the modern era. In the NMP era, we more frequently use local procurement and often do not

deploy the plane to retrieve the organ until the local team has assessed the graft. This has allowed us to offset the increased number of dry runs by reducing the cost-per-run. The back-to-base model offers benefits in this sense versus device-to-donor, as the perfusion device and plane are not required to travel to assess an organ, which may again help reduce the costs of using this technology.

Waitlist time and mortality are multifactorial, and machine perfusion is not the only change that has occurred over the study period from 2010 to present. For example, there have been several UNOS allocation policy changes since 2010. These include the 2013 "Share-35" rule, allowing for organ allocation to those with a MELD score $>$ 35 points outside of their home procurement region. This rule did increase the organ transplant rate, but unfortunately did not improve waitlist mortality.[23] Perhaps the most notable change was the acuity circle revision enacted on February 4, 2020, allowing for organ donation within 500 miles in most recipients, which has somewhat reduced both waitlist times and waitlist mortality since enactment.[23,24] This study does demonstrate that the latter rule had also a clear impact on waitlist time and mortality at our included programs. The impact of the acuity circle revision at our center seems to have been accelerated by the implementation of the NMP program. We hypothesize this is due to synergistically increased access to more marginal donors, both from increasing the range a program can travel for a liver and in increasing our ability to use more organs otherwise deemed unsuitable. The latter of these is supported by the significant increase in the DRI of transplanted organs without a corresponding reduction in post-LT 1-year survival. The future impact of machine perfusion on allocation policy cannot be predicted, but the demonstrated changes in waitlist outcomes are quite promising and should possibly factor into ongoing national policy changes. This study should not reflect exclusively the impact of NMP on waitlist times but rather be placed in context of potentially accelerating the impact of the acuity circle policy, and all findings cannot be clearly attributed to a single intervention.

In addition to the above-stated benefits of increased organ access, NMP also offers significant logistical benefits, both patient-facing and provider-facing.[20,21] Patient-facing benefits include, as shown in this study, a reduction in pre-LT admissions for waitlisted patients. This likely relates to easing of previous time pressures associated with SCS times. These challenges dictated our previous practice, which was to admit patients immediately on acceptance of a liver offer. Many of these admissions resulted in "patient-facing dry runs," where a patient was admitted for transplant but then discharged when a donor organ was declined or a DCD donor did not proceed. Our new practice is to admit most patients after donor liver acceptance after donor hepatectomy with visual, flush, and biopsy assessments of the liver graft. We are, therefore, now able to avoid a significant number of unnecessary hospital admissions, along with their associated health care and travel costs and patient or provider time burden. There are also procurement dry runs, which were less expensive and resulted in significantly less travel distance in the NMP era. Additionally, by transplanting patients earlier in the disease course, it is possible that we are reducing admissions associated with complications of end-stage liver disease, though this cannot be specifically assessed with this data set. This also has resulted in a reduction in MELD-escalation on the waitlist, possibly due such a short time between listing and transplant, as well as reduction in cost of health care during this period. Provider-facing benefits include flexibility for surgical and surgical-support staff with tailored transplant timings based on available resources, supported by organ viability assessment during perfusion. Future studies should investigate the impact of these benefits on costs associated with transplant programs, including the impact on intensive care unit and hospital stay, complications requiring interventions, and patient-facing costs comparing machine perfusion with cold storage preservation.

This study does have limitations. The most important potential limitation of the study is the variable exposure time between groups. Specifically, those listed in the NMP era had reduced exposure time to the waitlist and less time to experience mortality without LT. We attempted to account for this by using incidence per listed-patient-year and time-to-event analyses, but this cannot remove the possibility that longer exposure time could alter results. Longer-term follow-up is needed to confirm the lasting impact of these approaches and to confirm that post-transplant outcomes $>$6 months are equivalent. While the use of center-level data allows for improved granularity and for assessment of the impact of a standardized program at 2 centers, it may also limit the applicability to other centers nationwide. There is known regional and center-level variability in waitlist time and mortality, and thus it cannot be established how well the implementation of machine perfusion would affect other centers outcomes. With a short time period included in the machine perfusion era, the long-term impact of this newly implemented preservation program cannot be assessed with robustness. To this latter point, improvements in waitlist mortality are important, but only if they do not come at the expense of outcomes after transplant, which has been the national ongoing concern with increased acceptance of riskier grafts. Thus, while our center-level 6-month survival in transplanted patients was equivalent, this finding is limited by short follow-up and a relatively smaller sample size. Further studies must look critically at a variety of short-term and longer-term post-LT outcomes to ensure that machine perfusion and the

associated changes in organ acceptance rates are of maximal benefit to those receiving LT. Only admissions and costs of care at the transplant centers could be obtained. Many patients are admitted at other centers for liver-related and liver-unrelated care while waitlisted, and thus both of these metrics are likely underestimations of the true health care burden for patients in each era. There was a significant reduction in the number of patients with HCC during the NMP era, a finding we truly cannot explain. We have slowly moved our center to aggressive pretreatment of these patients, possibly leading to a transient reduction in transplanted patients. However, this is not a strong explanation, and we cannot explain the finding, and acknowledge this could confound analysis. Finally, there are differences in baseline populations between the described eras that may lead to faster transplant times in the NMP era, as well as differences in UNOS allocation policies that could not be matched for analysis. However, as our aim was to assess the impact of machine perfusion on waitlist times program wide, we feel that longitudinal comparison before and after implementation remains highly clinically relevant.

CONCLUSIONS

Since the programmatic implementation of normothermic machine perfusion for LT, transplant candidates benefited from significantly shorter waiting time and lower waitlist mortality without compromising short-term post-transplant survival rates. This seems to indicate that ex situ machine perfusion is accelerating improvements in waitlist management and reduces health care costs that were seen during the acuity circle era. Such a beneficial effect may be supported by a timelier transplantation with an increased use of riskier grafts. Future studies should confirm positive long-term outcomes after LT with machine perfusion and examine the impact of these techniques on costs associated with liver transplant as juxtaposed to the inherent increased cost of the machine preservation.

AUTHOR CONTRIBUTIONS

The study was conceptualized and conducted under the direction of Koji Hashimoto, Charles Miller, and Andrea Schlegel. Data collection and analysis were performed by Chase J. Wehrle, Abby Gross, and Hanna Hong. Manuscript drafting was performed by Chase J. Wehrle and Koji Hashimoto. Critical manuscript review was performed by all authors.

CONFLICTS OF INTEREST

Andrea Schlegel consults for Bridge-to-Life Ltd. David C.H. Kwon advises Medtronics and Fujifilm. The remaining authors have no conflicts to report.

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How to cite this article: Wehrle CJ, Hong H, Gross A, Liu Q, Ali K, Cazzaniga B, et al. The impact of normothermic machine perfusion and acuity circles on waitlist time, mortality, and cost in liver transplantation: A multicenter experience. Liver Transpl. 2025;31:438–449. https://doi.org/10.1097/LVT.0000000000000412