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Use of Machine Perfusion in Pediatric Liver Transplantation

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ABSTRACT

Introduction: Machine perfusion (MP) can help expand the donor pool, yet its use in pediatric liver transplantation (LT) has been limited. We aimed to compare the characteristics and outcomes of children undergoing LT with vs. without MP.

Methods: We retrospectively compared children (< 18 years) undergoing first LT with vs. without MP using United Network for Organ Sharing data (01/01/2016–12/31/2024). The MP group was compared to all non-MP and to propensity score matched non-MP LT recipients.

Results: Forty MP LT recipients were compared to 3857 all non-MP and 40 matched non-MP recipients. Compared to all non-MP recipients, MP recipients had a higher laboratory MELD/PELD score (median 16.5 vs. 12.0, $p = 0.03$) and were more likely to receive split grafts (42.5% vs. 21.6%, $p = 0.001$) allocated at a national level (65.0% vs. 40.8%, $p = 0.007$) from older donors (median 16.0 vs. 11.0 years, $p < 0.001$) with longer organ preservation times (median 15.0 vs. 6.5 h, $p < 0.001$). Although not statistically different, DCD liver grafts were used in 20.0% of MP LTs compared to 11.1% of all non-MP LTs ($p = 0.08$). Compared to matched non-MP recipients, MP recipients were more likely to have ascites (47.2% vs. 19.4%, $p = 0.02$). There was no significant difference regarding patient or graft survival between the MP and all non-MP ($p = 0.68$ and $p = 0.80$) or the matched non-MP groups ($p = 0.28$ and $p = 0.14$).

Conclusion: MP can support LT in sick pediatric recipients using split grafts, while allowing for prolonged preservation times and national-level allocation at a larger radius, without impacting survival.

1 | Introduction

The increasing demand for donor liver grafts has led to a broader use of extended criteria donors [1], which have been associated with inferior outcomes. As a result, machine perfusion (MP) has been introduced as a method of increasing oxygen and nutrient supply to the donor graft, maintaining homeostasis and normal metabolic activity, and assessing function in real-time [2, 3]. When compared to static cold storage of donor organs, MP has been associated with reduced preservation-related graft injury

Abbreviations: DCD, donation after circulatory death; LT, liver transplantation; MELD, model for end-stage liver disease; MP, machine perfusion; PELD, pediatric end-stage liver disease; UNOS, united network for organ sharing.

and greater organ utilization [4, 5]. As a result, MP has been increasingly utilized in adult liver transplantation (LT) with improved outcomes, especially when using grafts from donation after circulatory death (DCD) [6–8].

In contrast to adult LT, MP is uncommonly utilized in pediatric LT [3] despite ongoing waitlist morbidity and mortality. Over the past decade, pediatric LT waitlist mortality ranged between 5 and 8 deaths per 100 patient-years in the United States [9]. Younger children are especially disadvantaged on the LT waitlist due to graft-recipient size mismatch and limited availability of whole grafts [10]. Despite the opportunities that MP can offer and increased interest among the pediatric LT community, there is limited evidence on the use of MP in pediatric LT. MP carries great potential benefit particularly for DCD grafts and ex vivo liver splitting; however, ongoing barriers to the use of MP include cost and institutional factors [11]. In fact, the use of DCD in adult LT has increased over time, while it still remains an underutilized resource in pediatric LT representing only 0.49% of grafts used in pediatric LT between 1993 and 2017 [12, 13].

The aim of this study was to use national transplant registry data to compare the characteristics and post-LT survival of children undergoing LT with versus without the use of MP in the United States.

2 | Methods

2.1 | Patient Cohort

Patient transplant data were obtained from the United Network for Organ Sharing (UNOS) Standard Transplant Analysis and Research data file (released in January 2025). The UNOS database administers the Organ Procurement and Transplantation Network under a contract with the US Department of Health and Human Services. It contains data on all transplant candidates listed for solid organ transplantation in the United States since October 1987. No Institutional Review Board approval was required as all data were publicly available in a de-identified form.

This retrospective cohort study included all children (< 18 years) undergoing a first deceased donor LT between 01/01/2016 and 12/31/2024. Patients were grouped into MP and non-MP groups and the start date for this cohort was selected based on the first year of MP use in the UNOS database. Retransplants were excluded. As this study intended to report on the overall use of MP in pediatric LT in the United States, all types of MP were considered eligible for inclusion. The term organ preservation time was used for the variable cold ischemia time available in UNOS.

2.2 | Statistical Analysis

Categorical variables were reported using frequencies and percentages, whereas continuous variables were reported using medians and interquartile ranges. Differences between patient groups were assessed using the chi-square test for categorical variables and the Mann–Whitney *U* test for continuous variables. The Pearson's correlation coefficient was used to evaluate changes in the use of MP among all pediatric LTs over time.

Posttransplant patient and graft survival were the primary outcomes of interest, with patient mortality and graft loss being the events of interest, respectively. Patients were censored at the last follow-up. The Kaplan–Meier method was used to determine the 1-year patient and graft survival rates. The log-rank test was used to assess the differences in post-transplant patient and graft survival between the MP and non-MP groups. In addition to the overall comparison between the MP and all non-MP groups, propensity score matching was performed using the MatchIt package in R (version 4.4.2) with 1:1 nearest neighbor matching using recipient age and sex, donor age, DCD status, and LT year as the matching variables with propensity scores estimated via logistic regression (Figure 1), which generated the matched non-MP group. Cohort development and statistical analyses were conducted using Stata IC 16.0 (StataCorp LLC, College Station, Texas, United States).

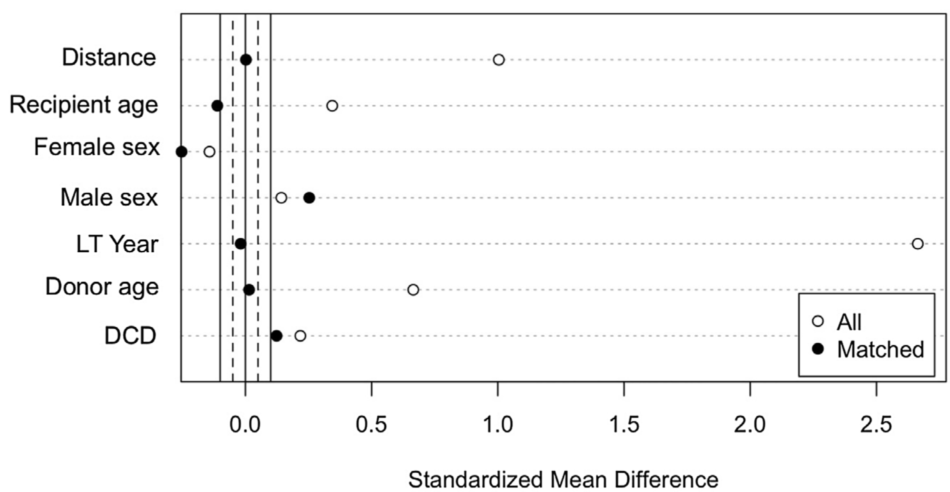

FIGURE 1 | Standardized mean differences for baseline covariates before and after propensity score matching. Open circles represent the unmatched cohort, and filled circles represent the matched cohort. "Distance" refers to the propensity score matching process, specifically the absolute difference in propensity scores between matched pairs.

3 | Results

3.1 | Overall Comparison of MP and Non-MP Groups

A total of 40 MP pediatric LT recipients were identified in UNOS and compared to 3857 non-MP pediatric LT recipients. Thirty-seven children underwent normothermic MP (92.5%) and two hypothermic oxygenated MP (5.0%), while for one the type of MP was not available (2.5%). Notably, the percentage of pediatric LTs performed using MP significantly increased over time with only 0.2% MP use in 2016 versus 6.0% use in 2024 (rho 0.72, $p = 0.03$; Figure 2). Compared to all non-MP patients, MP patients weighed more (median 31.8 vs. 14.6 kg, $p = 0.047$; min weight in MP group: 5.5 kg), were less likely to be White (27.5% vs. 48.1%, $p = 0.01$), had a higher laboratory Model for End-stage Liver Disease (MELD)/Pediatric End-stage Liver Disease (PELD) score (median 16.5 vs. 12.0, $p = 0.03$), higher serum creatinine (median 0.4 vs. 0.3 mg/dL, $p = 0.007$), and lower albumin (median 3.1 vs. 3.4 g/dL, $p = 0.007$). Detailed comparison of recipient characteristics between the two groups is provided in Table 1.

Compared to all non-MP patients, MP patients were more likely to receive split grafts (42.5% vs. 21.6%, $p = 0.001$), grafts from older donors (median 16.0 vs. 11.0 years, $p < 0.001$; min age in MP group: 7 years), grafts from donors who weighed more (median 65.0 vs. 40.5 kg, $p < 0.001$; min donor weight in MP group: 27.6 kg), and grafts with a longer organ preservation time (median 15.0 vs. 6.5 h, $p < 0.001$). Additionally, the distance from the donor hospital to the transplant center was longer in the MP group (median 698.2 vs. 516.7 km, $p = 0.001$) and allocation was more commonly performed at a national level in the MP group compared to all non-MP group (65.0% vs. 40.8%, $p = 0.007$). Although not achieving statistical significance, liver grafts from DCD were used at a higher rate of 20.0% in the MP group compared to 11.1% in all non-MP group ($p = 0.08$). Detailed comparison of donor characteristics between the two groups is provided in Table 2.

The 1-year patient survival rate was 96.2% in the MP group vs. 94.5% in the all non-MP group with no statistically significant difference between the two groups (log-rank test $p = 0.68$; Figure 3A). The 1-year graft survival rate was 93.7% in the MP group versus 92.2% in the all non-MP group with no statistically significant difference between the two groups (log-rank test $p = 0.80$; Figure 3B). None of the cases of graft loss in the MP group were due to biliary complications or diffuse cholangiopathy, while seven cases of graft loss in the non-MP group were due to diffuse cholangiopathy.

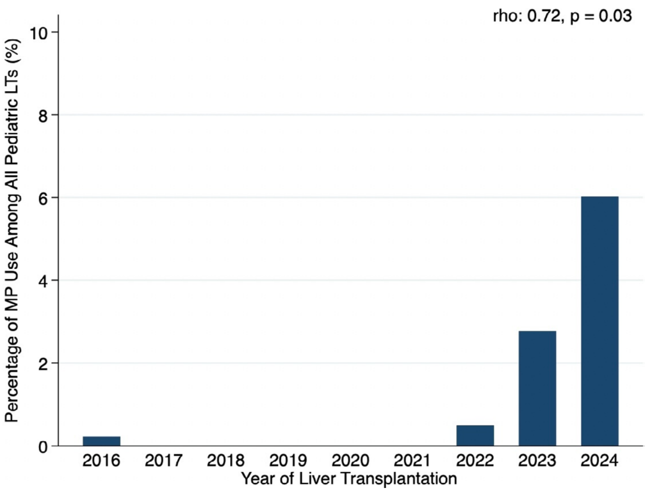

FIGURE 2 | Bar plot demonstrating the percentage of MP use among all pediatric LTs over time.

3.2 | Propensity Score Matched Comparison of MP and Non-MP Groups

Compared to matched non-MP patients, MP patients were more likely to have ascites (47.2% vs. 19.4%, $p = 0.02$) and lower albumin levels (median 3.1 vs. 3.7 g/dL, $p = 0.005$). Detailed comparison of recipient characteristics between the two groups is provided in Table 1. Regarding donor characteristics, both the organ preservation time (median 15.0 vs. 6.1 h, $p < 0.001$) and the distance from the donor hospital to the transplant center were longer in the MP group compared to the matched non-MP group (median 698.2 vs. 568.6 km, $p = 0.01$). Liver grafts from DCD were used in 20.0% of LTs in the MP group compared to 15.0% of LTs in the matched non-MP group ($p = 0.56$). Detailed comparison of donor characteristics between the two groups is provided in Table 2.

The 1-year patient survival rate was 96.2% in the MP group versus 100% in the matched non-MP group with no statistically significant difference between the two groups (log-rank test $p = 0.28$; Figure 3C). The 1-year graft survival rate was 93.7% in the MP group vs. 100% in the matched non-MP group with no statistically significant difference between the two groups (log-rank test $p = 0.14$; Figure 3D).

4 | Discussion

This retrospective UNOS registry study shows that MP use in children continues to increase over time and is not associated with increased patient mortality or graft loss. More specifically, there was no difference in post-LT survival of MP recipients despite a higher use of split grafts, grafts with longer organ preservation time allocated more frequently at a national level, and recipients with higher MELD/PELD scores at the time of LT. Although not statistically different, the proportion of DCD grafts in the MP group reached 20% compared to 11.1% in the all non-MP group. These findings highlight that MP can support LT in sick pediatric recipients using technical variant grafts, and grafts that experience longer organ preservation time typically allocated at a national level and at a larger radius without negatively impacting post-LT survival outcomes.

Several randomized clinical trials have demonstrated the advantages of MP over static cold storage regarding reduced ischemia reperfusion injury, ischemic biliary complications, and early allograft dysfunction [4, 14–17]. However, these studies have primarily included adult LT recipients, and thus the use of MP in pediatric LT has been limited. A recent study from France showed that hypothermic oxygenated MP in ex situ split grafts for 14 children mitigated ischemia reperfusion injury compared to static cold storage without negatively impacting outcomes or survival [18]. Prior to that study, only

TABLE 1 | Comparison of recipient characteristics between MP and non-MP groups.

Variable[a]	MP ($n = 40$)	All—comparison: All non-MP ($n = 3857$)	All—comparison: p	Matched—comparison: Matched non-MP ($n = 40$)	Matched—comparison: p
Recipient age (years)	8.5 (0.5–14.0)	3.0 (0.0–10.0)	0.07	9.0 (1.0–14.0)	0.71
Waitlist time (days)	62.5 (8.5–134.5)	56.0 (17.0–145.0)	0.64	48.0 (15.0–138.5)	0.95
Height (cm)	130.7 (71.0–158.5)	92.0 (71.0–138.0)	0.07	133.3 (77.8–157.5)	0.63
Weight (kg) ($n = 3894$)	31.8 (9.1–60.2)	14.6 (8.8–34.1)	0.047	28.5 (11.3–58.9)	0.60
Sex			0.38		0.26
Female	17 (42.5%)	1908 (49.5%)		22 (55.0%)	
Male	23 (57.5%)	1949 (50.5%)		18 (45.0%)	
Race/ethnicity			0.01		0.37
White	11 (27.5%)	1855 (48.1%)		18 (45.0%)	
Black	6 (15.0%)	662 (17.2%)		4 (10.0%)	
Hispanic	14 (35.0%)	944 (24.5%)		9 (22.5%)	
Other	9 (22.5%)	396 (10.3%)		9 (22.5%)	
Insurance type			0.96		0.12
Private	15 (37.5%)	1432 (37.1%)		22 (55.0%)	
Public/Other/Unknown	25 (62.5%)	2425 (62.9%)		18 (45.0%)	
Diagnosis			0.20		0.32
Biliary atresia	14 (35.9%)	1130 (29.4%)		7 (18.0%)	
Other cholestatic liver disease	6 (15.4%)	455 (11.8%)		4 (10.3%)	
Metabolic liver disease	3 (7.7%)	662 (17.2%)		6 (15.4%)	
Tumor	2 (5.1%)	442 (11.5%)		3 (7.7%)	
Acute liver failure	2 (5.1%)	346 (9.0%)		3 (7.7%)	
Autoimmune hepatitis	0 (0.0%)	94 (2.5%)		4 (10.3%)	
Congenital hepatic fibrosis	2 (5.1%)	75 (2.0%)		2 (5.1%)	
Other	10 (25.6%)	660 (16.7%)		10 (25.6%)	
Laboratory MELD/PELD score	16.5 (8.5–23.0)	12.0 (0.0–22.0)	0.03	13.5 (6.5–24.0)	0.34
Albumin (g/dL)	3.1 (2.7–3.5)	3.4 (2.8–3.9)	0.007	3.7 (3.0–4.1)	0.005
Total bilirubin (mg/dL)	4.3 (0.7–12.3)	3.3 (0.6–15.4)	0.97	3.2 (1.0–10.5)	0.84
International normalized ratio	1.3 (1.1–1.8)	1.3 (1.1–1.8)	0.61	1.3 (1.1–2.0)	0.50
Serum creatinine (mg/dL) ($n = 3880$)	0.4 (0.2–0.7)	0.3 (0.2–0.5)	0.007	0.4 (0.3–0.7)	0.74
Serum sodium (mEq/L)	137.0 (134.0–140.0)	138.0 (136.0–140.0)	0.12	138.0 (137.0–140.5)	0.053
Previous abdominal surgery ($n = 3808$)	20 (55.6%)	1828 (48.5%)	0.40	18 (50.0%)	0.64
Portal vein thrombosis ($n = 3839$)	3 (8.3%)	216 (5.7%)	0.49	0 (0.0%)	0.07
Ascites[b] ($n = 3028$)	17 (47.2%)	1191 (39.8%)	0.37	6 (19.4%)	0.02
Encephalopathy[b] ($n = 3001$)	9 (25.7%)	783 (26.4%)	0.93	9 (30.0%)	0.70

(Continues)

Variable[a]	MP ($n=40$)	All—comparison: All non-MP ($n=3857$)	All—comparison: p	Matched—comparison: Matched non-MP ($n=40$)	Matched—comparison: p
Dialysis within prior week ($n=3864$)	6 (15.0%)	305 (8.0%)	0.10	6 (15.4%)	0.96
Intensive care unit status ($n=3858$)	6 (16.2%)	686 (18.0%)	0.78	10 (27.0%)	0.26
Simultaneous transplants					
Heart	0 (0.0%)	24 (0.6%)	0.62	1 (2.5%)	0.31
Lung	0 (0.0%)	3 (0.1%)	0.86	0 (0.0%)	—
Small intestine	0 (0.0%)	177 (4.6%)	0.17	1 (2.5%)	0.31
Pancreas	0 (0.0%)	179 (4.6%)	0.16	1 (2.5%)	0.31
Kidney	3 (7.5%)	155 (4.0%)	0.27	3 (7.5%)	1.00
Post-LT length of stay (days) ($n=3729$)	17.0 (11.0–24.0)	16.0 (11.0–30.0)	0.58	16.0 (8.0–32.0)	0.95

Note: Data are presented as median (interquartile range) for continuous variables and as frequency (percentage) for categorical variables.
Abbreviations: MELD, model for end-stage liver disease; PELD, pediatric end-stage liver disease.
[a]All variables refer to the values at the time of liver transplantation unless otherwise specified.
[b]> 5% missing data.

individual case reports on the use of hypothermic oxygenated MP had been published [3], as well as a report on two children with biliary atresia in whom normothermic MP facilitated ex situ split LT in the United States [19]. A recent survey completed by 32 transplant surgeons and hepatologists indicated that most respondents were more likely to consider DCD grafts, grafts with transaminase levels > 500, and those with anticipated prolonged organ preservation time if these grafts were preserved using normothermic MP [11]. Although the use of DCD grafts in pediatric LT is scarce, current evidence supports similar outcomes between the use of DCD and donation after brain death grafts [13]. The findings of this study already demonstrate the higher use of grafts with significantly longer organ preservation time. As both MP and non-MP groups had similarly low donor aminotransferase levels, further studies are needed to determine whether MP can be used to expand the biochemical criteria for graft selection. Although the MP group included donors who were statistically older and weighed more compared to the all non-MP group, the overall donor population in both groups remained predominantly pediatric. Thus, the clinical relevance of the older versus younger distinction should be interpreted with caution. Future endeavors should evaluate the use of MP in grafts from smaller donors or even grafts transplanted in smaller recipients.

The importance of using MP in pediatric LT should be emphasized as a solution to several logistical issues. It is well known that biliary atresia is the most common indication for pediatric LT [9]. Although most of these children undergo a Kasai hepatoportoenterostomy prior to LT in an attempt to promote bile drainage, this procedure can lead to dense intra-abdominal adhesions and increase the difficulty of the dissection at the time of native liver hepatectomy [20]. Despite the increasing use of living donor LT especially for younger biliary atresia patients [21], the vast majority of children still receive deceased donor grafts, the availability of which cannot be planned. This can pose a challenge in cases of difficult and prolonged recipient hepatectomy or liver implantation. As a result, the advent of MP permits safe prolongation of graft preservation time during prolonged hepatectomies [22]. In a similar fashion, MP can be useful in multiorgan pediatric transplantation, where prolonged operative time is anticipated. In fact, the findings from this study highlight that equivalent survival outcomes were achieved between pediatric LT with versus without MP, while allowing for prolonged preservation times and national level allocation. The significance of this finding also applies to "orphan" liver grafts ("livers that no one wants") after cross-clamping that may not be allocated because of some abnormality on visual inspection, concerns over procurement injury, or because the intended recipient was ultimately not suitable. In such cases, the use of MP can provide adequate time for additional assessment until an appropriate recipient is identified and prepared for surgery [22, 23]. Another area where MP can be very useful is with ex vivo liver splitting [24, 25]. The higher proportion of split grafts in the MP group in our study underscores the feasibility of MP in facilitating the use of more split grafts. Lastly, MP allows for national allocation of organs at a larger radius, as well as for sequential LTs in the case of multiple organs simultaneously accepted by the same center.

The findings of this study need to be interpreted within the context of its limitations. Firstly, it is a retrospective observational cohort study using transplant registry data. Secondly, the relatively small sample size in the MP group increases the risk for type II statistical error. Moreover, our study is prone to misclassification bias since we used the term organ preservation time in lieu of the UNOS variable cold ischemia time, which we assume includes on-pump time given the significantly longer duration in the MP group. Although no multivariable analysis was performed for this study, we cannot exclude the potential impact

TABLE 2 | Comparison of donor characteristics between MP and non-MP groups.

Variable	MP ($n=40$)	All—comparison: All non-MP ($n=3857$)	All—comparison: p	Matched—comparison: Matched non-MP ($n=40$)	Matched—comparison: p
Donor age (years)	16.0 (13.0–17.0)	11.0 (2.0–17.0)	< 0.001	16.0 (13.5–17.5)	0.96
Pediatric donor	31 (77.5%)	2898 (75.1%)	0.73	30 (75.0%)	0.79
Donor weight (kg) ($n=3894$)	65.0 (54.6–71.9)	40.5 (14.8–64.0)	< 0.001	61.3 (48.6–68.8)	0.13
Sex			0.10		0.26
Female	20 (50.0%)	1437 (37.3%)		15 (37.5%)	
Male	20 (50.0%)	2420 (62.7%)		25 (62.5%)	
Aspartate aminotransferase	37.5 (22.5–76.0)	45.0 (25.0–88.0)	0.21	47.5 (30.0–94.5)	0.16
Alanine aminotransferase	30.0 (19.0–66.5)	35.0 (21.0–65.0)	0.66	32.0 (16.5–51.5)	0.44
Organ preservation time (hours) ($n=3824$)	15.0 (12.0–17.9)	6.5 (5.2–8.0)	< 0.001	6.1 (5.2–7.2)	< 0.001
Donation after circulatory death	8 (20.0%)	429 (11.1%)	0.08	6 (15.0%)	0.56
Distance from donor hospital to transplant center (km)	698.2 (505.6–1425.1)	516.7 (200.0–863.0)	0.001	568.6 (294.5–756.5)	0.01
Allocation type			0.007		0.55
Local	4 (10.0%)	913 (23.7%)		7 (17.5%)	
Regional	10 (25.0%)	1370 (35.5%)		11 (27.5%)	
National	26 (65.0%)	1574 (40.8%)		22 (55.0%)	
Cause of death			0.88		0.72
Anoxia	16 (40.0%)	1765 (45.8%)		12 (30.0%)	
Cerebrovascular injury/stroke	2 (5.0%)	264 (6.8%)		4 (10.0%)	
Head trauma	21 (52.5%)	1708 (44.3%)		23 (57.5%)	
Central nervous system tumor	0 (0.0%)	11 (0.3%)		0 (0.0%)	
Other	1 (2.5%)	109 (2.8%)		1 (2.5%)	
Graft type			0.001		0.16
Whole	17 (42.5%)	2674 (69.3%)		24 (60.0%)	
Partial/reduced	6 (15.0%)	349 (9.1%)		7 (17.5%)	
Split	17 (42.5%)	834 (21.6%)		9 (22.5%)	

Note: Data are presented as median (interquartile range) for continuous variables and as frequency (percentage) for categorical variables.

of center-level effects on our findings. In addition, transplant registries in the United States lack data granularity, especially regarding post-LT complication variables, such as early allograft dysfunction or ischemic biliary complications, which are important variables that need to be compared in the future for pediatric LT with versus without MP. Yet none of the instances of graft loss in the MP group were related to biliary complications or diffuse cholangiopathy. Since MP can facilitate multiorgan transplants, we decided to include them in this cohort, which may limit our ability to assess the impact of MP on isolated LT. Lastly, the individualized decision-making on the use of MP in each case is not available in US transplant registries.

In conclusion, this initial US report of MP in pediatric LT demonstrates a significant increase in the use of MP. Furthermore, MP can support LT in sick pediatric recipients using technical variant grafts, allowing for significant prolongation of organ preservation in challenging cases and a higher proportion of organ allocation at a national level and at a larger radius, without negatively impacting survival outcomes. Further prospective evaluation of the effects of MP on long-term survival and other post-LT complications, such as early allograft dysfunction and ischemic biliary complications is warranted, to continue optimizing graft selection and preservation strategies. Standardized protocols and multicenter collaborations will be essential to

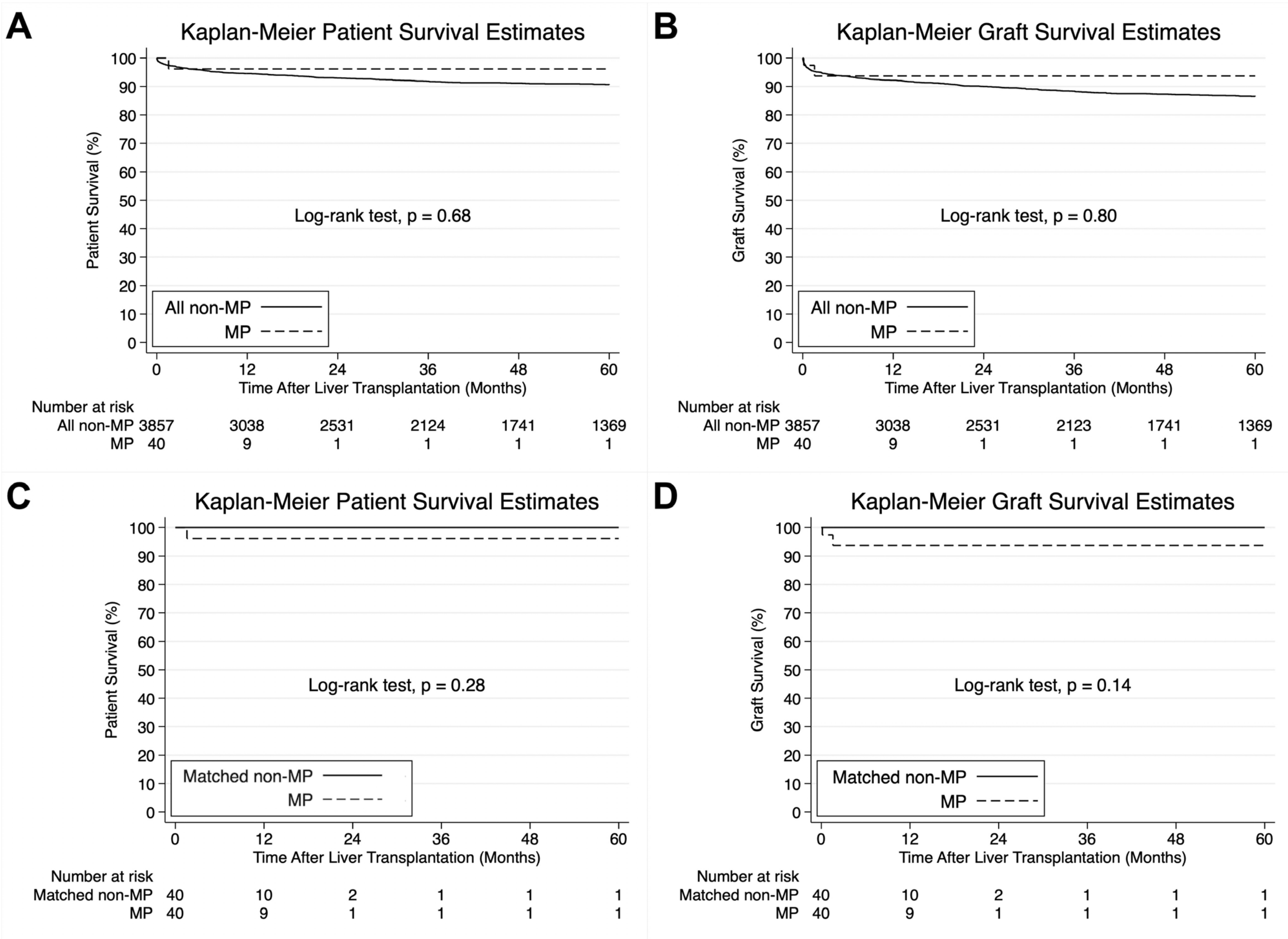

FIGURE 3 | Kaplan–Meier patient (A) and graft (B) survival curves showing no statistically significant difference with vs. without the use of MP in the entire cohort. Kaplan–Meier patient (C) and graft (D) survival curves showing no statistically significant difference with versus without the use of MP in the matched cohort.

fully elucidate the benefits of MP in pediatric LT and pave the way for broader clinical adoption.

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The authors have nothing to report.

Conflicts of Interest

S.A.T. serves as a consultant for Ipsen and Mirum Pharma. The rest of the authors of this manuscript have no conflicts of interest to disclose.

Data Availability Statement

The data reported here were supplied by the United Network for Organ Sharing as the contractor for the Organ Procurement and Transplantation Network and can be available upon request at: https://optn.transplant.hrsa.gov/data/view-data-reports/request-data. The interpretation and reporting of these data are the responsibility of the author(s) and, in no way, should be seen as an official policy of or interpretation by the OPTN or the U.S. Government.

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