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Addressing extreme size mismatch in pediatric intestinal transplantation: Outcomes of intestinal length reduction

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Abstract

Background: Bench liver reduction, with or without intestinal length reduction (LR) (coupled with delayed closure and abdominal wall prostheses), has been a strategy adopted by our program for small children due to the limited availability of size-matched donors. This report describes the short, medium, and long-term outcomes of this graft reduction strategy.

Methods: A single-center, retrospective analysis of children that underwent intestinal transplantation (April 1993 to December 2020) was performed. Patients were grouped according to whether they received an intestinal graft of full length (FL) or following LR.

Results: Overall, 105 intestinal transplants were performed. The LR group ($n=10$) was younger (14.5 months vs. 40.0 months, $p=.012$) and smaller (8.7 kg vs. 13.0 kg, $p=.032$) compared to the FL group ($n=95$). Similar abdominal closure rates were achieved after LR, without any increase in abdominal compartment syndrome (1/10 vs. 7/95, $p=.806$). The 90-day graft and patient survival were similar (9/10, 90% vs. 83/95, 86%; $p=.810$). Medium and long-term graft survival at 1 year (8/10, 80% vs. 65/90, 71%; $p=.599$), and 5 years (5/10, 50% vs. 42/84, 50%; $p=1.00$) was similar.

Conclusion: LR of intestinal grafts appears to be a safe strategy for infants and small children requiring intestinal transplantation. This technique should be considered in the situation of significant size mismatch of intestine containing grafts.

KEYWORDS
graft function, intestinal failure, intestinal transplantation, liver/intestine transplant

Abbreviations: ACS, abdominal compartment syndrome; FL, full length; IF, intestinal failure; IFALD, intestinal failure-associated liver disease; ISBtx, isolates small bowel transplant; LR, length reduction; LSBtx, liver and small bowel transplant; MVtx, multivisceral transplant; UK, United Kingdom; US, United States of America.

1 | INTRODUCTION

Children that develop life-threatening complications of irreversible intestinal failure (IF) should be considered for intestinal transplantation.[1,2] Since the initial attempts at this procedure in the 1960s, outcomes have improved considerably.[2–4] At present, approximately 30% of intestinal transplants in both the United States and the United Kingdom are performed in children.[5,6] A higher susceptibility of intestinal failure-associated liver disease (IFALD) in children has necessitated more than 50% of intestinal grafts to be transplanted in conjunction with the liver.[5–8] Obtaining an adequate size-matched intestine containing graft for small children is challenging, and many may miss their therapeutic window of opportunity for transplantation because of clinical deterioration during a prolonged wait.[9,10] Age and size-matched pediatric donors are extremely rare in the United Kingdom and Europe in general. Although the median age for a child awaiting intestinal transplant in the United Kingdom is at present 3 years of age, 20 years ago most of the candidates were less than 2 years of age, weighing less than 10 kg and needed combined liver replacement.[8,11,12] Therefore, at this time we adopted the approach of length reduction (LR) of the intestinal graft as a life-saving option for very small transplant candidates.

Overall, most children needing intestinal transplantation have a small-sized abdominal cavity[6] and their abdominal domain may be further contracted by a preceding intestinal resection leading to short gut syndrome, abdominal wall scarring from previous laparotomies, stoma placement, and hepatosplenomegaly.[9] Therefore, the pool of donors who can provide a suitable size-matched intestinal or multivisceral graft is very small as the median (IQR) weight of pediatric donors in the United Kingdom is 46 (14–62) kg.[13] This is further demonstrated by Rushton et al, who reported only 4 potential small intestine donors were <20 kg over a two-year period in the United Kingdom.[9] During the same time period, there were up to 10 children on the national waitlist for an intestine-containing graft.[6] This scarcity of organs contributes to excessive wait times for transplantation, with associated higher morbidity and mortality.

To facilitate access to pediatric intestinal and multivisceral transplantation in a climate of organ scarcity, our institution has adopted the strategy of bench reduction of the liver with or without intestinal LR as a means of increasing the pool size of suitable donors.[12] This approach is one of the reasons our waitlist mortality has fallen for children in need of intestinal transplantation.[12] Bench reduction of large liver grafts has been shown to facilitate safe transplantation into small recipients and is an accepted strategy to avoid "large for size" and abdominal compartment (ACS) syndrome following liver transplantation.[14] Volume reduction of either (or both) the liver and intestinal component of composite liver and intestinal grafts has been reported via case reports or small series since the late 1990s.[8,15,16] Hepatic reduction achieves size-matching of the liver component, but extreme donor mismatch requires additional measures. These include staged abdominal wall closure, and intestinal length reduction to reduce the intestinal bulk of the composite graft, which are strategies used to fit the graft into the limited abdominal domain. The initial experience at our institution has been reported previously, however literature that reports the short, medium, and long-term outcomes of length-reduced intestinal grafts with or without liver reduction is lacking.[8] The aim of this study was to compare the short- and longer-term outcomes of patients that received a full-length (FL) intestinal graft with those that received a length-reduced (LR) graft.

2 | METHODS

A single-center, retrospective observational cohort study of all children that underwent intestinal transplantation at our center between April 1993 and January 2020 was performed. Patients were grouped according to whether they received FL or LR intestinal graft. All patients that received an intestine containing graft as an isolated organ (ISBtx), in combination with the liver (LSBtx), in combination with the stomach (modified multi-visceral, modified MVtx) or in combination with stomach and liver (multi-visceral, MVtx) were included. Demographic, donor, and clinical variables were obtained from our small bowel transplant database and hospital medical records. Outcomes of interest were early (<90 days) complications including intestinal anastomotic leak, gastrointestinal perforation, obstruction, abdominal compartment syndrome, graft loss, and patient death. A comparison of the time until commencement of enteric feed and parenteral nutrition (PN) cessation was also performed. Long-term graft and patient survival were assessed at 1, 3, 5, and 10 years. Due to the retrospective and observational nature of this study, human research ethics board approval was not required.

The surgical techniques of donor organ procurement, liver reduction, and graft implantation at our institution have been described in detail previously.[8,17] If required, liver reduction was performed via an extra-glissonian approach on the back table at the recipient center, achieving either a reduced full left lobe graft or a reduced left lateral liver graft.[8,17] Intestinal length reduction was achieved via a segmental resection of the distal jejunum and a subsequent hand-sewn entero-enterostomy to restore continuity. This was performed after establishing adequate vascular inflow and outflow of the graft, when it was possible to better assess mismatch of the intestinal component of the composite graft, and therefore it did not impact cold ischemic time. The aim was to resect between 60 and 100 cm of intestine, leaving at least 180–200 cm of intestinal length for the intestine-containing graft. Additional measures adopted to overcome size mismatch included the use of abdominal wall prostheses (Permacol®, Medtronic) which was usually coupled with "delayed" or "staged" abdominal closure.[18] Due to size discrepancy between donor and recipient, a colonic segment was not included in most intestine-containing grafts. The length of bowel resected was dependent on the discrepancy between the size of the graft and the recipient's abdominal domain, at the discretion of the operating surgeon, and the ability to achieve the first stage of closure of the abdomen in a safe manner.

All patients were subsequently managed according to the routine postoperative care of that time period. The postoperative immunosuppressive regime has remained the same since 2002, comprising

an interleukin-2 receptor antagonist, tacrolimus, and steroids as standard, with an antimetabolite agent included for patients identified as being at higher risk of rejection.[19]

Statistical analysis was performed using SPSS (*Version* 25.0. IBM Corp). Median (interquartile range) values are reported. Continuous variables that followed the normal distribution were compared using independent samples *t*-tests and those that did not follow the normal distribution were compared with the Mann–Whitney *U* test. Categorical variables were compared using the Chi-Square test. Two-sided tests of significance were utilized and a *p* value ≤.05 was considered statistically significant.

3 | RESULTS

During the study period, 105 intestinal transplants were performed in 97 patients. The FL and LR intestine group comprised 95 and 10 grafts respectively. Figure 1 demonstrates the flow of the study and the type of grafts in each group. The patients that received an LR intestinal graft were younger (14.5 months vs. 40.0 months, $p = .012$) and smaller (8.7 kg vs. 13.0 kg, $p = .032$). Both the donor–recipient age (2.1 vs. 1.5, $p = .082$) and weight (2.2 vs. 1.5, $p = .051$) ratios were higher in the LR group but did not attain statistical significance. The causes of intestinal failure and time spent on the transplant waitlist did not differ between groups (Table 1). The weight *Z*-scores of the recipients in each group were similar, as shown in Table 1 and Figure 2.

A higher proportion of the LR group received a liver-containing graft (9/10, 90% vs. 59/96, 61%; $p = .092$). In the subgroup of patients that received a liver-containing allograft (68/105, 65%), a significantly higher proportion of patients in the LR group also had a reduced liver (8/9, 89% vs. 27/59, 46%; $p = <.026$). The cold ischemic time (CIT) was not significantly longer in the LR group (382 min vs. 386 min, $p = .593$). The intraoperative blood product requirement was similar between groups, as was the strategy adopted for abdominal closure (Table 2). Delayed/staged abdominal closure was adopted in 4/10 (40%) and 24/95 (25%) of the LR and FL groups, respectively. Abdominal wall closure using a biological mesh was used in 1/10 (10%) and 14/95 (15%) in the LR and FL groups respectively. In total, the combination of a liver reduction, small bowel length reduction, and delayed abdominal closure was performed in four children and one of these experienced ACS.

The incidence of early complications in each group is demonstrated in (Table 3). The length of admission to the intensive care unit was 3 days for FL and 7 for LR groups respectively ($p = .182$). The total length of hospital admission was higher for the LR group (89 days vs. 45 days) but did not attain statistical significance (.080). The time to commencement of enteric feed (6 days vs. 5 days, $p = .538$) and PN cessation (24 vs. 20, $p = .308$) was similar across groups. Data pertaining to the exact time intravenous hydration was ceased is lacking. However, in the majority of instances, this occurred at the same time as the PN was stopped. The rate of ACS, intestinal anastomotic leak, intestinal perforation, and obstruction in the first 90 days was comparable between groups (Table 2).

The 90-day graft and patient survival (9/10, 90% vs. 83/95, 86%; $p = .810$) did not differ significantly between groups. In the FL group, 12 patients died in the first 90-days as a result of multi-organ failure (3), acute rejection (3), infection (2), pulmonary hemorrhage ($n = 1$), intra-operative cardiac arrest ($n = 1$), portal vein thrombosis ($n = 1$) and unknown ($n = 1$). One child in the LR group died in the first 90 days due to multi-organ failure. Six patients in the FL group were retransplanted at a median of 54 (range: 49–69) months. Two children in the LR group underwent intestinal retransplantation for chronic rejection, one at 24 months and the other at 85 months. The 1-, 3-, 5-, and 10-year survival did not differ significantly between groups (Table 3). The weight *Z*-scores of both groups increased from pre-transplant to 1-year posttransplant (Figure 2).

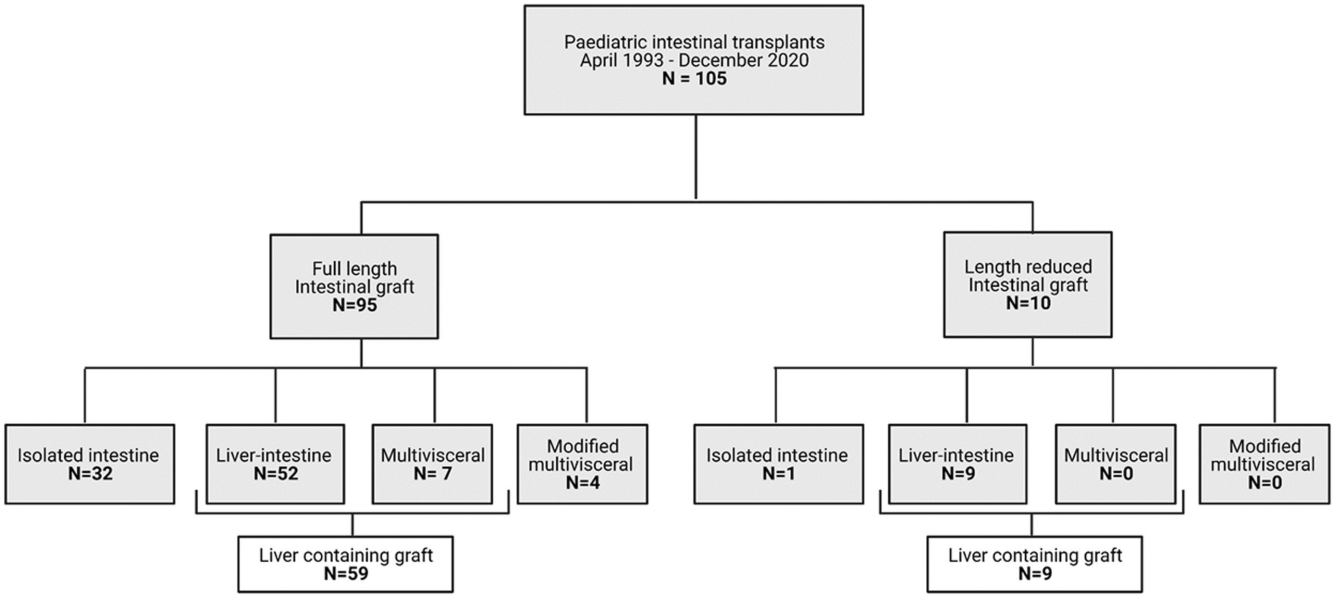

FIGURE 1 Study flow and graft types. Flow diagram of different graft types in each group.

TABLE 1 Demographics of participants.

	Total sample $N = 105$	Total sample ($n = 105$)		
		FL intestine $N = 95$	LR intestine $N = 10$	p
Female	43 (41%)	37 (38%)	6 (60%)	.198
Recipient age, months (IQR)	38 (17–78)	40.0 (18.8–82.5)	14.5 (10.7–32.3)	**.012**
Recipient weight, kg (IQR)	12.6 (9.0–21.4)	13.0 (9.3–21.6)	8.7 (7.9–12.2)	**.032**
Waitlist duration, days (IQR)	125 (63–225)	127 (58–241)	104 (75–145)	.443
Indication				
Short bowel	55 (53%)	49 (52%)	6 (60%)	.688
Dysmotility	30 (29%)	27 (28%)	3 (30%)	
Mucosal disorders	12 (11%)	12 (13%)	0 (0%)	
Other	8 (6%)	7 (7%)	1 (10%)	
Preoperative TPN only	61 (61%)	53 (70%)	8 (89%)	.538
Donor age, months (IQR)	72 (24–144)	72.0 (24.0–150.0)	78 (24–147)	.849
Donor/recipient age ratio (IQR)	1.7 (0.85–3.25)	1.5 (0.7–3.3)	2.1 (1.6–9.0)	.082
Donor weight, kg (IQR)	22 (14–41)	22 (14–41)	24 (13.5–42.0)	.860
Donor/recipient weight ratio (IQR)	1.59 (1.13–2.6)	1.5 (1.1–2.6)	2.2 (1.5–3.4)	.051
Recipient weight Z-score	−1.32 (−2.25 to −0.26)	−1.32 (−2.19 to −0.17)	−1.27 (−2.42 to −0.60)	.472

Abbreviations: FL, full-length intestinal graft; RL, reduced-length intestinal graft.
Bold values signify a p value $< .05$.

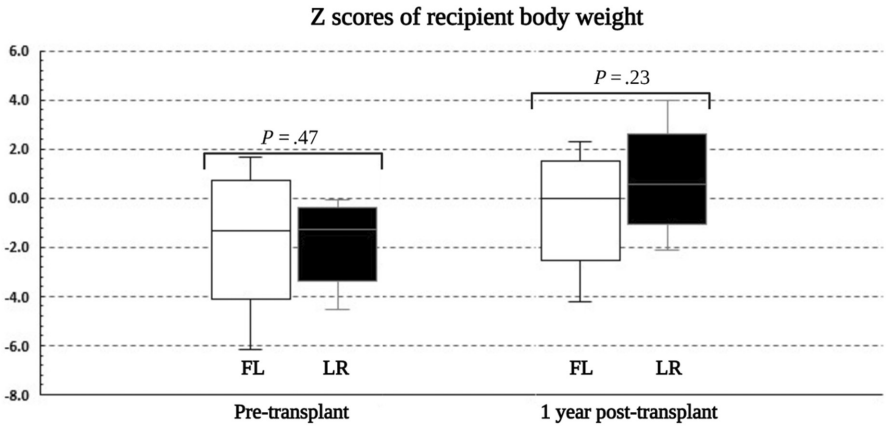

FIGURE 2 Box plot demonstrating the recipient weight Z-score prior to transplant and at 1 year follow-up. Both the full-length (FL) and the length-reduced (LR) groups increased the median weight Z score. p Value assessed with the Mann–Whitney U test.

In the group that received a liver-containing graft ($N = 68$), there was no difference in the timing of commencement of enteric feeds (5 days vs. 6 days, $p = .621$), cessation of TPN (20 days vs. 26 days, $p = .324$), length of stay in hospital (60 days vs. 59 days, $p = .152$) or ICU (5 days vs. 2 days $p = .849$) for those that received a full liver compared to a reduced liver. In addition, the group that received a full liver had a similar 90-day (24/29, 83% vs. 28/35, 80%; $p = .78$) and 5-year (12/26, 46% vs. 15/33, 45%; $p = .96$) graft survival to the group that received a reduced liver. The subgroup of patients that received a liver and intestine-containing graft is shown in Figure 3, and separated based on whether they received a full liver and full intestine (Figure 3A,B), reduced liver but full intestine (Figure 3C,D, red) or reduced liver and reduced intestine (Figure 3C,D, red) Recipients of a full liver and full intestine graft had lower graft-recipient weight and age ratios.

4 | DISCUSSION

The graft reduction technique, as a lifesaving option, became apparent early in our program because the children referred were frequently very young infants with severe IFALD, and many were either too sick for transplantation or did not survive long enough to receive an appropriately sized graft.[10,12,20] The association of a bilirubin ≥100 μmoL/L in the setting of intestinal failure was previously associated with a 6-month survival of 19%, therefore these recipients could not afford to wait a prolonged period for transplantation. Furthermore, it was apparent that the group of patients with IF that were too sick for transplant listing were in the younger age range.[12] The results of this study show that grafts that undergo intestinal length reduction, with or without liver reduction, have short, medium, and long-term outcomes that are comparable with full-length

TABLE 2 Graft and operative characteristics.

		Total sample ($n = 105$)		
	Total sample $N = 105$	FL intestine $n = 95$	LR intestine $n = 10$	p
ABO identical	81 (81%)	71 (73%)	10 (100%)	.116
Type of graft				
Isolated intestine	33 (31%)	32 (34%)	1 (10%)	.206
Liver and intestine	61 (60%)	52 (55%)	9 (90%)	
Multivisceral	7 (4%)	7 (7%)	0 (0%)	
Modified multivisceral	4 (4%)	4 (4%)	0 (0%)	
Liver-containing graft	64 (64%)	59 (61%)	9 (90%)	.092
Reduced liver	35 (35%)	27 (46%)[a]	8 (88%)[a]	**.026**
Colon containing graft	3 (3%)	2 (2%)	1 (11%)	.171
Cold ischemic time, min (IQR)	388 (347–465)	386 (327–462)	382 (356–496)	.593
Intraop RBC requirement, mL (IQR)	350 (200–652)	350 (200–650)	495 (242–1097)	.422
Intraop FFP requirement, mL (IQR)	427 (0–750)	400 (0–750)	798 (450–1340)	.069
Abdominal closure				
Primary closure	56 (57%)	53 (56%)	5 (50%)	.772
Prosthetic closure	14 (14%)	14 (15%)	1 (10%)	
Two stage closure	26 (27%)	24 (25%)	4 (40%)	

Abbreviations: FFP, Fresh frozen plasma; RBC, Red blood cells.

Bold values signify a p value $< .05$.

[a]Percentage of subgroup that received a liver-containing graft.

grafts. The recipient weight and age of the children that received a liver-containing LR graft was significantly lower than the FL, signifying that this is a subgroup of small IFALD children with extremely limited graft options. Despite considerable size mismatch with a donor–recipient weight ratio of 2.2, abdominal closure rates in the LR group were not significantly different from those of FL (1.5), however, ACS remains a risk despite the incorporation of both staged abdominal closure and length reduction.

Data reporting the outcomes of length-reduced deceased donor grafts in comparison with those of a full length is scarce. Reyes et al.[15] demonstrated that a liver-intestinal graft from an adult donor, that contained only the left lateral segment of the liver, could be safely transplanted into a pediatric recipient. Subsequently, Nery et al.[16] reported two cases of transplanting grafts that had undergone volume reduction via both liver graft hepatectomy and a segmental small bowel resection. The early experience from our unit confirmed that the strategy of using LR bowel combined with liver graft reduction was feasible and safe even in infants and children with a small abdominal cavity.[8] Bench reduction of the liver to a left lateral segment graft using an extraglissonian approach produces a size-matched liver graft but does not address the issue of the large volume intestinal and mesenteric component of the graft. Furthermore, postreperfusion intestinal edema occurs commonly, and this further exacerbates the challenges posed by the limited abdominal domain. As the edema of the intestinal component settles, the definitive abdominal closure can be achieved as a staged process. Despite a reduction in graft size and staged closure, ACS still occurred in one recipient. Since the year 2000, our institution has adopted an approach of systematic staged abdominal closure following approximately 50% of intestinal transplants to prevent this dangerous complication.[18] The technique utilized has previously been described, however, it does not eliminate the possibility of ACS entirely.[18] ACS occurred with both prosthetic patches and staged closure in both those that received LR or FL intestinal grafts. This reinforces the fact that the surgeon must always be mindful of this issue when attempting to close the abdomen, in either a primary or delayed manner, following intestinal transplantation.

A segmental intestinal resection represents an additional insult to the graft, requires an additional anastomosis, and reduces the potentially useful absorption area. Despite an additional enteric anastomosis in the graft, this did not appear to increase the rate of enteric leak, perforation, or obstruction. Anastomotic strictures were not evident in the LR group. To ensure the intestinal anastomosis is well vascularized and nutrient absorption not significantly impacted, our approach has been to remove a segment of distal jejunum after graft reperfusion.[8] Reduction of the distal jejunum results in a shortening of the anteroposterior dimensions of the intestinal and mesenteric component of the composite graft, without taking away the precious absorptive ileal surface area. An additional benefit of preserving the full length of ileum and resecting the jejunum is that the ileum demonstrates functional adaptation over time. Enteral feeding commencement and TPN cessation occurred within a similar

TABLE 3 Outcomes of participants.

	FL intestine $N = 95$	LR intestine $N = 10$	p
ICU length of stay, days (IQR)	3 (2–11)	7 (4–19)	.182
Hospital length of stay	45 (33–73)	89 (38–104)	.080
Timing of postop enteral feed, day	5 (3–8)	6 (3–10)	.538
Postop day TPN ceased (IQR)	20 (15–30)	24 (18–30)	.308
Day 3 tacrolimus level (ng/mL)	22.2 (15.8–28.1)	25.8 (14.0–30.5)	.424
Day 7 tacrolimus level (ng/mL)	18.5 (12.4–26.7)	18.4 (11.3–23.6)	.630
Early complications (<90 days)			
Abdominal compartment syndrome	7 (7%)	1 (10%)	.806
Intestinal anastomotic leak	13 (14%)	0 (0%)	.198
Intestinal perforation	7 (7%)	1 (10%)	.806
Intestinal obstruction	6 (7%)	2 (20%)	.140
Small bowel rejection	70 (74%)	9 (90%)	.627
Severe acute intestinal rejection	18 (19%)	2 (20%)	1.00
PTLD	18 (19%)	2 (22%)	.987
1-year weight Z-score	−0.02 (−1.02 to 0.78)	0.78 (−0.77 to 2.08)	.229
90-day graft survival	83/95 (86%)	9/10 (90%)	.810
90-day patient survival	83/95 (86%)	9/10 (90%)	.810
1-year graft survival	65/90 (71%)	8/10 (80%)	.599
1-year patient survival	64/90 (71%)	8/10 (80%)	.553
3-year graft survival	51/87 (57%)	6/10 (60%)	.933
3-year patient survival	49/87 (56%)	7/10 (70%)	.407
5-year graft survival	42/84 (50%)	5/10 (50%)	1.00
5-year patient survival	44/84 (52%)	6/10 (60%)	.648
10-year graft survival	26/67 (39%)	4/10 (40%)	.942
10-year patient survival	27/67 (40%)	4/10 (40%)	.986

Abbreviations: ICU, intensive care unit; PTLD, posttransplant lymphoproliferative disorder.

postoperative period in both groups, demonstrating that the additional intestinal resection in the LR group did not compromise early enteric nutrition. The LR intestine did not have an impact on the absorption of immunosuppressive medication and there was no difference in tacrolimus doses or levels observed. In more than one way, this is similar to the experience reported after the transplantation of segments of intestine from living donors. Tzvetanov et al.[21] reported that the function of the grafts (either isolate bowel or a combination of partial liver and bowel grafts) was satisfactory.

An alternative option for a select group of children with IF and life-threatening IFALD is an isolated liver transplant as an initial procedure.[22] Studies have demonstrated the ability of isolated liver transplant to facilitate weaning of PN in up to 82% of children with short bowel syndrome.[22–24] The resolution of portal hypertensive enteropathy, anorexia, bowel edema, and improvement in synthetic liver function following isolated liver transplant may allow gastrointestinal adaptation and enteral autonomy.[22] However, if underlying poor function of bowel rather than portal hypertension is contributing to IFALD, this can recur in the transplanted graft prior to weaning from PN and is a major cause of mortality in this group.[22,24]

The limitations of this study are its small study size and its retrospective nature and the fact that the study period spans several decades. It is well-reported that the outcomes of intestinal transplantation have improved since the 1990s.[18,25] In short, a series of new strategies were introduced in the last 2 decades that improved the care of infants with intestinal insufficiency and prevented the early progression towards IFALD. These included liver-preserving PN strategies, bowel length, and function-sparing approaches which have been extremely efficient in avoiding the need for transplantation early in life. It has been instrumental in reducing the need for the strategy of LR at our institution in the last 10 years. Other contributing strategies were (1) active networking and development of regional/national intestinal failure policies and care protocols, (2) early referral to our center – before the onset of advanced liver disease, and (3) prioritization of organs to children in need of a combined liver-intestine graft over those requiring a liver in isolation.[9] In parallel to improved outcomes for intestinal transplantation, the incidence of intestinal transplantation has decreased worldwide due to better-integrated care of patients with IF and IFALD with the current world figures amount to some 100 such grafts annually.

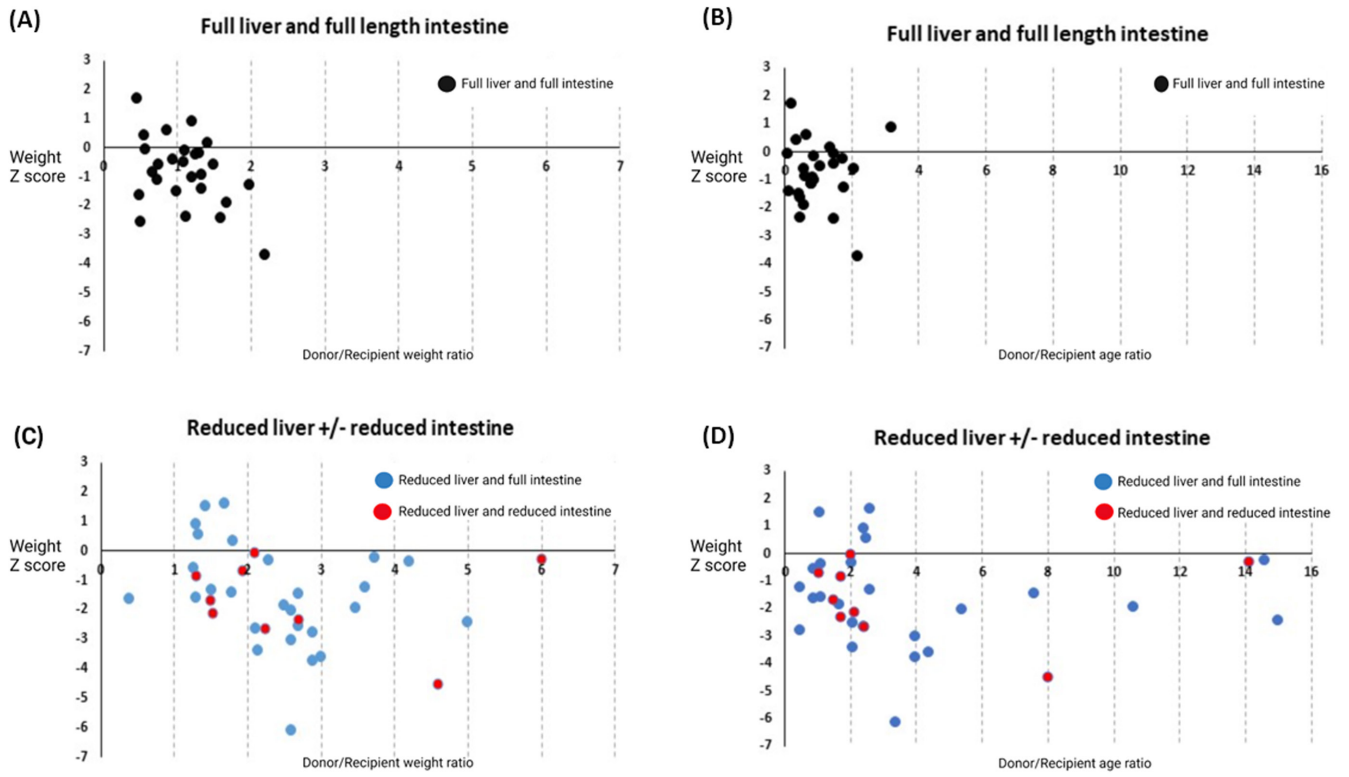

FIGURE 3 Scatter plot of the subgroup that received a liver and intestine containing graft, demonstrating the relationship between donor–recipient weight (A and C) and age (B and D) recipients weight *Z*-score. The group is divided based on whether they received a full liver and full intestine (black dots), reduced liver and full intestine (blue), and reduced liver and reduced intestine (red), recipients of the full-sized grafts are clustered at the lower end of donor–recipient ratio axis. Those that received reduced grafts have a much wider distribution of *Z* scores, donor–recipient age, and weight ratios.

In comparison to the present 10-year graft and patient survival of 48.5% and 61.7%, respectively, in the first half of the 1990s, it was significantly lower at 26.7% and 34.7%.[25] In the patients that have achieved 10 years follow-up, both of our groups were comparable. However, many of the patients that received an LR graft were transplanted at a time in which the outcomes from IT overall were less than in the most recent era. This means the survival following this technique, if applied in modern times, may be higher than we report. Another study limitation is that we are not able to provide exact data on the timing of independence from parenteral hydration, a useful outcome measure to assess intestinal graft function. As alluded to in the results section, parenteral hydration was ceased at the time of PN in the vast majority of cases and we have not observed a difference between children with full or reduced-length grafts.

In conclusion, the length reduction of an intestinal allograft is a surgical strategy that can be used to facilitate the transplantation of grafts from larger donors into smaller pediatric recipients. It may allow timely and lifesaving intestinal transplantation of a child who would not otherwise survive for a prolonged period on the waitlist.

AUTHOR CONTRIBUTIONS

Data collation: MC, GLG, AP. Data analysis: AH. Writing first draft: AH, GLG, DFM. Review and editing: AP, SB, JH, DK, JDVG, YHO, HH, MTPRP, KS.

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CONFLICT OF INTEREST STATEMENT

Angus Hann has no conflicts of interest to disclose. Girish Gupte has no conflicts of interest to disclose. Adithya Pathanki has no conflicts of interest to disclose. Maria Coelho has no conflicts of interest to disclose. Sue Beath has no conflicts of interest to disclose. Jane Hartley has no conflicts of interest to disclose. Deirdre Kelly has no conflicts of interest to disclose. Jan De Ville De Goyet has no conflicts of interest to disclose. Ye H Oo has no conflicts of interest to disclose. Hermien Hartog has no conflicts of interest to disclose. Thamara PR Perera has no conflicts of interest to disclose. Khalid Sharif has no conflicts of interest to disclose. Darius F Mirza has no conflicts of interest to disclose.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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