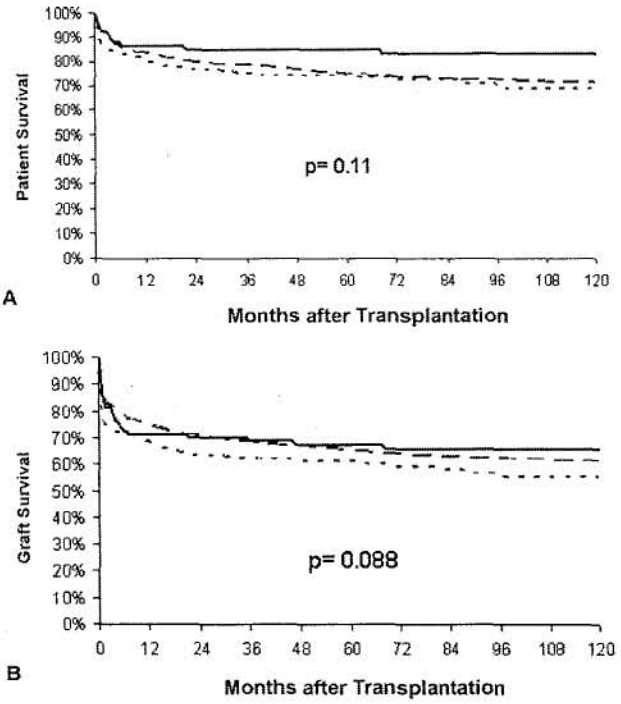

Figure 2. Overall survival of different graft types after liver transplantation. (A) Patient; (B) graft. Solid line, living donor; dashed line, whole liver; dotted line, split-graft liver transplantation.

tion, SL-ER graft, donor age older than 45 years, and cold ischemia time > 10 hours. In children, Table 4 shows that a history of previous LT and use of split grafts were associated with lower survival outcomes.

Table 3. Multivariate Analysis of Patient and Graft Survival in Adults

Variables	Hazard ratio	p Value
Patient survival		
Recipient age >60 y	1.6	0.0002
Previous LT	2.6	<0.0001
Graft type		
Whole	1	
SLT	2	0.0008
LDLT	0.8	0.6320
Donor age >45 y	1.5	0.0361
Cold ischemia time >10 h	1.4	0.0066
Graft survival		
Previous LT	1.8	<0.0001
Graft type		
Whole	1	
SLT	1.9	0.0010
LDLT	1.1	0.6572
Donor age >45 y	1.4	0.0223
Cold ischemia time >10 h	1.3	0.0077

LDLT, living-donor segmental graft liver transplantation; LT, liver transplantation; SLT, split-graft liver transplantation.

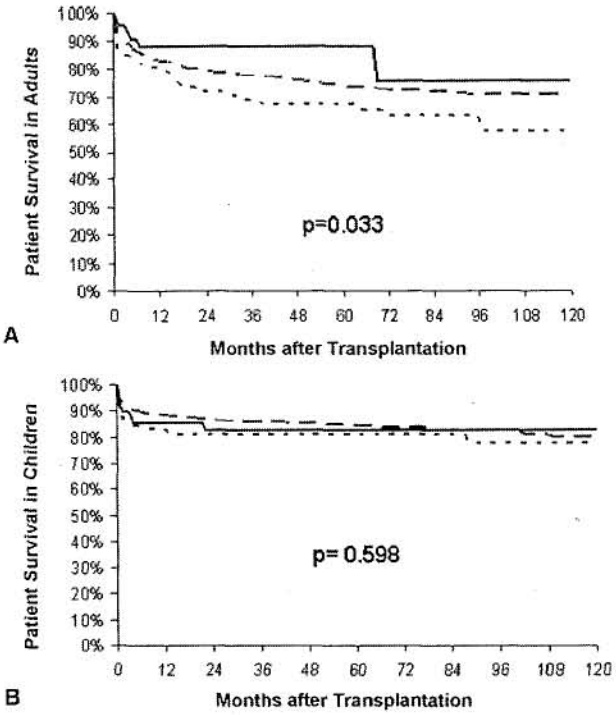

Figure 3. Patient survival after liver transplantation. (A) Adult. Solid line, living-donor right liver graft; dashed line, whole liver; dotted line, split extended right liver graft. (B) Children. Solid line, living-donor left lateral liver graft; dashed line, whole liver; dotted line, split-graft left-lateral liver transplantation.

Graft survival

Figure 2B demonstrates that overall 10-year graft survival outcomes for SLT, LDLT, and WLT were comparable (55% versus 65% versus 62%, respectively; p = 0.088). Graft survival curves in adults and children are compared separately in Figure 4. There were no significant differences

Table 4. Multivariate Analysis of Patient and Graft Survival in Children

Variables	Hazard ratio	p Value
Patient survival		
Previous LT	4.9	<0.0001
Graft type		
Whole	1	
SLT	2.2	0.0011
LDLT	1.7	0.1923
Graft survival		
Previous LT	1.7	0.0031
Graft type		
Whole	1	
SLT	1.5	0.0198
LDLT	1.1	0.8433

LDLT, living-donor segmental graft liver transplantation; LT, liver transplantation; SLT, split-graft liver transplantation.

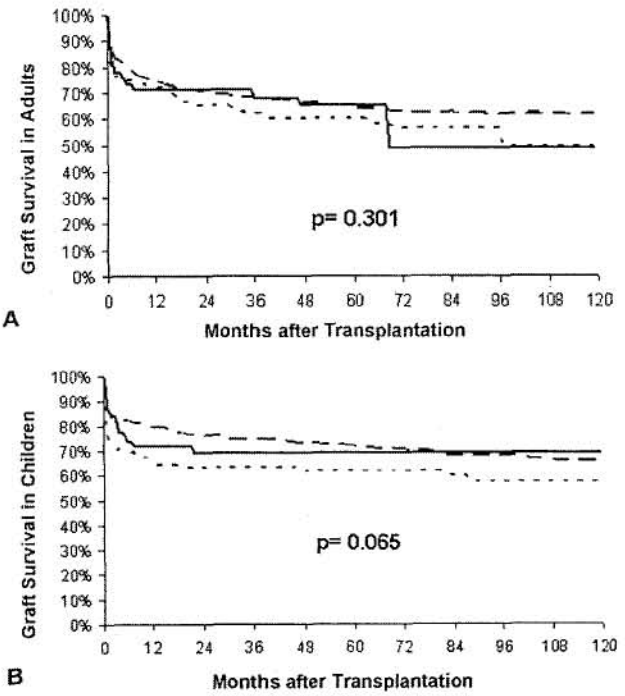

Figure 4. Graft failure-free survival after liver transplantation. (A) Adult. Solid line, whole liver; dashed line, split extended right liver graft; dotted line, living-donor right liver graft. (B) Children. Solid line, living-donor left lateral liver graft; dashed line, whole liver; dotted line, split-graft left-lateral liver transplantation.

in graft survival for all graft types in both adults (Fig. 4A) and children (Fig. 4B).

Multivariate analysis of graft survival in adults is shown in Table 3. The predictors of graft failure included history of previous LT, SL-ER grafts, donor age older than 45 years, and cold ischemia time > 10 hours. In children, history of previous LT and SL-LL graft were independent predictors of diminished survival (Table 4).

Causes of loss

For both adults and children, sepsis and multi-organ system failure was the most common cause of patient death. Regarding graft failure, recurrence of liver disease and chronic rejection were frequent causes of graft loss in adults. The noteworthy difference between the three groups was that recurrence of liver disease in transplanted segmental grafts from deceased and living donors was more common than in whole-organ grafts (50% versus 56% versus 16%, respectively; $p = 0.0133$). For children, chronic rejection and hepatic artery thrombosis were common reasons for graft loss. There were no significant differences in causes of graft failure among the three groups.

Complications

The major posttransplant complications for various graft types are compared in Table 5. In adults, there were no differences except for a higher rate of retransplantation in recipients of living-donor grafts. In children, there was a higher frequency of primary graft nonfunction in split grafts because of increased use in urgent and redo transplantations. Living-donor grafts had a higher rate of portal venous thrombosis than whole grafts.

DISCUSSION

This study compared longterm outcomes for whole and segmental grafts in adult and pediatric liver transplant recipients. Earlier studies report conflicting short- and midterm survival outcomes. Although single-center studies[6,7,11] demonstrated no difference in 1-, 3-, and 5-year outcomes after SLT and WLT, registry data report SLT as an independent predictor of poor patient outcomes for both adults and children.[20-23]

Our study showed equivalent overall longterm outcomes after whole, split, and living-donor graft LT. When results were analyzed separately by recipient age, there were distinct differences in outcomes and factors that affect survival. Although the 10-year graft survival after whole, split, and living-donor transplantation was comparable in adults, the patient survival was lower for split grafts compared with whole grafts when used in retransplants and critically ill recipients. Patients who require retransplanta-

Table 5. Complications

	Adult							Children						
	SL-ER (n = 72)		LD-R (n = 41)		Adult-WL (n = 2,433)		p	SL-LL (n = 109)		LD-LL (n = 49)		Ped-WL (n = 284)		p
Complication	n	%	n	%	n	%	Value	n	%	n	%	n	%	Value
Primary graft nonfunction	4	5.5	5	12.2	206	8.4	0.4811	9	8.3	2	4.1	5	1.8	0.0097
Biliary complications	3	4.2	6	14.6	178	7.3	0.1126	3	2.7	3	6.1	9	3.2	0.5632
Hepatic artery thrombosis	3	4.2	3	7.3	89	3.7	0.5112	6	5.5	2	4.1	19	6.7	0.7597
Portal vein thrombosis	0		0		24	1	0.763	4	3.7	4	8.2	2	0.7	0.0037
Retransplantation	5	6.9	9	22	271	11.1	0.0476	24	22	8	16.3	44	15.5	0.3035

Adult-WL, adult deceased-donor whole-organ graft; LD-LL, living-donor left lateral graft; LD-R, living-donor right graft; Ped-WL, pediatric deceased-donor whole-organ graft; SL-ER, split extended right graft; SL-LL, split left lateral graft.

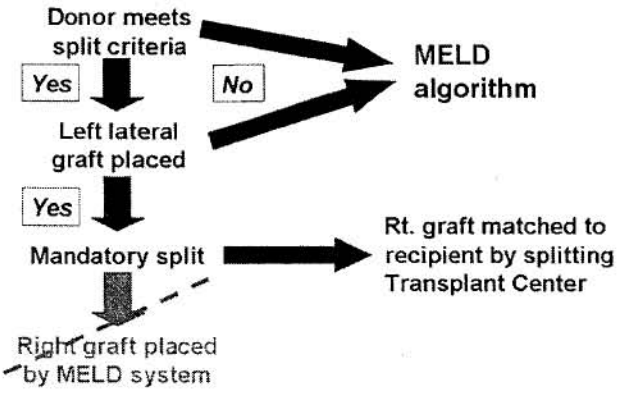

Figure 5. Proposed organ allocation system for optimal use of split liver grafts. MELD, Model for End-Stage Liver Disease.

tion of the liver have higher acuity of illness, including multi-organ system failure, and undergo complex redo transplantation procedures that may be associated with hemodynamic instability during the perioperative period. These operative circumstances, in addition to both donor graft and recipients predictors, affect patient outcomes after transplantation and should be considered in the allocation of split grafts to recipients.

We found it interesting as for graft failure, that recurrence of liver disease was more common in segmental grafts from both deceased and living donors compared with whole grafts. A possible explanation may be that ischemia and reperfusion injury inherent in segmental grafts synergistically activates and perpetuates stellate cells leading to accelerated fibrosis in cases of hepatitis C infection[24] or immunologic mechanisms in malignancy and autoimmune liver diseases.[25-27] Another theory that may explain a more severe recurrence of hepatitis C after segmental liver transplantation is attributed to intense proliferation and regeneration of the hepatocytes in segmental grafts that augment viral translation and replication.[28,29] The relationship between hepatocellular injury, hepatic proliferation, and viral replication remains unproved, and several studies have shown similar frequency of disease recurrence and outcomes between whole grafts and segmental grafts.[30,31]

For children, segmental grafts from deceased and living donors have increased available organs for smaller and younger recipients and have significantly decreased the pediatric waitlist mortality. Several studies have reported conflicting results after LT with segmental liver grafts in children using registry data. Although analysis of the United Network of Organ Sharing (UNOS) database by Becker and colleagues[32] demonstrated comparable short-term outcomes between SLT and WLT, several studies using the same pooled data from the United Network of Organ Sharing[33] and transplant registry data from the Studies of Pediatric Liver Transplantation (SPLIT)[22] reported inferior outcomes after SLT compared with WLT. We found no significant differences in longterm patient and graft survival outcomes between whole and segmental liver grafts in pediatric recipients.

In summary, our study demonstrates equivalent overall longterm outcomes for whole and segmental grafts in adult and pediatric liver transplant recipients. The major challenge toward optimal use of these grafts lies in the organ allocation policy. Under the current MELD system, each split graft is allocated to patients according to their MELD scores. Because the patient with the highest MELD score receives the organ, this system allocates the split graft to the sickest transplant candidates and limits graft-to-recipient matching, which is crucial for best results. Allocation of the split extended right grafts to adults with lesser acuity of illness may improve patient survival outcomes. We propose an alternate system to allow optimal use of split grafts (Fig. 5). If the donor fails to meet split criteria or the left lateral graft is not allocated to a recipient, the whole organ is assigned by the MELD algorithm. But when the donor meets split criteria and the left lateral graft is allocated, the liver is split, and rather than allocating the right graft through the MELD system, the right graft instead is matched to an ideal recipient by the splitting transplant center. An organ allocation system with such flexibility would encourage adult-to-child candidate pairing from the same transplantation center and allow preoperative surgical and logistic planning to minimize graft ischemia duration. This proposal aims to optimize graft-to-recipient matching that not only would substantially reduce the loss of lives on the transplant waiting list but also improve outcomes after liver transplantation.

Author contributions

Study conception and design: Hong, Yersiz, Farmer, Ghobrial, Hiatt, Busuttil
Acquisition of data: Hong, Duffy, Nonthasoot, Collins
Analysis and interpretation of data: Hong, Duffy
Drafting of manuscript: Hong, Yersiz, Farmer, Duffy, Ghobrial, Nonthasoot, Collins, Hiatt, Busuttil
Critical revision: Hong, Hiatt, Busuttil

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REFERENCES

1. Broering DC, Wilms C, Lenk C, et al. Technical refinements and results in full-right full-left splitting of the deceased donor liver. Ann Surg 2005;242:802–812.
2. Humar A, Ramcharan T, Sielaff TD, et al. Split liver transplan-

tation for two adult recipients: an initial experience. Am J Transplant 2001;1:366–372.
3. Emond JC, Whitington PF, Thistlethwaite JR, et al. Transplantation of two patients with one liver. Analysis of a preliminary experience with 'split-liver' grafting. Ann Surg 1990;212:14–22.
4. Rogiers X, Malago M, Habib N, et al. In situ splitting of the liver in the heart-beating cadaveric organ donor for transplantation in two recipients. Transplantation 1995;59:1081–1083.
5. Goss JA, Yersiz H, Shackleton CR, et al. In situ splitting of the cadaveric liver for transplantation. Transplantation 1997;64: 871–877.
6. Yersiz H, Renz JF, Farmer DG, et al. One hundred in situ split-liver transplantations: a single-center experience. Ann Surg 2003;238:496–505.
7. Wilms C, Walter J, Kaptein M, et al. Long-term outcome of split liver transplantation using right extended grafts in adulthood: A matched pair analysis. Ann Surgery 2006;244:865–872.
8. Humar A, Beissel J, Crotteau S, et al. Whole liver versus split liver versus living donor in the adult recipient: an analysis of outcomes by graft type. Transplantation 2008;85:1420–1424.
9. Merion RM, Campbell DA Jr. Split-liver transplantation: one plus one doesn't always equal two. Hepatology 1991;14:572–574.
10. Cardillo M, De Fazio N, Pedotti P, et al. Split and whole liver transplantation outcomes: a comparative cohort study. Liver Transpl 2006;12:402–410.
11. Gridelli B, Spada M, Petz W, et al. Split-liver transplantation eliminates the need for living-donor liver transplantation in children with end-stage cholestatic liver disease. Transplantation 2003;75:1197–1203.
12. Lee KW, Cameron AM, Maley WR, et al. Factors affecting graft survival after adult/child split-liver transplantation: analysis of the UNOS/OPTN data base. Am J Transplant 2008;8:1186–1196.
13. Busuttil RW, Farmer DG, Yersiz H, et al. Analysis of long-term outcomes of 3,200 liver transplantations over two decades: a single-center experience. Ann Surg 2005;241:905–916.
14. Wiesner RH, McDiarmid SV, Kamath PS, et al. MELD and PELD: application of survival models to liver allocation. Liver Transpl 2001;7:567–580.
15. Busuttil RW, Colonna JO 2nd, Hiatt JR, et al. The first 100 liver transplants at UCLA. Ann Surg 1987;206:387–402.
16. Busuttil RW, Goss JA. Split liver transplantation. Ann Surg 1999;229:313–321.
17. Jurim O, Shackleton CR, McDiarmid SV, et al. Living-donor liver transplantation at UCLA. Am J Surg 1995;169:529–532.
18. Ghobrial RM, Saab S, Lassman C, et al. Donor and recipient outcomes in right lobe adult living donor liver transplantation. Liver Transpl 2002;8:901–909.
19. Colombani PM, Lau H, Prabhakaran K, et al. Cumulative experience with pediatric living related liver transplantation. J Pediatr Surg 2000;35:9–12.
20. Adam R, Cailliez V, Majno P, et al. Normalised intrinsic mortality risk in liver transplantation: European Liver Transplant Registry study. Lancet 2000;356:621–627.
21. Burroughs AK, Sabin CA, Rolles K, et al. Three-month and 12-month mortality after first liver transplant in adults in Europe: predictive models for outcome. Lancet 2006;367:225–232.
22. Diamond IR, Fecteau A, Millis JM, et al. Impact of graft type on outcome in pediatric liver transplantation: a report From Studies of Pediatric Liver Transplantation (SPLIT). Ann Surg 2007; 246:301–310.
23. Merion RM, Rush SH, Dykstra DM, et al. Predicted lifetimes for adult and pediatric split liver versus adult whole liver transplant recipients. Am J Transplant 2004;4:1792–1797.
24. Ramirez S, Perez-Del-Pulgar S, Forns X. Virology and pathogenesis of hepatitis C virus recurrence. Liver Transpl 2008;14 (Suppl 2):S27–35.
25. Fisher RA, Kulik LM, Freise CE, et al. Hepatocellular carcinoma recurrence and death following living and deceased donor liver transplantation. Am J Transplant 2007;7:1601–1608.
26. Man K, Lo CM, Xiao JW, et al. The significance of acute phase small-for-size graft injury on tumor growth and invasiveness after liver transplantation. Ann Surg 2008;247:1049–1057.
27. Tamura S, Sugawara Y, Kaneko J, et al. Recurrence of primary sclerosing cholangitis after living donor liver transplantation. Liver Int 2007;27:86–94.
28. Zimmerman MA, Trotter JF. Living donor liver transplantation in patients with hepatitis C. Liver Transpl 2003;9:S52–57.
29. Gaglio PJ, Malireddy S, Levitt BS, et al. Increased risk of cholestatic hepatitis C in recipients of grafts from living versus cadaveric liver donors. Liver Transpl 2003;9:1028–1035.
30. Bozorgzadeh A, Jain A, Ryan C, et al. Impact of hepatitis C viral infection in primary cadaveric liver allograft versus primary living-donor allograft in 100 consecutive liver transplant recipients receiving tacrolimus. Transplantation 2004;77:1066–1070.
31. Humar A, Horn K, Kalis A, et al. Living donor and split-liver transplants in hepatitis C recipients: does liver regeneration increase the risk for recurrence? Am J Transplant 2005;5:399–405.
32. Becker NS, Barshes NR, Aloia TA, et al. Analysis of recent pediatric orthotopic liver transplantation outcomes indicates that allograft type is no longer a predictor of survivals. Liver Transpl 2008;14:1125–1132.
33. Abt PL, Rapaport-Kelz R, Desai NM, et al. Survival among pediatric liver transplant recipients: impact of segmental grafts. Liver Transpl 2004;10:1287–1293.

Discussion

DR LYNT B JOHNSON (Washington, DC): I would like to thank Dr Hong and Dr Busuttil for the privilege of discussing their paper and congratulate the authors on yet another large single center experience in liver transplantation.

Methods to successfully increase availability of donor organs are necessary given the continued shortage of organ donors. This shortage is particularly acute for patients with end-stage liver disease since there are not alternative methods for liver function replacement as there is for patients with end-stage renal disease.

The authors show that in their large single center experience the longterm overall patient and graft survival were similar between patients with split liver transplants, whole liver transplants, and live donor liver transplantation with a median follow-up of five years. But the adult ten-year patient survival was worse with split liver extended right grafts. And this leads to several questions for the authors.

The majority of split liver extended right grafts in adults were used for patients requiring urgent transplantation. Ordinarily, these patients would have access to adult whole liver grafts if they were status I or II liver failure. Does the center have an internal policy of splitting ideal donor grafts obtained in adult extended right graft along with a