

Outcome After Intestinal Transplantation From Living Versus Deceased Donors

A Propensity-matched Cohort Analysis of the International Intestinal Transplant Registry

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Objective: To describe the worldwide experience with living donation (LD) in intestinal transplantation (ITx) and compare short-term and long-term outcomes to a propensity-matched cohort of deceased donors.

Background: ITx is a rare life-saving procedure for patients with complicated intestinal failure (IF). Living donation (LD)-ITx has been performed with success, but no direct comparison with deceased donation (DD) has been performed. The Intestinal Transplant Registry (ITR) was created in 1985 by the Intestinal Transplant Association to capture the worldwide activity and promote center's collaborations.

Methods: Based on the ITR, 4156 ITx were performed between January 1987 and April 2019, of which 76 (1.8%) were LD, including 5 combined liver-ITx, 7 ITx-colon, and 64 isolated ITx. They were matched with 186 DD-ITx for recipient age/sex, weight, region, IF-cause, retransplant, pretransplant status, ABO compatibility, immunosuppression, and transplant date. Primary endpoints were acute rejection and 1-/5-year patient/graft survival.

Results: Most LDs were performed in North America (61%), followed by Asia (29%). The mean recipient age was: 22 years; body mass index: 19kg/m²; and female/male ratio: 1/1.4. Volvulus (N=17) and ischemia (N=17) were the most frequent IF-causes. Fifty-two percent of patients were at home at the time of transplant. One-/5-year patient survival for LD and DD was 74.2/49.8% versus 80.3/48.1%, respectively ($P=0.826$). One-/5-year graft survival was 60.3/40.6% versus 69.2/36.1%, respectively ($P=0.956$). Acute rejection was diagnosed in 47% of LD versus 51% of DD ($P=0.723$).

Conclusion: Worldwide, LD-ITx has been rarely performed. This retrospective matched ITR analysis revealed no difference in rejection and in patient/graft survival between LD and DD-ITx.

Keywords: intestinal transplantation, intestinal transplant registry, living donation, propensity-score matching

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Intestinal transplantation (ITx) is a life-saving procedure for patients suffering from intestinal failure (IF) and complications of long-term parenteral nutrition (PN). However, the outcome remains hampered by surgical complexity, graft susceptibility to ischemia/reperfusion, and rejection.^{1–3} Living donation (LD) holds the potential of improving ITx outcome by

better graft quality and HLA-matching, reducing cold ischemia time and suppressing waiting time.^{4,5} Gruessner and Sharp described the first standardized procedure for intestinal LD and transplantation in 1997.⁶ Since then, the technique has spread worldwide.^{5,7} Most of the literature on LD-ITx originates from case reports or single-center series until recently. Gruessner reported the first descriptive analysis of an international LD-ITx cohort based on literature.⁸

The International Intestinal Transplant Registry (ITR) was created by the Intestinal Transplantation Association in 1985 to centralize global ITx-activity. In 2014, the ITR was estimated to capture 95% of ITx-experience, from more than 27 countries.⁹ No matched comparison has been performed between LD and deceased donation (DD)-ITx. We aim to provide a descriptive analysis of the worldwide LD-ITx-experience and compare it with a propensity-matched DD-ITx cohort.

METHODS

Study-design and Population

The data of this retrospective, multicenter, observational and matched-cohort analysis were extracted from the ITR after approval by the Intestinal Rehabilitation and Transplantation Association (IRTA) (May 17, 2019). In all, 4156 ITx were performed between January 9, 1987 and April 17, 2019, divided into different graft types: isolated ITx, combined liver-ITx (cLi-ITx), multivisceral (MvTx), and modified multivisceral. Exclusion criteria were unknown donor type and unreliable data.

Descriptive Analysis

Data collected for descriptive analysis were: geographical distribution, donor/recipient age, waiting-list duration, recipient body mass index, recipient sex, pretransplant status, ABO compatibility, HLA mismatches (donor/recipient discrepancy for HLA-A, -B, -DR), graft type, simultaneous kidney transplant, indication, hospitalization, immunosuppression (induction/maintenance), acute rejection, 1-/5-year patient and graft survival, renal replacement therapy (RRT), serum creatinine level (last follow-up), posttransplant lymphoproliferative disease (PTLD) and infection. In addition, 2 subanalyses within the LD cohort were performed: (1) pediatric (<18 y) versus adult recipients; and (2) low-volume (N=1) versus medium-volume (N=1-6) versus high-volume (N≥6) centers (N=total volume/center).

Propensity-score Matching

From a total of 76 LD-ITx, 64 (86%) were isolated ITx. To reduce confounding, only this graft type was selected for matching. The other graft types [ITx-colon (n=7), cLi-ITx (n=5)] were excluded. The propensity score was calculated using the following data: recipient age, sex, weight, region, indication, graft number, pretransplant status [home, hospitalized, intensive care unit (ICU)], ABO compatibility, immunosuppression (induction/maintenance) and transplant year.

A multiple imputation model compensated for missing data: 100 imputed data sets per missing data were created based on matching variables and outcomes (patient survival and graft removal) to obtain a mean propensity score for each patient. Using a greedy matching algorithm with 0.7caliper, LD patients were matched to DD through the log-it of their mean propensity score (1:4 fashion).

Outcome

Primary outcome included acute rejection and 1-/5-/10-year patient survival. Secondary outcomes were patient status (last follow-up), graft function, cause of graft removal, 1-/5-/10-year graft survival, RRT, serum creatinine level (last follow-up), PTLD, and infection. Patient status was defined as alive (with functioning graft or graft removed) or dead/lost to follow-up. Graft function was defined as dependence (/not) on PN/intravenous fluids. Causes of graft loss/removal were patient death, rejection, PTLD, poor graft function, infection, surgical complications, and other.

Statistics

Descriptive data were analyzed using GraphPadPrism9.3.1. Matched-cohort analysis was performed using SAS9.4. Continuous variables were reported by median (min-range) for post-transplant hospitalization by mean ± SD. Categorical variables were characterized using absolute numbers/frequencies (%). Groups were compared using 2-sample *t*-test for continuous and χ^2 /Fisher exact for categorical variables. Statistics were 2-sided and assessed at a significance level of 0.05. No adjustments were made for multiple comparisons.

Among the analyzed outcomes, acute rejection, patient status, graft function, and reasons for graft removal were compared using χ^2 test. Patient/graft survival was assessed using Kaplan-Meier and log rank. Patients who survived with functioning grafts were censored at the last follow-up.

RESULTS

Study Population (Supplemental Digital Content, Figure 1, <http://links.lww.com/SLA/E824>)

The ITR recorded 4156 ITx, of which 69 were excluded for unknown donor type and 46 for unreliable data (LD cohort: 6 MvTx, 1 duodenum-inclusive graft, 1 unknown graft type; DD cohort: 21 unknown graft types, 17 grafts without ITx). The 4041 remaining were divided according to donor type: 76 LD-ITx (2%), 3965 DD-ITx (98%).

Demographic Analysis of Overall Living versus Deceased Donation Cohort (Supplemental Digital Content, Table 1, <http://links.lww.com/SLA/E822>)

Among 76 LD-ITx, 43 (57%) were performed in North America (31 in Illinois, Chicago), and 19 (25%) in Middle-East/Asia (see Figure, Supplemental Digital Content 1, <http://links.lww.com/SLA/E781> geographical distribution). Donor age [31.5years (18 to 61)] was higher compared with the DD cohort [(8 (0 to 65); $P<0.001$)]. Recipient age was similar for LD and DD [17.8 y (0.6 to 60) versus 16 (0 to 73.3); $P=0.746$]. Waiting-list time for LD was shorter compared with DD (0 months (0 to 32) versus 3.8 (0 to 131); $P=0.012$). Regarding pretransplant status, 39 (51%) LD recipients were home and 37 (49%) were hospitalized [3 (4%) in ICU]. In contrast, a larger proportion of DD cohort (71%) were home ($P<0.001$). Eighty-one percent of LD/recipient pairs were ABO-identical versus 85% in the DD cohort ($P=0.432$). Ninety-five percent of the LD/recipient pairs had ≤3 HLA mismatches versus 13% in the DD cohort ($P<0.001$). In the LD cohort, 71 (93%) received an isolated ITx (7 with colon) and 5 (7%) cLi-ITx. In contrast, 62% of the DD cohort received combined grafts (29% cLi-ITx, 22% MvTx, 10% modified multivisceral), whereas 38% underwent isolated ITx (6% including colon) ($P<0.001$). No kidneys were included with the LD versus 207 (5%) in the DD cohort ($P=0.032$). Leading transplant indications in LD were short bowel syndrome (SBS)

75% versus 59% in the DD cohort ($P=0.004$); and motility disorders 13% versus 14% in the DD cohort ($P>0.999$). Most frequent maintenance immunosuppression in LD were calcineurin inhibitors (86%) and steroids (82%) versus calcineurin-inhibitors (95%) ($P=0.057$) and steroids (79%) in DD ($P=0.246$). Three LD recipients (4%) were off immunosuppression versus 1% in the DD cohort ($P=0.03$).

Posttransplant hospitalization was 114 days (± 162) in the LD cohort versus 75 (± 75) in the DD cohort ($P=0.008$). The acute rejection rate was 50% in LD versus 44% in DD ($P=0.444$). One-/5-year patient survival was 74%/52% for LD versus 74%/54% for DD ($P=0.986/0.779$). One-/5-year graft survival was 61%/44% for LD versus 68%/46% for DD ($P=0.155/P=0.335$). No significant difference was observed between the 2 cohorts regarding renal function posttransplant (RRT: 9% vs. 6% ($P=0.485$); creatinine level: 0.88mg/dl versus 1.3mg/dl ($P=0.223$); for LD cohorts and DD cohorts, respectively). PTLT and infection rates were similar between both groups.

Pediatric versus Adult Recipients (Supplemental Digital Content, Table 2, <http://links.lww.com/SLA/E823>)

Of 76 LD, 39 (51%) recipients were pediatric (<18 y). Donor age was 27 years (19 to 56) and lower than in adult recipients (34 (19.2 to 60); $P=0.005$). Children were more often hospitalized pretransplant compared with adults (72% vs. 24%; $P<0.001$) and received less ABO-identical organs (68% vs. 93%; $P=0.036$). All 5 cLi-ITx recipients were pediatric. The main transplant indication was 72% SBS in pediatrics versus 78% in adults ($P=0.6$), followed by 15% motility disorders versus 11%, respectively ($P=0.737$). Posttransplant hospitalization was 192 days (± 214) in pediatrics versus 47 (± 39) in adults ($P=0.006$). The acute rejection rate was 48% in pediatrics versus 52% in adults ($P>0.999$); 1-/5-year patient survival for pediatrics and adults was 71%/52% versus 78%/52% ($P=0.444/P=0.684$); and 1-/5-year graft survival was 59%/46% versus 64%/41%, respectively ($P=0.580/P=0.794$). Dividing the study-period in 3 era, short-term outcomes improved over time (see Table/Figure, Supplemental Digital Content 2, <http://links.lww.com/SLA/E781> survival according to transplant-era).

LD-ITx Center Volume (Supplemental Digital Content, Table 2, <http://links.lww.com/SLA/E823>)

The LD-ITx-activity was distributed among 21 centers. From 76 LD-ITx, 8 (11%) were transplanted in 8 low-volume, 37 (49%) in 12 medium-volume, and 31 (41%) at a single high-volume center(s) (Illinois, CA). One-/5-year patient survival was 75%/50% for low-volume, 77%/53% for medium-volume, and 71%/50% for high-volume center(s) ($P=0.891/P=0.951$). One-/5-year graft survival was 37%/25% for low-volume, 67%/41% for medium-volume, and 61%/51% for high-volume center(s) ($P=0.375/P=0.373$).

Propensity-matched Analysis

Sixty-four LD-isolated ITx were matched with 1215 DD-isolated ITx (1:4 fashion). Within the LD-ITx cohort, 37 patients had 4 matches, 4 had 3 matches, 4 had 2 matches, 18 had 1 match, and 1 had no match (excluded), resulting in 63 LD-ITx versus 186 DD-ITx, for propensity-matched analysis. Demographic variables, indications and immunosuppression were similar between both cohorts (Table 1).

Primary outcome: Acute rejection rate was similar between both cohorts: 47% in LD-ITx versus 51% in DD-ITx ($P=0.723$).

One-/5-/10-year patient survival for LD and DD were 74%/50%/46% versus 80%/48%/39%, respectively ($P=0.826$) (Fig. 1A).

Patient status at last follow-up was identical between LD and DD: patients alive with functioning graft 27% versus 30%; alive with graft removed 19% versus 18%; and dead/lost to follow-up 54% versus 53%, respectively ($P=0.920$). No difference in graft function was observed (full function accounting for 70% in LD-ITx versus 54% in DD-ITx; $P=0.127$). Graft rejection was the first cause of graft removal in both groups (72% in LD versus 88% in DD; $P=0.082$). One-/5-/10-year graft survival was 60%/41%/33% for LD versus 69%/36%/26% for DD ($P=0.956$) (Fig. 1B). RRT was similar between both cohorts (8% LD vs. 5% DD; $P=0.621$) as well as creatinine level (0.88mg/dl LD vs. 1.1 mg/dl DD; $P=0.768$). No difference was shown regarding PTLT and infection.

DISCUSSION

In this ITR propensity-matched analysis, 63 LD-ITx were compared with 186 DD-ITx. Outcomes were similar for acute rejection, graft function, 1-/5-/10-year patient, and graft survival. This global experience suggests that LD is a valuable alternative (however not superior) to DD-ITx.

In 1964, one year after the first liver transplantation (Starzl, Pittsburgh, PA), Deterling transplanted at Boston Floating Hospital (USA) an ileal segment from a mother to a child who suffered from mesenteric thrombosis.^{10,11} This case was the first transplanted extrarenal LD organ.⁸ The child died early posttransplant.^{8,12,13} Another case of LD-ITx was done by Fortner (New York, USA) in 1970 between 2 sisters. The recipient was the longest survivor (79 days) after ITx in the pre-cyclosporine era.^{13,14} In 1988, Deltz (Kiel, Germany) reported on a 42-year-old female with mesenteric thrombosis who received an intestinal graft from her identical sister. She became PN-free and survived 5 years.¹⁵

The technique of LD was standardized in 1997.⁶ After preoperative evaluation of the vascular pedicle,^{7,16} 60 cm (<2 y) up to 180 to 200 cm (adults) of ileum is procured. The last 30 to 40 cm of ileum and ileocecal valve are left intact to maintain vitamin-B12 and bile salts resorption,⁷ avoid diarrhea, and bacterial overgrowth. Ileum is preferred over the jejunum for vascular anatomic reasons and for its adaptative capacity.¹⁷⁻²¹

In the recipient, the ileal graft artery and vein are anastomosed end-to-side to the aorta and caval vein, and intestinal continuity is restored under the protection of an ileostomy.⁸ Several single-center reports and even combined segmental liver and bowel LD were described.^{22,23} The ITR included 7 cases (1 before 1997) in which a colon segment was co-transplanted, which is not recommended given the importance of preserving the donor's ileocecal valve.

Data on LD-ITx outcomes remain scarce, apart from 11 LD-ITx reported by Benedetti²⁴ and recently 40 by Wu.²⁵ The latter included 15 children and 25 adults (6 identical twins LD-ITx). This series (not captured by ITR) reports a 1-/5-year patient and graft survival of 80%/66.7% and 72.4%/60%, which compares favorably to the ITR data.²⁵ The largest single-center analysis on DD-ITx, including 500 ITx/MvTx in 453 patients (1990-2008), reported 1-/5-/10-year survival of 85%/61%/42%.²⁶ In the long-term, these data seem comparable to the ITR survival.

All ITR LDs were adults. The relationship between LD and recipients is not captured, but it will be in the future. The main indication for LD-ITx was SBS with life-threatening PN complications, similar to the DD cohort. The registry included 5 pediatric cLi-ITx with severe intestinal and liver failure in urgent

TABLE 1. Propensity-Matched Cohort Analysis of Intestinal Transplantation From Living Versus Deceased Donors

	Statistic	LD-ITx (N = 63)	DD-ITx (N = 186)	P
Variables used for matching				
Age at transplant (y)	Median (min–max)(n)	20 (0.6–57)(63)	20 (0–73)(186)	0.406
Weight at transplant (kg)	Median (min–max)(n)	42 (5–93)(43)	45 (5–107)(126)	0.775
Recipient gender	—	—	—	0.954
Female	n/N (%)	26/63 (41)	76/186 (41)	—
Male	n/N (%)	37/63 (60)	110/186 (59)	—
Region	—	—	—	0.447
Europe	n/N (%)	6/62 (10)	13/180 (7)	—
North America	n/N (%)	38/62 (61)	126/180 (70)	—
Middle-East/Asia	n/N (%)	18/62 (29)	41/180 (23)	—
Indication				
Short bowel syndrome	n/N (%)	53/63 (84)	143/186 (77)	0.286
Motility disorder	n/N (%)	5/63 (8)	20/186 (11)	0.633
Tumor	n/N (%)	3/63 (5)	2/186 (1)	0.105
Other	n/N (%)	1/63 (2)	12/186 (6)	0.194
Mucosal Defect	n/N (%)	1/63 (2)	5/186 (3)	> 0.999
Retransplant	n/N (%)	0/63 (0)	4/186 (2)	0.575
Graft Number	—	—	—	0.972
1	n/N (%)	57/60 (95)	167/176 (95)	—
2	n/N (%)	3/60 (5)	9/176 (5)	—
Pretransplant status	—	—	—	0.138
Home	n/N (%)	33/63 (52)	112/185 (60)	—
Hospitalized	n/N (%)	29/63 (46)	73/185 (40)	—
ICU	n/N (%)	1/63 (2)	0/185 (0)	—
ABO Compatibility	—	—	—	0.838
Identical	n/N (%)	37/41 (90.2)	98/110 (89)	—
Compatible	n/N (%)	4/41 (9.8)	12/110 (11)	—
MIS				
None	n/N (%)	3/63 (5)	5/186 (3)	0.420
Anti-Lymphocyte	n/N (%)	19/63 (30)	49/186 (26)	0.557
Mycophenolate Mofetil Cept/Myfortic	n/N (%)	18/63 (29)	38/186 (20)	0.181
Tacrolimus	n/N (%)	52/63 (82)	159/186 (86)	0.574
Orthoclone	n/N (%)	6/63 (10)	12/186 (6)	0.416
Cyclophosphamide	n/N (%)	3/63 (5)	3/186 (2)	0.159
Cyclosporine	n/N (%)	3/63 (5)	6/186 (3)	0.572
Steroids	n/N (%)	51/63 (81)	143/186 (77)	0.501
Rapamycine	n/N (%)	6/63 (10)	17/186 (9)	0.928
IL-2 Antagonist	n/N (%)	9/63 (14)	25/186 (13)	0.866
Other	n/N (%)	14/63 (22%)	35/186 (19%)	0.557
Year of transplant	—	—	—	0.231
≤ 1994	n/N (%)	2/63 (3)	10/186 (5)	—
1995–1999	n/N (%)	15/63 (24)	32/186 (17)	—
2000–2004	n/N (%)	23/63 (36)	51/186 (27)	—
2005–2009	n/N (%)	14/63 (22)	56/186 (30)	—
2010–2014	n/N (%)	5/63 (8)	30/186 (16)	—
2015–2019	n/N (%)	4/63 (6)	7/186 (4)	—
Variables not used for matching				
Height at transplant (cm)	Median (min–max)(n)	160 (61–185)(41)	157 (58–193)(118)	0.730
BMI at transplant (kg/m ²)(> 18y)	Median (min–max)(n)	20 (14–29)(24)	22 (14–37)(65)	0.139
HLA mismatch	—	—	—	< 0.001
≤ 3	n/N (%)	36/39 (92)	21/112 (19)	—
> 3	n/N (%)	3/39 (8)	91/112 (81)	—
Primary outcome				
Acute rejection	n/N (%)	16/34 (47)	25/49 (51)	0.723
Patient Survival	—	—	—	0.826
1 y	Est. (95% CI)	74 (61;83)	80 (74;85)	—
5 y	Est. (95% CI)	50 (36;62)	48 (40;55)	—
10 y	Est. (95% CI)	46 (32;58)	39 (31;46)	—
Secondary Outcome				
Patient status	—	—	—	0.920
Alive (functioning graft)	n/N (%)	17/63 (27)	55/186 (30)	—
Graft removed	n/N (%)	12/63 (19)	33/186 (18)	—

TABLE 1. (Continued)

	Statistic	LD-ITx (N = 63)	DD-ITx (N = 186)	P
Death/Lost to follow-up	n/N (%)	34/63 (54)	98/186 (53)	—
Graft function	—	—	—	0.127
Full function	n/N (%)	21/30 (70)	56/103 (54)	—
Partial or no function*	n/N (%)	9/30 (30)	47/103 (46)	—
Cause for graft removal	—	—	—	0.082
Rejection	n/N (%)	13/18 (72)	45/51 (88)	—
PTLD	n/N (%)	1/18 (6)	2/51 (4)	—
Poor graft function	n/N (%)	1/18 (6)	2/51 (4)	—
Infection (non-PTLD)	n/N (%)	0/18 (0)	1/51 (2)	—
Surgical	n/N (%)	0/18 (0)	1/51 (2)	—
Other	n/N (%)	3/18 (17)	0/51 (0)	—
Graft Survival (nonsensitized to death)	—	—	—	0.956
1 Year	Est. (95% CI)	60 (47;71)	69 (62;75)	—
5 Year	Est. (95% CI)	41 (28;52)	36 (29;43)	—
10 Year	Est. (95% CI)	33 (21;45)	26 (20;34)	—
Kidney function	—	—	—	—
Need for RRT	n/N (%)	2/24 (8)	3/60 (5)	0.621
Dialysis	n/N (%)	1/2 (50)	1/3 (33)	> 0.999
Kidney transplant	n/N (%)	1/2 (50)	2/3 (67)	> 0.999
No RRT described	n/N (%)	0/2 (0)	0/3 (0)	> 0.999
Creatinine at follow-up (mg/dl)($> 18y$)	Median (min-max)(n)	0.88 (0.25–4.3)(11)	1.1 (0.58–3.05)(13)	0.768
Complications	—	—	—	—
PTLD	n/N (%)	1/38 (3)	7/116 (6)	0.680
Infection	n/N (%)	5/63 (8)	8/186 (4)	0.324

*Dependence on parenteral nutrition or intravenous fluids.

BMI indicates body mass index; CI, confidence interval; DD-ITx, deceased donation intestinal transplantation; ICU, intensive care unit; IL-2, interleukin 2; ITx, intestinal transplantation; LD-ITx, living donation intestinal transplantation; MIS, maintenance, immunosuppression; PTLD, posttransplant lymphoproliferative disease; RRT, renal replacement therapy.

need of transplant.^{8,23,27} Pediatric LD-ITx were more frequently in-hospital at the time of transplant and had a longer post-transplant hospital stay, suggesting that they were sicker compared with adults. No difference in rejection or patient/graft survival was observed between pediatrics and adults. Interestingly, no difference in outcome was seen between different volume centers. Most probably, centers with limited LD-ITx have well-established DD-ITx programs.

LD has intrinsic benefits that could lead to a better outcome. An LD graft is of excellent quality and does not suffer from additional trauma associated with brain death. Like for all LD-transplant procedures, the cold ischemia time (not captured by ITR) can be very short.²⁴ Another advantage of an elective LD-ITx is that the recipient may receive immunosuppression or desensitization protocols pretransplant.²⁸ Graft-recipient size-matching data were missing, but it can be anticipated that LD-ITx in adults will result in a better size-match since only one-third of the small bowel is transplanted, probably causing less difficulties to close the abdominal wall.^{23,29,30} In the case of LD-ITx, it is possible to enlarge the abdominal domain of the recipient pretransplant (eg, tissue expanders).³¹ Despite these theoretical benefits, our propensity-score analysis did not reveal a superior outcome (regarding rejection, graft function, graft, and patient survival).

The fact that HLA-matching would improve outcome was not supported by our analysis. Despite a better HLA-matching, the rejection rate was 47% in the LD cohort, and remained the leading cause of graft removal. However, Wu et al observed no acute or chronic rejection in 6 LD-ITx with fully HLA-matched donors. Therefore, it can be argued that LD should strongly be considered when a full HLA-matched donor is available, even pre-emptively.²⁵ Of note, 15 cases of successful LD-ITx between HLA-identical donor/recipient pairs have been reported

(see Table, Supplemental Digital Content 3, <http://links.lww.com/SLA/E781> overview reported HLA-identical LD-ITx).^{13,14,21,24,25,32–37}

Our data may suggest the utilization of LD-ITx in more ill patients, given their increased hospitalized status. It may represent the best option for infants who need a liver and intestine and may succumb before finding a size-matched DD. In clinical scenarios of immunodeficiency, bone marrow transplant and LD-ITx from the same donor may result in sustained graft tolerance.

Finally, LD may represent the only option for IF patients with no/limited access to DD-ITx. This probably explains the proportion of Asian LD-ITx, where DD is generally less supported for cultural/religious reasons.^{8,30,38}

The ITx field has tremendously changed with the widespread use of autologous reconstruction resulting in better long-term survival.³⁹ The introduction of GLP-2 analogues have significantly improved intestinal rehabilitation and will further increase the number of patients who can be weaned-off PN and avoid transplantation.⁴⁰ However, both strategies offer no solution for patients suffering from life-threatening PN complications that have always been the indication of ITx with its inherent risks of alloimmunity and long-term immunosuppression.

This study does not address donor safety since only limited ITR data are available. However, based on the reported series, the overall risk of intestinal donation (segmental bowel resection) is limited and probably lower than that for kidney/liver donation. No simultaneous living kidney and intestinal donation was reported, probably by concern for donor safety.^{41,42} There have been no reported deaths or major complications.^{43–48} Wu et al reported in 40 donors 1 intraoperative bleeding, 1 small bowel obstruction (conservatively treated), and 1 incisional hernia.⁴⁸ Donor's weight decreased during the first months

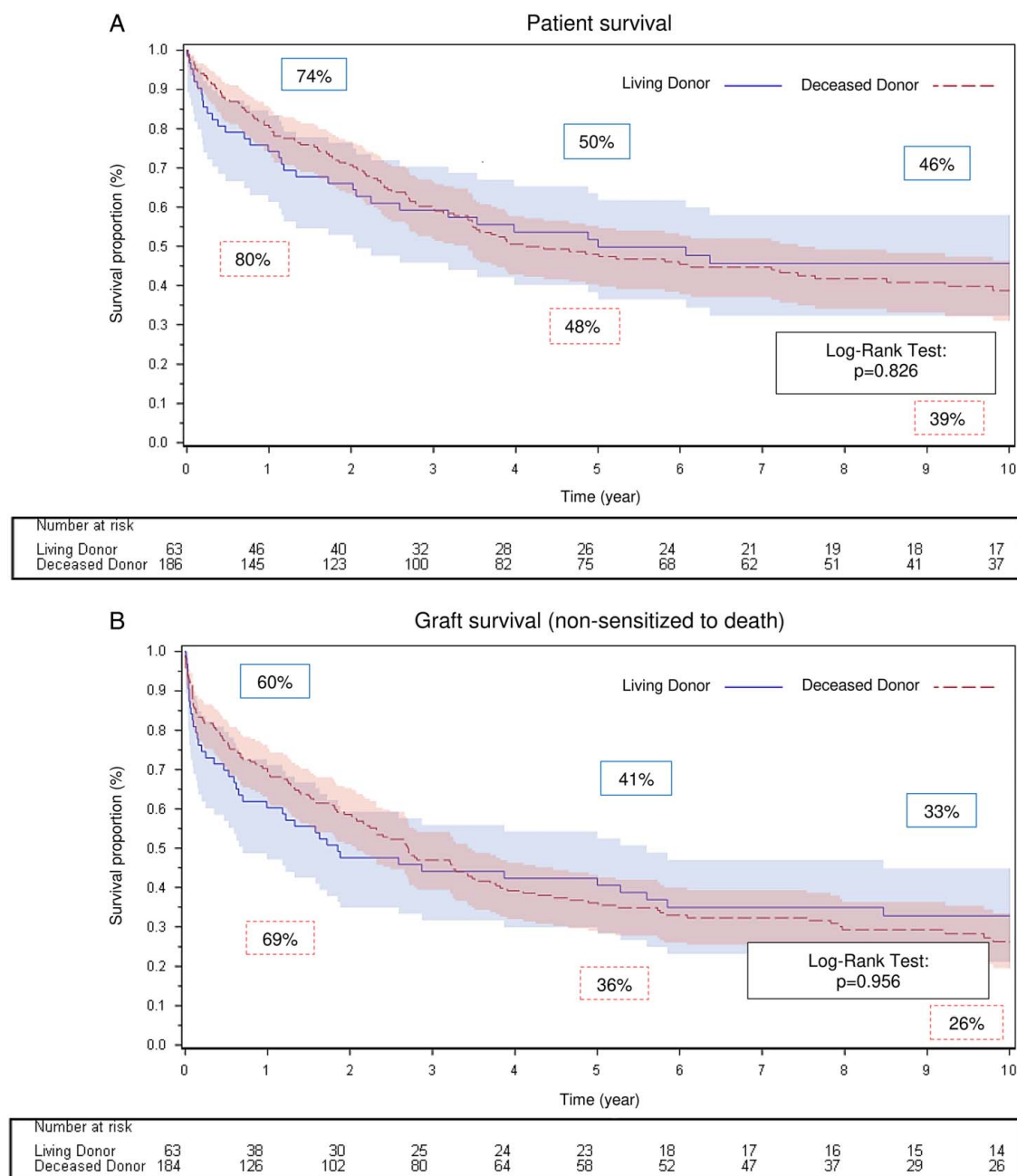


FIGURE 1. Patient and graft survival of matched living and deceased intestinal transplantation cohorts (Kaplan-Meier). Patient survival (A). Graft survival (non-sensitized to death) (B).

postoperatively, but was restored at 1 year. The most prevalent discomfort was an increase in bowel movements in 2 donors (5%) who were occasionally on antidiarrhea medication after 1 year. Vitamin-B12 was reduced until 3 years postdonation without clinical repercussion, and in some donors, a better metabolic profile was observed, confirming the experience of 25 LD-ITx published by Ghafari et al⁴⁷ and our own observation (Leuven). These results tend to confirm the safety of LD-ITx for the donor in the short term and long term.

This study – the first propensity-matched analysis on LDITx – has limitations inherent to its retrospective nature.

Although the propensity-score analysis did take hospital status into account, we cannot exclude that hospitalized LD recipients were sicker at the time of transplant and that potential confounders have been missed. The LD-ITx cohort was small, and a relatively high number of registry data, including details on complications, were missing.

CONCLUSION

Outcome after LD-ITx seems similar to DD-ITx for rejection and survival. LD-ITx offers a valuable option to

shorten the waiting time and provides access to life-saving ITx in countries with no/limited access to DD. Defining the optimal patient population for LD-ITx is an important clinical priority, and donor safety should be rigorously studied.

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DISCUSSANT

Andreas Tzakis (Weston, United States)

This is a comparison of living versus deceased donor intestinal transplantation. It is based on data collected from all over the world over the last 30 years. The main limitation of the study is that the existing data are limited, inconsistent and have been collected over a very long period during which so many variables changed. Nevertheless, there are clear conclusions. For one, there is no difference in the results between living and deceased donor transplants. Living donor transplants are now performed where access to deceased donors is very limited. Also, a supreme indication for living donation is between monozygotic twins because of the immunologic advantage.

The number of intestinal transplants has been decreasing worldwide over time. This is partly because patients are rescued with intestinal rehabilitation, which has improved dramatically. The other reason is that the long-term results of intestinal transplantation have not significantly improved. So, the question remains as to whether intestinal transplantation is still necessary, in view of the progress made in intestinal rehabilitation.

In 2023, intestinal transplantation is still necessary for a great number of patients. At the same time, there is a need for better results. The current study shows that the most common cause of graft failure is rejection. The most common cause of death is sepsis. What kind of rejection was observed: acute, chronic, or acute on chronic?

What is the sepsis due to: over-immunosuppression, a translocation in a failing graft, or multi-organ failure? How are the patients followed? Are they followed with endoscopies on clinical indications or by protocol? These data are missing from the registry, and consequently, from the manuscript. A central problem is that there is no accepted marker of intestinal rejection, and the diagnosis requires invasive testing.

Together with the group from Hospital Necker, we used serum citrulline for the purpose of early intestinal graft rejection. We showed that it correlates with intestinal injury, just as serum creatinine correlates with renal injury. If you did not use serum citrulline, then what did you use? Markers, such as free donor DNA, as well as combined detection of abnormal microRNA expression, can improve diagnostic accuracy, mainly in lower rejection grades.

I want to congratulate the authors for this review. They were able to extract clear conclusions from confusing data and gave us the opportunity to review the current status of intestinal transplantation.

Response From Laurens J. Ceulemans (Leuven, Belgium)

Dear Dr. Tzakis, thank you for your expert opinion. It is a privilege to have you as first discussant. Unlike our hypothesis, this paper demonstrates no significant survival advantage for living over deceased donation, and therefore, living donation is not a strategy per se that will improve the long-term outcome after intestinal transplantation. This should be critically acknowledged; however, I think that there are some specific indications for living donation: First, as a pre-emptive transplant in patients with TPN-induced, yet still reversible, liver disease, to avoid the need for a liver transplant; Second, in pediatric cases, when parents understand that TPN (Total Parenteral Nutrition) is not a static process, but that, over time, its complications continue to progress and can become life-threatening (eg, infections, loss of vascular access); Third, for small children in need of a combined liver-intestinal transplant, for whom a suitable donor will not be found in time; a combined liver-intestinal living donation can be the only life-saving option; Fourth, if a suitable HLA identical or twin donor is available, which has been reported to result in an excellent outcome, avoiding rejection (an overview of performed cases is provided in the supplement of the paper); Fifth, this immunological benefit may also play an important role in transplant candidates with high PRA or increased immunological risk who have an available related living donor; Sixth, for cultural reasons, in Asian countries, or for logistical reasons (as an example, in Leuven, we performed a living donation for a Polish lady, who had no access to deceased donation in her home country); Seventh, application of immunomodulatory strategies when optimal donor cell augmentation can be realized prior to transplant.

Regarding intestinal transplant in general, I believe that we should stop referring to this life-saving procedure as a negative option with poor long-term outcomes. Looking back on our own experience in Leuven and to ERA III of the Pittsburgh Protocol, a 5-year survival of 65 to 70% has been attained.

In Leuven, I am also responsible for the lung transplant unit, and in 2020, the International Society for Heart and Lung Transplantation reported a 5-year survival of 59%. Nevertheless, 5000 lung transplants are performed annually worldwide. This procedure is generally accepted as a life-saving solution for patients who are often less sick than the candidates that we evaluate today for intestinal transplantation. I think that we should continue to push the field further. For this, we should embrace what has been done in the past regarding the markers and try to find a way to differentiate between the diagnosis of rejection versus infection. Our absolute priority should be the development of immunomodulatory strategies (eg, T-reg therapy) from which the intestine could benefit the most and which can be optimally implemented in the setting of living donation.