Living Donor Intestinal Transplantation
Recipient Outcomes

Guosheng Wu, MD, PhD,*‡‡ Chaoxu Liu, MD,* Xile Zhou, MD, PhD,* Long Zhao, MD, PhD,* Weitong Zhang, MD,* Mian Wang, MD† Qingchuan Zhao, MD, PhD,* and Tingbo Liang, MD, PhD‡§∥

Objective: To examine outcomes of living-donor intestinal transplant (LDITx) recipients.

Background: LDITx is not routinely performed because of surgical risks to the donor and the potential inferior physiologic performance of the segmental graft. However, data on the effectiveness of LDITx are scarce.

Design: This retrospective cohort study included patients undergoing LDITx between May 1999 and December 2021 in intestinal transplant programs in 2 university-affiliated hospitals in China.

Results: Actuarial survival rates were 80%, 72.7%, 66.7% for patient and 72.4%, 63.6%, 60% for graft at 1, 3, and 5 years, respectively. Recipients with >3/6 HLA-matched grafts had superior patient and graft survival rates than those with ≤3/6 HLA-matched grafts (P <0.05). There were 12 deaths among the recipients, with infection being the leading cause (41.7%), followed by rejection (33.3%), surgical complications (16.7%), and others (8.3%). There were 16 graft losses among the recipients, with acute cellular rejection being the predominant cause (37.5%), followed by infection (25%), technical failure (12.5%), chronic rejection (12.5%), and others (12.5%). With an average follow-up of 3.7 (range, 0.6–23) years, the rates of acute and chronic rejection were 35% and 5%, and the rate of cytomegalovirus disease and post-transplant lymphoproliferative disease was 5% and 2.5%, respectively. Of the 40 patients, 28 (70%) are currently alive and have achieved enteral autonomy.

Conclusions: LDITx is a valuable treatment option for patients with end-stage intestinal failure. Improved immunosuppression, better HLA matching, and shorter cold ischemia times were associated with reduced rates of rejection, viral-mediated infection and improved graft survival.

Keywords: intestinal transplantation, living donor, recipient outcomes

From the *Intestinal Transplant Center, the First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China; †Department of Gastrointestinal Surgery, the First Affiliated Hospital, Fourth Military University, Xi’an, China; ‡Department of Hepatobiliary and Pancreatic Surgery, the First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China; §Zhejiang Provincial Key Laboratory of Pancreatic Disease, the First Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou, China; and ||Zhejiang University Cancer Center, Zhejiang University, Hangzhou, China. ✉liangtingbo@zju.edu.cn; guosheng_wu@zju.edu.cn.

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Becauso of the scarcity of organs and the growing transplant waiting list, organ donation from living donors has been developed as an attractive alternative to deceased donation. Currently, more than 6000 living-organ donations are reported each year in the United States and 30,000 worldwide.1,2 The kidney and liver are the most commonly transplanted organs from living donors. Accumulating evidence indicates that kidney transplantation from a living donor offers superior long-term patient and graft survival.3 Although technically successful and ethically permissible around the world, the use of living donation creates a unique situation in which the treatment approach involves not only the patient with end-stage organ disease, but also the living organ donor.

Most intestinal transplants have been undertaken using grafts procured from deceased donors.4,5 Unlike kidney and liver transplantation, the use of living donation for intestinal transplantation (ITx) has been limited as the deceased donor supply largely exceeds the current demand. According to recent data from the International Intestinal Transplant Registry (ITR), only 78 (1.9%) out of 4156 patients transplanted up to September 2019 worldwide have been reported as living donors.6 Despite potential risks to the donor, living-organ donation can offer substantial advantages over the deceased donation, particularly in terms of the elective nature of the procedure, better HLA matching, shorter cold ischemia times, and reduced waiting times. Moreover, the use of living donors can provide greater opportunity to implement desensitization protocols in the setting of highly sensitized ITx candidates.7–9 Also, in the areas where deceased donors are scarce, living donor ITx (LDITx) may become an important treatment option for patients who require ITx.

To date, there is a paucity of data regarding the safety and effectiveness of LDITx. The published results of retrospective case reports and case series are limited by the small numbers of patients, study methods, and a lack of donor and recipient long-term outcomes.5,10 Although preliminary outcomes appear encouraging, the role of LDITx has not yet been established. From 1999 to 2021, our team has performed 40 LDITx procedures and hereby we report our short-term and intermediate-term clinical outcomes of recipients after this procedure.

METHODS

In May 1999, an intestinal transplant program was initiated at the First Affiliated Hospital, the Fourth Military Medical University, Xi’an, and later joined by the First Affiliated Hospital, Zhejiang University School of Medicine, Zhejiang, China. We retrospectively analyzed all the patients who underwent LDITx between May 1999 and December 2021. All the clinical data were prospectively recorded by a single research
assistant. The study protocols were approved at each site by the institutional review board or ethics committee. All the donors provided written informed consent.

In most instances, LDITx was considered only for patients with irreversible intestinal failure and life-threatening complications of total parenteral nutrition (TPN) when a suitable deceased donor organ was not available. However, when an HLA-identical sibling or identical-twin living donor was available, transplantation was performed without serious TPN-related complications. In our practice, LDITx was also to be considered if the patient was unable or unwilling to undergo long-term TPN.

The process of living-donor selection and the techniques of a segmental bowel resection have been described previously.8,11 In brief, ~150 to 220 cm of the distal ileum was estimated, beginning from 20 cm from the ileocecal junction and bowel division was performed with a linear cutting gastrointestinal anastomosis stapler. The proximal end of the allograft was anastomosed to the remaining recipient duodenum or jejunum. A temporary ileostomy, 10 cm proximal to the ileocolostomy, was performed to monitor graft function and endoscopic surveillance biopsy.

Except for 4 patients in the early period, all others received induction therapy including a single dose of rituximab on day −2 and anti-thymoglobulin (ATG) on day −1. ATG was then continued for 3 to 5 doses until therapeutic levels of tacrolimus were obtained. The recipient was maintained on tacrolimus and mycophenolate mofetil with early steroid withdrawal. The target trough levels of tacrolimus were 15 to 20 ng/mL during the first month, 10 to 15 ng/mL during the next 6 months, and 8 to 10 ng/mL thereafter. Antiviral prophylaxis consisted of intravenous ganciclovir for 2 weeks, followed by oral valganciclovir for 6 to 9 months after transplant.

Surveillance ileal biopsies were performed twice a week. After hospital discharge, biopsies were performed bi-weekly for the initial three months and then bio-monthly within the first year. Acute cellular rejection (ACR) was diagnosed, based on standard histopathological and clinical criteria.12 Diagnosis of acute antibody-mediated rejection was based on the presence of circulating donor-specific antibodies (DSA), acute tissue damage, C4d deposition, and intestinal allograft dysfunction.13

The results are reported as ranges, means, SD, and proportions as appropriate. Quantitative parameters were compared by univariate analysis using paired or unpaired Student t test. Qualitative parameters were compared using the χ2 test. Survival was calculated using the method of Kaplan and Meier method. A P significance was set at P < 0.05.

RESULTS

Forty patients underwent LDITx consecutively. Twenty-five patients were adults aged 36.7 ± 13.1 years and weighed 49.3 ± 5.6 kg. Fifteen were children aged 11.4 ± 5.5 years and weighted 31.2 ± 18.5 kg. Recipients had been on TPN for 13.8 ± 8.9 months before transplantation (Table 1). The estimated length of the residual intestine was 25.4 ± 56.7 cm. The etiology of intestinal failure is shown in Figure 1.

The indications for LDITx are listed in Table 2. The most common indications were liver dysfunction, followed by central venous catheter-related sepsis/thrombosis, ultra-short bowel syndrome, desmoids associated with familial adenomatous polyposis, frequent severe dehydration, congenital mucosal disease, and others. In our series, 7 (17.5%) of 40 recipients had evidence of liver dysfunction before transplantation, with a median of serum total bilirubin level of 62 µmol/L (range, 45–125 µmol/L).

Pretransplant needle liver biopsies showed portal fibrosis without bridging in 6 patients and with bridging in 1. Of note, 7 patients were unable or unwilling to accept long-term TPN.

### TABLE 1. Characteristics of the Recipients and Donors

| Characteristics | Outcome (N = 40) |
|-----------------|-----------------|
| **Recipient**   |                 |
| Age (y)         | 27.3 ± 16.4     |
| M/F ratio       | 13:12           |
| Adult/child ratio | 25:15       |
| Height (cm)     | 155.2 ± 30.1    |
| Weight (kg)     | 42.5 ± 14.9     |
| Body mass index (kg/m²) | 16.6 ± 2.7 |
| Estimated remnant (cm) | 25.4 ± 56.7 |
| Duration of TPN before transplant (mo) | 13.8 ± 8.9 |
| IVC present, n (%) | 6 (15) |
| Prior abdominal operations per patient | 3.4 ± 2.8 |

| **Donor** |                   |
|-----------|--------------------|
| Age (y)   | 44.1 ± 11.5        |
| M/F ratio | 25:15              |
| Length of bowel resection (cm) | 184.8 ± 18.8 |
| Cold ischemia times (min) | 71.7 ± 25.7 |

| CMV serostatus |                   |
|----------------|--------------------|
| D−/R− | 5                  |
| D−/R+   | 12                 |
| D+/R+   | 12                 |
| D+/R−   | 8                  |

| Immunological variables |                   |
|-------------------------|--------------------|
| ABO compatible but not identical, n (%) | 2 (5) |
| HLA (A, B, DR) mismatches, n (%) | 0 | 6 (15) |
| ≤ 3 | 32 (80) |
| > 3 | 2 (5) |
| Anti-HLA donor-specific antibody, n (%) | 7 (15) |
| Positive cross-match, n (%) | 3 (7.5) |

FIGURE 1. The etiology of end-stage intestinal failure in 40 patients undergoing a living-donor intestinal transplant.
Donors were aged 44.1 ± 11.5 years and weighted 66.2 ± 10.9 kg. The estimated length of intestinal donation was 184.8 ± 18.8 cm. The ABO blood types of the donor and recipient were identical in 37 (92.5%), compatible but nonidentical in 2 (5%), and incompatible in 1 (2.5%).

The number of HLA matches [A, B, and donor-recipient (DR)] was 6/6 identical in 6 (15%), 5 to 3/6 in 32 (80%), and <3/6 in 2 (25%). The D/R pretransplant serostatus (+, positive; -, negative) was: D+/R+ in 10, D-/R+ in 10, D+/R- in 5, and D-/R- in 5 patients. Preformed DSA was detected in 7 (17.5%) of the 40 patients, of whom 3 presented a positive flow cross-match at the time of transplant (Table 1).

Twenty-eight (70%) of 40 patients are currently alive with a median follow-up of 3.7 (range: 0.6–23) years. Patient and graft survival after surgery are shown in Figures 2A–F. The actuarial patient survival rates at 1, 3, and 5 years were 80%, 72.7%, and 66.7%, respectively. There was no difference between the adult and pediatric LDITx recipients. Recipients with >3/6 HLA-matched grafts had superior patient and graft survival outcomes than those with ≤3/6 HLA-matched grafts (P < 0.05). There were 12 deaths among living donor recipients, with infection being the leading cause in 5 (41.7%), followed by rejection in 4 (33.3%), surgical complications in 2 (16.7%), and tacrolimus-related heart failure in 1 (8.3%). At the same time points, the actuarial graft survival rates were 72.5%, 63.6%, and 60%, respectively. There were 16 graft losses among LDITx recipients. The most common cause of graft loss was ACR in 6 (37.5%), infection in 4 (25.0%), technical failure in 2 (12.5%), chronic rejection in 2 (12.5%), and other causes in 2 (12.5%). Four patients died of a functioning allograft.

The postoperative complications are shown in Table 3. A total of 18 episodes of ACR were identified in 14 (35%) of 40 recipients with a mean of 1.3 ± 0.7 episodes per patient. Twenty-six patients (65%) did not experience any episode of ACR. Notably, 6 HLA-identical transplants experienced 0 episode of rejection, which was significantly different from the rates of non–HLA-identical transplants (0 vs. 41.2%, P = 0.05). The median time to the first episode of ACR was 54 days (range, 39–387 days). Most rejection episodes occurred within 1 year, particularly in the first 3 months after transplantation. The pathological severity of these rejection episodes was interpreted as minimal in 2, mild in 4, moderate in 5, and severe in 7 patients. Severe ACR occurred in 6 (15%) of the 40 patients. Four rejection episodes (26.7%) responded well to adjustment in the maintenance immunosuppression or additional pulsed tapered steroids. Five ACR episodes (33.3%) required ATG with resolution and 6 episodes (40%) required enterectomy. Two patients were diagnosed with mixed ACR and antibody-mediated rejection, both of which were associated with severe rejection and early graft loss. Chronic rejection occurred in 2 patients (5%).

Fifteen (31%) of the 40 recipients developed surgical complications, including intestinal anastomotic leaks in 4, intra-abdominal hemorrhage in 2, intestinal perforation in 2, intra-abdominal abscess in 2, vascular thrombosis in 1, and submucosal hemorrhage in 4. Ten (25%) of the 40 recipients underwent reoperations within 90 days of the initial procedure.

Currently, all recipients with functioning grafts were weaned off TPN. Enteral nutrition was initiated at a median of 14 days (range, 10–25 days), and the median weaning time was 27 days (range, 21–49 days). Thirty-six patients discharged from the hospital had completely discontinued parenteral nutrition.

There were 32 episodes of bacterial infections in 14 patients, with a median of 2.4 episodes per patient. The most common site of infection was the abdomen (46.9%, 15/32), followed by blood (25.0%, 8/32), lung (12.5%, 4/32), wound (9.4%, 3/32), and urine (6.2%, 2/32). Overall, there were 20 isolates, of which 45.0% (9/20) were gram-negative bacteria, 35.0% (7/20) were gram-positive bacteria, 10.0% (2/20) were anaerobes, and 10.0% (2/20) were Candida species.

Two (5%) of the 40 patients developed cytomegalovirus (CMV) disease: CMV enteritis in 1 and CMV pneumonitis in 1. The patient with CMV pneumonitis was successfully managed medically, but the other patient was lost to CMV enteritis treatment. Varicella zoster virus infections occurred in 2 (5.0%) and pneumocystis pneumonia in 1 (2.5%), all of which were successfully treated medically.

Epstein-Barr (EB) viremia occurred in 3 patients (7.5%). Of them, 1 patient developed post-transplant lymphoproliferative disease (PTLD), which presented with persistent intractable mesenteric adenopathy and ileal allograft bleeding. Unfortunately, the patient responded poorly to decreased immunosuppression and antiviral therapy and later died of sepsis.

Two patients (5%) underwent retransplantation after the loss of primary small bowel grafts. The times from graft explantation to retransplantation were 4 and 16 months, respectively. The first patient with strong DSA underwent a combined auxiliary partial liver and intestine from a deceased donor across a positive cross-match. Currently, he has a well-functioning graft 24 months after the procedure. The second patient underwent retransplantation with an isolated small bowel graft and has been doing well 8 months after the transplant.

Two patients received grafts from blood type compatible but nonidentical donors. Both blood type A recipients received intestinal grafts from O donors. The first patient had an uneventful postoperative course, currently with a well-functioning allograft 6.1 year after the procedure. Unfortunately, the second patient developed immunologic hemolytic anemia 2 weeks after transplant and later died of bacterial pneumonia. In our previous report, we described a living donor transplant from a blood type AB donor to a recipient with an excellent short-term outcome. Two years later, the recipient developed multiple episodes of ACR, was subsequently complicated with CMV enteritis and died of multi-organ failure 4 years after ITx.

In these series, no patients developed graft-versus-host disease after transplantation.
DISCUSSION

In this report, we describe 40 LDITx cases and evaluate their short and intermediate outcomes of the recipient. Our results show that the patient and graft survival rates of LDITx are comparable to those of deceased donor transplants. Although severe ACR poses a major clinical challenge, there is a significant decrease in the overall rate of acute and chronic rejection. The incidences of CMV disease and PTLD were considerably low and no graft-versus-host disease was observed. With an average follow-up of 3.7 years, 28 (70%) of the 40 patients are currently alive and all the surviving patients who retain their grafts have been completely off TPN and have achieved enteral autonomy.

The overall patient and graft survival rates (80%/72.5% and 66.7%/60% at 1 and 5 years, respectively) compared favorably with those previously reported from ITR and in a large series of isolated ITx from deceased donors (patient and graft survival around 80%/70% and 60%/50% at 1 and 5 years, respectively).\(^4\)\(^1\)\(^4\)\(^1\)\(^6\) Similar to previous reports, rejection and infection were the major cause of patient death and graft loss. The incidence of acute and chronic rejection in our cohort was lower than that reported in most large series of the isolated ITx from deceased donors.\(^1\)\(^4\)\(^1\)\(^7\) Given more than 50% ACR rates and as high as 10% to 20% chronic rejection, our findings are significant, especially in a highly immunogenic isolated ITx.

FIGURE 2. Kaplan-Meier patient and graft survival curve. A, Overall patient survival. B, Overall graft survival. C, Patient survival comparing adults versus children. D, Graft survival comparing adults versus children. E, Patient survival comparing >3/6 HLA match versus ≤3/6 match. F, Graft survival comparing >3/6 HLA match versus ≤3/6 match.
A combination of better HLA matching, shorter ischemia time, and induction immunotherapy may contribute to lower rejection rates. Despite a remarkable decrease in the incidence of acute rejection, the severe form of ACR, also called exfoliative rejection, remains a major hurdle in the management of such patients, especially in the early postoperative period. Previous reports showed the incidence of exfoliative rejection as high as 15%, associated with extremely high morbidity and mortality.\(^\text{18}\) In our study, similar rates of exfoliative rejection with poor outcomes were observed. Our results also showed that although most ACR episodes progressed from mild to moderate and severe over a few days, some occurred abruptly. The presence of a preformed DSA and positive cross-match at the time of transplant seems to be associated with risk factors, but these factors remain underdetermined due to the small number of participants. Therefore, it is critical to closely monitor intestinal graft by endoscopy and biopsy to detect early signs of ACR and aggressively treat any confirmed episode to avoid progression toward a higher grade. A novel diagnostic tool, optimal immunosuppressive regimen, and treatment strategy for exfoliative rejection will contribute to more favorable outcomes.

While this study followed the evolving indications for ITx,\(^\text{19}\) six patients underwent presumptive ITx because HLA-identical donors were available. Since the early days of kidney transplantation, recipients of HLA-identical kidney grafts from a living donor have had excellent short- and long-term outcomes.\(^\text{3}\) Our results further confirm that living donor intestinal allografts from HLA-identical siblings confer greater immunologic advantages in terms of complications related to acute and chronic rejection. Despite a relatively shorter follow-up, no chronic rejection has occurred in any of the six patients who achieved full enteral autonomy. Therefore, based on our preliminary results, we suggest that when an HLA-identical sibling donor exists, a presumptive ITx should be performed to avoid TPN-related complications.

One of the major significant findings is that low rates of viral-mediated morbidity and mortality. Early studies have reported an incidence of PTLD as high as 31% after ITx. More recently, the combination of aggressive monitoring of viral loads, antiviral prophylaxis, and preemptive therapy, has lowered the incidence of PTLD to 12% to 15%.\(^\text{20,21}\) Moreover, the current reported rates of CMV infection after ITx are as high as 20% and CMV tissue-invasive disease around 7% to 16%, still adversely affecting graft survival.\(^\text{22,23}\) In our series, less-intense maintenance immunosuppression, shorter ischemia-reperfusion damage, and reduced ACR episodes may account for the decreased incidence of viral infection, particularly EBV and CMV diseases. However, viral infection, especially in pediatric ITx continues to be a challenge, likely reflecting immature protective immunity against viral exposure to transplant.\(^\text{24}\) Future research is needed to delineate the duration of antiviral prophylaxis and to develop novel preventive and therapeutic strategies for tissue-invasive viral disease.

Similar to other reports, vascular thrombosis is a rare but serious complication of ITx. Due to the short length and small caliber of the donor’s mesenteric vessels, it is often technically challenging to perform proper vascular reconstruction, particularly in living donor pediatric ITx.\(^\text{25}\) The use of an interposition vascular graft can facilitate intestine implantation and reduce the risk of vascular complications. In our hands, either an autologous or cryopreserved allogenic internal iliac artery and vein is an ideal option for SMA and SMV reconstruction as they can provide adequate length and size for segmental bowel grafts.\(^\text{26}\)

In ABO-compatible nonidentical solid-organ transplantation, the incidence of passenger lymphocyte syndrome (PLS) has been reported to be 9%, 29%, and 70% for kidney, liver, and heart-lung transplants, respectively.\(^\text{27,28}\) The exact incidence of PLS after ITx is unclear. To date, 6 cases of PLS following ITx have been reported with mixed clinical outcomes and all blood type O grafts were transplanted into A recipients. The high number of antigenic epitopes expressed in type A red blood cells has been hypothesized to be a conceivable reason. Similar to published cases, our PLS case underwent transplants from blood type A to O but failed after aggressive therapies including steroids, rituximab, and plasma exchange. Early diagnosis and appropriate treatment are key for at-risk individuals.

Our study has certain limitations. These include its retrospective nature and follow-up of <3 years for approximately half of the patients in the cohort. Thus, our findings will need to be confirmed in a multicenter study with long-term follow-up.

Our results support the use of LDITx when a suitable deceased donor is not available. The identification of recipients who can benefit from this procedure will further improve clinical outcomes. More experience and extensive follow-up are strongly encouraged to maintain the viability of these potentially life-saving programs.

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**TABLE 3. Postoperative Complications of Living Donor Transplants**

| Characteristics | N (%) |
|-----------------|-------|
| Rejection       |       |
| ACR             | 14 (35) |
| ACR, severe     | 6 (15) |
| Acute ABMR      | 2 (5)  |
| ACR <1 year, n (%) | 16 (88.9) |
| ACR >1 year, n (%) | 2 (11.1) |
| Chronic rejection | 2 (5)  |
| Infectious complications |       |
| Bacterial infection | 14 (35) |
| Fungal infection  | 4 (10) |
| VZV             | 2 (5)  |
| CMV disease      | 2 (5)  |
| PTLD            | 1 (2.5) |
| PCP             | 1 (2.5) |
| Surgical complications |       |
| Intestinal anastomotic leak | 4 (10) |
| Intestinal perforation | 2 (5)  |
| Intra-abdominal hemorrhage | 2 (5)  |
| Intra-abdominal abscess | 2 (5)  |
| Vascular thrombosis | 1 (2.5) |
| Submucosal hemorrhage | 4 (10) |

ABMR indicates antibody-mediated rejection; PCP, pneumocystis pneumonia; VZV, Varicella zoster virus.

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