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Should We Exclude Live Donor Liver Transplantation for Liver Transplant Recipients Requiring Mechanical Ventilation and Intensive Care Unit Care?

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Background. Patients with acute and chronic liver disease often require admission to intensive care unit (ICU) and mechanical ventilation support before liver transplantation (LT). Rapid disease progression and high mortality on LT waiting lists makes live donor LT (LDLT) an attractive option for this patient population. **Methods.** During 2000 to 2011, all ICU-bound and mechanically ventilated patients receiving an LDLT (n = 7) were compared to patients receiving a deceased donor LT (DDLT) (n = 38). **Results.** Both groups were comparable regarding length of pretransplant ICU stay (DDLT: 2 [1-31] days vs LDLT: 2 [1-8] days; $P = 0.2$), days under mechanical ventilation (DDLT: 2 [1-31] days vs LDLT: 2 [1-5] days; $P = 0.2$), pretransplant dialysis (DDLT: 45% vs LDLT: 43%; $P = 1$) and model for end-stage liver disease score (DDLT: 33 ± 8 vs LDLT: 33 ± 10; $P = 0.911$). Live donors median evaluation time was 24 hours (18-561 hours). As expected, median time on waiting list was significantly lower in the LDLT group (DDLT: 13 [0-1704] days vs LDLT: 10 [1-33] days; $P = 0.008$). Incidence of postoperative complications was numerically, albeit not significantly higher in the DDLT versus LDLT (68% vs 29%; $P = 0.08$). No difference was detected between LDLT and DDLT patients regarding 1-year (DDLT: 76% vs LDLT: 85%), 3-year (DDLT: 68% vs LDLT: 85%), and 5-year (DDLT: 68% vs LDLT: 85%) graft and patient survivals ($P = 0.41$). No severe donor complication occurred after live donation. **Conclusions.** The LDLT may provide a faster access to transplantation and therefore, offers an alternative treatment option for critically ill patients requiring ICU care and mechanical ventilation support at the time of transplantation.

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Liver transplantation (LT) is a successful and well-established therapy for patients with end-stage liver disease (ESLD). The reported 1-year survival after LT exceeds 80% for all patient populations.[1] However, the number of patients on LT waiting lists exceeds by far the number of available grafts. In most regions, around 20% to 30% of

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patients will die on the LT waiting list. Therefore, there is an urgent need for novel strategies to increase the donor pool, especially for critically ill patients that urgently require a LT.

Live donor LT (LDLT) is an attractive option to overcome this problem.[2,3] Live donor LT may provide a faster access to transplantation, shortening LT waiting times and thus, improving overall survival. However, LT outcome in critically ill patients requiring intensive care unit (ICU) management, intubation with mechanical ventilation, and often multiorgan failure is controversial.[4,5] The increased risk of postoperative mortality of these critically ill patients and the ethical concerns of an urgent donor work-up makes it unclear if LDLT is an appropriate alternative for this patient population. Moreover, many centers are reluctant to even offer LDLT to patients who are hospitalized in the ICU and require mechanical ventilation support.[6,7]

It has been suggested that patients with decompensated liver disease and high model for end-stage liver disease (MELD) scores should not be considered as candidates for LDLT.[8,9] These reports indicate that the risk taken by the live donors exceeds the benefits achieved by the recipients. However, the lack of data in this field limits transplant physicians, our patients, and their potential live donors to make an informed decision about LDLT as an option for critically ill patients.

To the best of our knowledge, evidence supporting the use of LDLT to treat decompensated liver disease in patients under mechanical ventilation support and ICU care at the time of transplant is scarce. Herein, we report a single-center experience of LDLT for the treatment of decompensated liver disease in adult patients requiring mechanical ventilation and ICU care at the time of transplant. The outcome of LDLT in critically ill patients was compared to the outcome of patients receiving deceased donor LT (DDLT) under the same circumstances. In this study, we were able to prove that LDLT offers a faster access to transplantation for critically ill patients.

MATERIALS AND METHODS

Study Design

Using a prospectively collected database, all adult patients receiving a LT at our institution between November 2000 and June 2011, were retrospectively analyzed. All decompensated liver disease patients requiring ICU management and mechanical ventilation at the time of LT were identified. Therefore, all critically ill patients who received a LDLT (n = 7) while being under mechanical ventilation and ICU care were compared to all ICU bound and ventilated patients receiving a DDLT (n = 38) during the same period.

University of Toronto Live Donor LT Listing Policies

At our institution, all patients on the liver transplant waiting list, irrespective of their disease etiology, disease severity, and MELD score are offered the opportunity to consider LDLT. Taking into account our program's results,[10,11] live donors and recipients are informed about their expected outcome after transplantation. In addition, based on past and recent data,[3,12] patients are advised that the overall survival rate for LDLT and DDLT is similar at our institution.

Recipients' Characteristics

The following recipient data were identified: age, sex, indication for LT, time on waiting list, biochemical profile, MELD score, days in ICU, and on mechanical ventilation support before LT. In addition, we collected information regarding inotropic drugs requirement to maintain adequate blood pressure and need of dialysis before transplantation. Of note, in our series, LT was only considered in ICU intubated patients if they fulfilled the following criteria: fraction of inspired O_2 (FiO_2), ≤40%; with a positive end-expiratory pressure, ≤10 mm Hg; low pressor requirements (norepinephrine, 0.10 μg/kg per minute; vasopressin, 2.4 μ/h); and absence of active infection. Patients not fulfilling these criteria were declined LT.

Donor, Graft, and Perioperative Characteristics

Live donor hepatectomies and organ procurement for deceased donations were performed as previously described.[11,13] Data corresponding to donor, graft, and perioperative characteristics were collected: age, sex, cold ischemia time and warm ischemia time, and type of biliary anastomosis. In patients receiving a live donor graft, duct-to-duct anastomosis was the preferred type of biliary reconstruction. Roux-en-Y biliary reconstruction was used for patients receiving a graft with multiple bile ducts. Also, we identified patients receiving antibody induction therapy, the type of agent used, and the postoperative immunosuppressive regimen. Baseline immunosuppression regimen was based either on Tacrolimus or Cyclosporine.

In addition, in the LDLT group, the time needed to evaluate each potential live donor was analyzed. The work-up time was defined as the period between the initiation of the first potential donor evaluation and the time in which donor surgery was initiated. Live donor outcomes were evaluated. In each case, we analyzed their short- and long-term complications.

Outcome After Transplantation

Biochemical markers of preservation/reperfusion injury (peak values of aspartate aminotransferase and alanine aminotransferase within 48 hours of transplantation) were recorded. Liver graft function was evaluated by measuring the decrease of international normalized ratio (INR) and bilirubin after transplantation.

Recipients' surgical outcomes were measured by the length of their postoperative ICU and hospital stay, as well as by the postoperative complications and mortality occurring in the first 30 days after transplantation. All major complications within 30 days were identified in donors and recipients. Postoperative major complications were defined as grades 3b to 5 (ie, requiring surgical intervention under general anesthesia or ICU admission or causing death, respectively) of the Dindo-Clavien validated classification system.[14] Also, all episodes of postoperative bacterial infections were registered. Incidences of biliary complications during the entire follow-up were identified for comparison between both groups. The incidence of acute cellular rejection episodes occurring within the first year after transplantation was also compared between both groups. Long-term outcome was analyzed by actuarial graft and patient survival at 1, 3, and 5 years.

Statistical Analysis

Data analysis was performed with the SPSS 22 statistical package (IBM, Chicago, IL). Data were presented as mean and standard deviation or with median and range when an abnormal distribution was present. Continuous variables were compared with Student *t* test when normally distributed. For abnormal distributions, a Mann-Whitney *U* test was used. χ^2 Test with Fisher correction was used to

evaluate differences between categorical variables. All tests were 2-tailed. Graft and patient survivals were calculated by the Kaplan-Meier method and compared with the log-rank test. Event for graft survival outcome was "graft failure" or "no graft failure." Graft failure was defined as death or retransplantation. Outcome for patient survival was "death" or "alive." A P value of 0.05 or less was considered as statistically significant.

RESULTS

During the study period, 1314 adult patients received a LT at the Multiorgan Transplant Program of the Toronto General Hospital, University of Toronto. Among these, 45 (3.4%) patients were transplanted while receiving ICU care and on mechanical ventilation support. From this group, 7 patients (16%) received a LDLT constituting our study group (LDLT group). The LDLT group (n = 7) was compared to the remaining 38 patients treated with a DDLT (DDLT group) under the same clinical conditions and during the same period. Median follow-up time after LT was 41 versus 48 months for the DDLT and LDLT patients, respectively (P = 0.35).

Recipient's Demographics and Preoperative Status

As shown in Table 1, both groups were comparable in terms of age and sex. Additionally, there was no difference between the DDLT and LDLT group regarding preoperative biochemical profile. Disease severity, measured by MELD score, days in ICU before transplantation, days under mechanical ventilation support, and need of dialysis before transplantation were comparable in both groups (Table 1). However, need of inotropic drug requirement before transplantation was significantly higher in the LDLT group (DDLT: 42% vs LDLT: 100%; P = 0.009). At time of intubation, median Glasgow coma score for the LDLT group was 7 (3-10). Although in the LDLT group, all patients required endotracheal intubation and mechanical ventilatory support for airway protection due to severe encephalopathy, in the DDLT group, this reason for endotracheal intubation was present in 71% of the patients (DDLT: 27 patients vs LDLT: 7; P = 0.44). In the rest of DDLT group, the causes of endotracheal intubation were distributed among the following: hemodynamic decompensation due to severe gastrointestinal bleeding in 4 cases (11%), respiratory insufficiency due to decompensated acute renal failure in 6 patients (16%), and bowel perforation and consequent sepsis in 1 patient (2%). Of note, in the last patient, the bowel perforation and consequent sepsis was the reason for ICU admission and intubation but at the time of transplantation the patient had already received the adequate treatment and had cleared his infection, allowing us to proceed with LT.

Fulminant hepatic failure (FHF) as cause of LT was similar between both groups (DDLT: 13 patients vs LDLT: 4 patients; P = 0.39). In those cases, the etiology of the FHF was unknown in 62% of the population. The remaining reasons of FHF were: drug toxicity (20%), autoimmune hepatitis (12%), and acute Budd-Chiari syndrome (6%) (Figure 1). As expected, median time on the waiting list was significantly lower in the LDLT group (DDLT: 13 (0-1704) days vs LDLT: 10 (1-33) days; P = 0.008).

Donor, Graft, and Perioperative Characteristics

Donor characteristics were similar between the DDLT and LDLT groups (Table 2). As expected, mean cold ischemia time was significantly lower in the LDLT group (DDLT: 494 minutes vs LDLT: 59 minutes; P = 0.0001). In contrast, mean warm ischemia time was similar in the DDLT and LDLT groups (45 minutes vs 32 minutes, respectively; P = 0.46). The LDLT was performed with a right lobe graft in all cases. None of the live donor grafts included the middle hepatic vein, and all had a graft-to-recipient weight ratio of 0.8 or greater. As expected, bile duct reconstruction using a Roux-en-Y reconstruction was significantly more common in the LDLT group (DDLT: 16% vs LDLT: 57%; P = 0.04). There was no difference between both groups regarding the use of thymoglobulin and basiliximab as induction agents (P = 0.4 and P = 0.34, respectively) (Table 2). Tracrolimus as immunosuppression-based regimen was the most commonly used (DDLT 61% vs LDLT 71%; P = 0.69).

Median work-up time needed for live donor evaluations was 24 (18-561 hours) hours. In 3 of 7 patients, the work-up was done within 24 hours. In 1 patient, it was done in 2 days, and in the other 2 patients, the donor work-up time was 16 and 24 days, respectively. As part of our donor

TABLE 1.

Preoperative characteristics of ICU patients on mechanical ventilation that received either DDLT or LDLT

	DDLT, n = 38	LDLT, n = 7	*P*
Age, y[a]	48 (±12)	44 (±16)	0.47
Male sex, %	16 (42)	4 (57)	0.68
INR[a]	3.41 (±1.79)	4.06 (±4.12)	0.53
Creatinine, μmol/L[a]	150 (±105)	152 (±136)	0.707
Bilirubin, μmol/L[a]	137 (±186)	189 (±163)	0.24
MELD at transplantation (without exception points)[a]	33 (±8)	33 (±10)	0.911
Pretransplant dialysis, %	17 (45)	3 (43)	1
Need of mechanical ventilation, d	2 (1-31)	1 (1-5)	0.209
Inotrope requirement (% patients)	16 (42)	7 (100)	0.009
ICU days before transplantation, d	2 (1-31)	2 (1-8)	0.207
FHF, %	13 (34)	4 (57)	0.39
Time on waiting list, d[b]	13 (0-1704)	10 (1-33)	0.008

[a] Mean and standard deviation.

[b] Median and range.

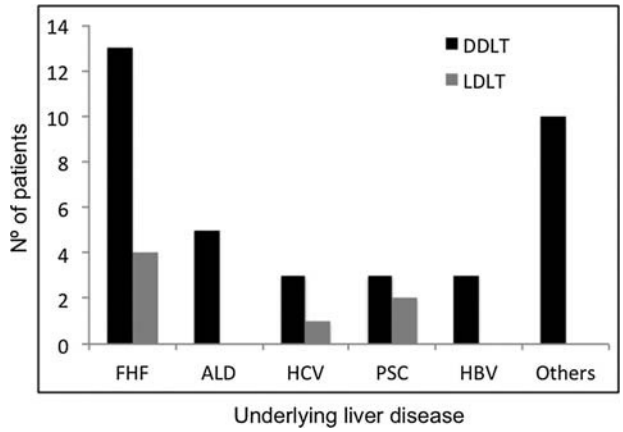

FIGURE 1. Indication for LT in the DDLT an LDLT groups. ALD, alcohol liver disease; HCV, hepatitis C virus; PSC, primary sclerosing cholangitis; HBV, hepatitis B virus.

evaluation process, all potential donors were offered in a confidential discussion the opportunity to withdraw from the live donation process by the live donor team providing a medical contraindication to the recipient and the family.

Early Outcome After Transplantation

As markers of reperfusion injury, peak levels of aspartate aminotransferase and alanine aminotransferase within 48 hours after transplantation were significantly lower in the LDLT patients (Table 3). Liver function was measured by the INR and bilirubin decrease within the first week after transplantation (pretransplant and day 7 difference). As shown in Table 3, INR and bilirubin decrease was similar in both groups. None of the live donor liver transplant patients developed a small for size syndrome in the postoperative course.

Incidence of bacterial infections after transplantation was not different between both groups (Table 3). Even though there was no statistical difference between both groups, DDLT had a trend toward higher incidence of major complications (Dindo-Clavien 3b, 4, or 5) occurring within the first 30 days after transplantation (DDLT: 26 (68%) vs LDLT: 2 (29%); $P = 0.086$). Although 13 (34%) patients in the DDLT group required a relaparotomy due to either an intra-abdominal sepsis or postoperative bleeding, only 1 (14%) patient required a relaparotomy in the LDLT group ($P = 0.4$). The 30-day mortality rate after transplantation was also comparable between groups (DDLT: 4 patients vs. LDLT: 1 patient; $P = 1$). The DDLT and LDLT recipients had the same ICU (DDLT: 6 [0-93] vs LDLT: 4 [1-6] days; $P = 0.26$) and hospital stay (DDLT: 33 [0-279] vs LDLT: 25 [4-43] days; $P = 0.24$) after transplantation.

The incidence of biliary complications occurring at any time point after transplantation was compared. Of note, all biliary complications occurred during the first year after transplantation. All biliary complications in this series presented as anastomotic strictures, and no bile leaks were identified. No difference was observed regarding the incidence of posttransplant biliary strictures between both groups (DDLT: 3 patients vs LDLT: 1 patient; $P = 0.5$).

Long-Term Outcome After Transplantation

The incidence of acute cellular rejection episodes occurring within the first year was not significantly different between both groups (DDLT: 34% vs LDLT: 14%; $P = 0.4$). No patient in the entire series needed a retransplantation. As shown in Figure 2, the 1-, 3-, and 5-year graft and patient survival was not statistically different for DDLT (73%, 68%, 68%) and LDLT (85%, 85%, 85%) patients ($P = 0.41$).

Live Donor Outcomes After Live Donor Hepatectomy

All donors experienced a full recovery after surgery and returned to their normal activities enjoying of good health. Median hospital stay for live donors was of 6 (5-9) days. In the entire series, none of them required admission to the ICU after surgery. No major complications occurred in their postoperative course (Dindo-Clavien ≥3b). Only 2 patients presented with a minor complication during the first 30 days after transplantation. One donor developed a urinary tract infection that was managed in an ambulatory manner with oral antibiotics. The second patient developed a pleural effusion that was drained under local anaesthesia.

DISCUSSION

We report the use of LDLT for the treatment of adult patients suffering from decompensated liver disease and who were on mechanical ventilation and ICU care at the time of transplantation. We demonstrate in a single North American institution experience that LDLT is an attractive treatment option for this patient population and can be performed with excellent outcome in critically ill patients. In addition, we were able to prove that LDLT offers a faster access to transplantation in comparison to DDLT, keeping donor morbidity to a minimum.

Shortage of liver grafts is the most important factor leading to deaths of patients on LT waiting lists. Therefore, this organ shortage has triggered the interest of increasing the donor pool by LDLT.[2] Decompensated liver disease patients have a very poor prognosis without LT.[15] In addition, the usual progressive decompensation and consequent multiorgan failure that these patients suffer once they are admitted to ICU translates in their benefit of proceeding with transplantation as soon as possible.[16,17] Hence, LDLT is an attractive option because live donor work-up can be accelerated, allowing a faster access to transplantation for this patient population.

To the best of our knowledge, there are no series in the English literature referring to the use of LDLT in patients requiring ICU care and mechanical ventilation support at the time of transplant. Most reports referring to the use of LDLT for the treatment of critically ill adult patients are focused on an acute liver failure scenario.[18-20] In 2002, Testa et al[2]

TABLE 2.

Donor and rerioperative characteristics of patients receiving an LT while being in ICU on mechanical ventilation

	DDLT, n = 38	LDLT, n = 7	*P*
Donor age, y[a]	45 (±15)	41 (±10)	0.48
Donor male sex, %	22 (58)	2 (29)	0.11
Cold ischemia time, min[a]	494 (±159)	59 (±22)	0.0001
Warm ischemia time, min[a]	45 (±14)	32 (±6)	0.46
Roux-en-Y, %	6 (16)	4 (57)	0.04
Antibody induction, %	30 (79)	5 (71)	0.61
Tacrolimus, %	23 (61)	5 (71)	0.69
Cyclosporine, %	23 (61)	3 (43)	0.43

[a] Mean and standard deviation

TABLE 3.

Postoperative outcome after LT in ventilated ICU patients

	DDLT, n = 38	LDLT, n = 7	*P*
PNF	0	0	—
AST peak, U/L[a]	1229 (±1525)	539 (±337)	0.019
ALT peak, U/L[a]	977 (±1020)	389 (±278)	0.046
INR peak[a]	2.78 (±0.81)	2.69 (±0.98)	0.78
Bilirubin peak, μmol/L[a]	253 (±243)	237 (±155)	0.73
INR decrease, pretransplantation day 7[a]	2 (±1.82)	2.93 (±4.06)	1
Bilirubin decrease (pretransplantation day 7), μmol/L[a]	9 (±232)	94 (±186)	0.3
Need of mechanical ventilation after transplantation, d	3 (1-46)	2 (1-6)	0.54
Dindo-Clavien 3b,4,5 within 30 days (% patients)	26 (68)	2 (29)	0.086
Relaparotomies	13 (34%)	1 (14%)	0.4
Bacterial infections within 30 d, %	15 (39)	1 (14)	0.392
Bacterial pneumonia within 30 d, %	11 (29)	0	0.168
30-day mortality, %	4 (11)	1 (14)	1
ICU stay, d†	6 (0-93)	4 (1-6)	0.26
Hospital stay, d[b]	33 (0-279)	25 (4-43)	0.24
Biliary complications within 1 year, %	3 (8)	1 (14)	0.5
Biliary strictures within 1 year, %	3 (8)	1 (14)	0.5
Acute cellular rejection episodes within first year (% patients)	13 (34)	1 (14)	0.4
Retransplantation (%)	0	0	—
1-/3-/5-year graft survival (%)	73/68/68	85/85/85	0.41
1-/3-/5-year patient survival (%)			

[a] Mean and standard deviation.

[b] Median and range.

PNF, primary nonfunction; AST, aspartate aminotransferase; ALT, alanine aminotransferase.

published the only case-series of LDLT for the treatment of decompensated chronic ESLD. In this series, the authors report 7 adult patients with decompensated chronic ESLD treated with LDLT. In this series, decompensated chronic ESLD was defined as a MELD score greater than 30 or a Child-Pugh-Turcotte score greater than 13. However, of the 7 patients included in their study, only 2 where in ICU care at the time of transplantation, and only 1 patient was on mechanical ventilation support. In addition, from the entire series, only 1 patient was in renal failure requiring renal replacement therapy. With a mean follow-up time of 15 months, the authors report an overall survival of 43%. Four of the 7 patients died within the first 200 days after transplantation.

In a previous report,[21] we were able to demonstrate the benefit of live donation for high MELD score patients. In the current study, we demonstrated that LDLT can be safely performed in critically ill patients requiring ICU management and mechanical ventilation support at the time of transplantation. Patients in both groups had comparable preoperative status and disease severity while waiting for LT (Table 1). Of note, in our series, all LDLT patients required intubation to protect the airway due to their advanced degree of encephalopathy. It is unclear what would be the outcome after LDLT for patients requiring mechanical ventilation support for other indications. However, excellent outcomes, not only in the short term but also in the long term were achieved. Need of mechanical ventilation support and bacterial pneumonia infections after transplant was not different between both groups.

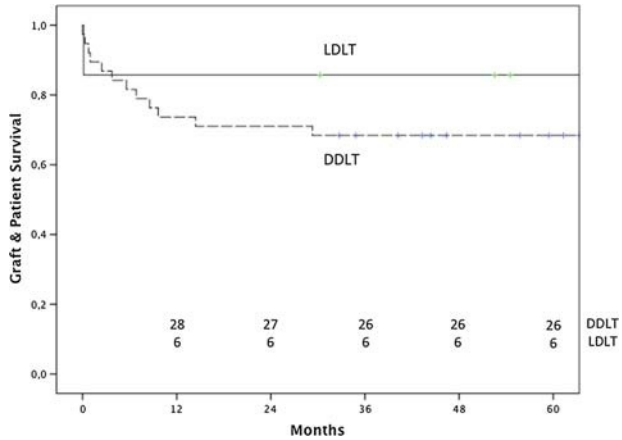

FIGURE 2. Graft and patient survival for intubated ICU patients after either DDLT or LDLT (*P* = 0.41).

Moreover, similar postoperative graft function, major complication rates, 30-day mortality, and survival were achieved in LDLT and DDLT recipients (Table 3). The ICU-dependent intubated patients are at great risk to become *too* sick for transplantation and drop off the transplant waiting list. Having a live donor available offers a significant benefit in this regard because the patient can proceed with transplant quickly, minimizing the risk of becoming not transplantable. In this series, median work-up time for potential live donors was of only 24 hours. We believe that this fast donor evaluation had an impact in the significantly shorter waiting time of the LDLT group (Table 1).

A shorter waiting time could possibly improve outcome after transplantation. Regardless of the recipient's clinical status and urgency for transplantation, the donor evaluation process must follow the same exact steps as for nonurgent cases. In this scenario, donor work-up is done in a limited period; therefore, coercion cannot be completely ruled out. However, great care must be taken to minimize the risk for

donor coercion. In our series, the median time between the initiation of donor evaluation and the recipient's transplantation was only 24 hours. Although faster than usual, donor work-ups were performed following the exact same protocols used for regular live donor evaluations done at our institution. All donors were assessed by 2 independent internal medicine physicians (not involved in the care of the potential recipient), 2 surgeons, and 1 transplant psychiatrist. In addition, all donor assessments were performed in single-person interviews away from the recipient treatment side. In these interviews, special attention was paid to detect any signs of coercion. Furthermore, it is policy in our center to offer the potential live donor a confidential way to opt out of the donation process by providing a medical reason to the recipient and the family.

At our institution, as soon as patients are active on the LT waiting lists for deceased donation, they are encouraged to consider LDLT, irrespective of their disease severity and etiology.[3,21] Potential donors and recipients are advised of our center's short- and long-term outcomes after LDLT. Thus, they can make an informed decision, whereas they opt for live donation or wait for a deceased donor. In our study, even though we report good outcome with both DDLT and LDLT for this patient population, availability of deceased donors is uncertain. Consequently, most centers will have a significant mortality on their waiting list. Moreover, the period of opportunity for patients in ICU care to receive an LT can be short because transplantation needs to be performed when patients are infection-free and stable. Therefore, based on this experience and on previous reports,[3,10,21] we consider that it is appropriate to continue to offer LDLT to critically ill patients suffering from a decompensated liver disease (Table 3). Besides, we prove that donor morbidity can be kept to a minimum. This correlates with previous results from our group where the overall donor complication rate was under 40%. Only less than 3% of our donor patients suffered major complications (Clavien $\geq$3b).[10,11]

This is the first single-center series using LDLT to treat critically ill liver disease patients being in ICU and on mechanical ventilation at the time of transplantation. However, the analysis has several limitations. It consists of a small sample size and a retrospective study design, which increases the risk of type II errors. In addition, LDLT was performed in a selected group of patients (ICU stay, <8 days and short-term need of mechanical ventilation, <5 days). Moreover, the results were obtained in a high-volume LDLT program and may not be generalizable to all liver transplant centers. However, we tried to balance these limitations by providing a DDLT control group for comparison as well as using a uniform protocol in a well-defined patient population who was treated entirely in a modern era.

In conclusion, our data suggest that LDLT can be safely used for treating critically ill patients requiring ICU management and mechanical ventilation support at the time of transplantation. The LDLT offers a predictable fast access to transplantation for this patient population, providing an excellent treatment option.

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