Right-Lobe Living-Donor Liver Transplantation in Adult Patients With Acute Liver Failure

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ABSTRACT

Background. Right-lobe living-donor liver transplantation (RLDLT) is an excellent option to reduce donor shortages for adult patients with acute liver failure (ALF). The aim of this study was to evaluate the etiologies and outcomes of 30 consecutive adult patients who underwent emergency RLDLT for ALF.

Methods. Between January 2007 and September 2011, we examined data from medical records of patients with ALF who underwent RLDLT.

Results. Their mean age was 32.2 ± 13.05 years. The etiologies of ALF were acute hepatitis B ($n = 11$; 36.6%), hepatitis A ($n = 4$; 13.3%), drug intoxication ($n = 4$; 13.3%), pregnancy ($n = 2$; 6.7%), hepatitis B with pregnancy ($n = 1$; 3.3%), mushroom intoxication ($n = 1$; 3.3%), and unknown ($n = 7$; 23.3%). The mean hepatic coma grade (Model for End-Stage Liver Disease score) was 34.13 ± 8.72. The 43 (48.7%) postoperative complications were minor (grades I–II) and 44 (51.3%) were major (grades III–V). Reoperation was required in 14 of 30 (47%) recipients (grades IIIb–IVa). Deaths occurred owing to pulmonary ($n = 2$), cardiac ($n = 1$), septic ($n = 2$), or encephalopathic ($n = 4$) complications. The mean durations of intensive care unit stay and postoperative hospitalization were 3.2 ± 2.3 and 29.5 ± 23 days, respectively. The survival rate was 70%. The mean follow-up duration was 305 days (range, 1–1582).

Conclusion. Liver transplantation is potentially the only curative modality, markedly improving the prognosis of patients with ALF. The interval between ALF onset and death is short and crucial because of the rapid, progressive multiorgan failure. Thus, RLDLT should be considered to be a life-saving procedure for adult patients with ALF, requiring quicker access to a deceased-donor liver graft and a short ischemia time.

ACUTE LIVER FAILURE (ALF) is a devastating clinical syndrome with a persistently high mortality rate despite advances in critical care.[1,2] The condition is characterized by coagulopathy and hepatic encephalopathy resulting from acute, severe liver damage. It frequently evolutes rapidly to coma and death owing to increased intracranial pressure, coagulopathy, metabolic disturbances, hemodynamic instability, acute renal failure, systemic infection, gastrointestinal bleeding, and multiorgan failure.[3] Thus, ALF is an extremely complicated condition with a poor chance of spontaneous healing.[4]

While alternative supportive techniques, of hepatocyte transplantation or extracorporeal perfusion are considered to be experimental, artificial or bioartificial extracorporeal liver support systems have not significantly improve mortality from ALF.[5–7] Currently, liver transplantation (OLT) is the only definitive treatment modality with well-demonstrated efficacy. Living-donor liver transplantation (LDLT) has emerged as a successful means to partially overcome the refractory shortage of deceased donor grafts caused by the increasing demands of patients with ALF. Thus, worldwide experience in adult-to-adult right-lobe living-donor liver transplantation (A-RLDLT) with low risk has rapidly increased both in elective and emergency situation.[8,9]

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Although deceased donor grafts are shared nationwide in Turkey, priority is given to patients with ALF. However, a donor may not be available within the required period for an ALF patient because of the deceased donor shortage. We initiated RLDLT for elective and emergency OLT procedures in 2007; it now accounts for 92% of our activity (n = 643 procedures). No donor mortality has occurred to date. The aim of this study was to evaluate the etiologies and outcomes of 30 consecutive adult patients who underwent emergency RLDLT for ALF.

METHODS

We reviewed retrospectively the outcomes of patients with ALF who underwent emergency RLDLT between January 2007 and September 2011. The study protocol was approved by our ethics committee and institutional review board. ALF was defined according to the criteria of the American Association for the Study of Liver Disease.[2] All patients underwent a standardized evaluation to determine the cause of ALF, with the participation of experts from the departments of transplant surgery, gastroenterology, radiology, anesthesiology, and neurology.

When a patient with ALF was referred to our center for transplantation, our multidisciplinary team performed comprehensive medical and psychosocial evaluations to determine suitability for OLT. We excluded patients with contraindications, such as florid alcohol or drug abuse, systemic organ ischemia, or an unfavorable social prognosis regarding compliance post-transplantation. After we established the ALF diagnosis and the need for urgent RLDLT using King's College Hospital criteria,[10] counseling was provided to the families, and the patients were placed on the National Organ Coordinating Center list (status I) for an emergency cadaveric OLT. Close relatives were asked to consider volunteering as donor candidates. All patients with ALF and donor candidates were evaluated by the same multidisciplinary team. Evaluation of a living donor candidate did not preclude or delay deceased donor OLT; cadaveric OLT was performed if an appropriate liver became available during this process. If parents wished to be considered for A-RLDLT, a specialist member of our transplant team performed the initial assessment. A date was then set for surgery unless a suitable cadaveric donor liver became available in the interim.

Adequate selection of donors is a key prerequisite for A-RLDLT, demanding a comprehensive, labor-intensive, multidisciplinary process including medical, psychosocial, and surgical–anatomic evaluations. The investigation protocol for donors included serum electrolytes, liver functions, full blood analysis, coagulation studies, serology for human immunodeficiency virus and hepatitis B and C viruses, electrocardiography, chest radiography, and multislice spiral computed tomography. Negative serologic findings for viral hepatitis and ABO blood group compatibility were mandatory. Volumetric assessment of the right lobe liver graft and total liver, calculation of the liver steatosis ratio, and vascular anatomy evaluation were performed using computed tomographic angiography in the radiology department. Donors with graft-to-recipient weight ratios (GRWRs) >0.8% and liver steatosis <20% were accepted for OLT. Multiple arteries, bile ducts, and various types of portal veins in the donor liver were not considered to be contraindications for donation. Finally, informed consent was obtained from the volunteer donor in the absence of other family members. All donor cases were approved by independent institutional committees.

We previously described the detailed surgical technique for right lobe living-donor hepatectomy.[11] Management during the first post-transplantation week included daily blood studies and echo Doppler ultrasound examinations of hepatic perfusion within the first 3 days for early detection of transplant vascular thrombosis. Prophylactic antibiotics were used routinely. All patients also received Tac-based immunosuppressive therapy, maintaining blood levels between 10 and 15 ng/mL during the first month and 5 and 10 ng/mL for the next few months. Methylprednisolone therapy (10 mg/kg) started intraoperatively was continued postoperatively at 10 mg/kg per day tapered to 1 mg/kg per day at 2 weeks and 0.25 mg/kg per day at 3 months, with a progressive switch to alternate-day therapy at 1 year followed by subsequent withdrawal.

We evaluated causes of ALF, as well as recipients and donor demographic features, laboratory test findings, surgical details of the donor and recipient procedures, hospitalization duration, mean follow-up, pre- and postoperative medical outcomes, and patient survival. Overall donor and recipient complication rates were graded using the modified Clavien classification.[12] Continuous variables are reported as mean values ± standard deviations; categorical variables, as numbers and percentages.

RESULTS

During the study period, 643 cadaveric plus LDLTs were performed including 30 (4.7%) adult patients with ALF who underwent A-RLDLT. The mean age of these 30 patients, namely 13 (43.3%) men and 17 (56.7%) women, was 32.2 ± 13.05 years. The etiologies of ALF among RLDLT cases were acute hepatitis B (n = 11; 36.6%), hepatitis A (n = 4; 13.3%), drug intoxication (n = 4; 13.3%), pregnancy (n = 2; 6.7%), hepatitis B with pregnancy (n = 1; 3.3%), mushroom intoxication (n = 1; 3.3%), or unknown (n = 7; 23.3%). The mean Model for End-Stage Liver Disease score was 34.13 ± 8.72. Patient demographic features are summarized in Table 1.

The mean GRWR was 1.3 ± 0.3%. The mean interval between the transplantation decision and the procedure was 19.7 ± 23.6 hours. The mean duration of cold ischemia for living-donor liver grafts was 154.35 ± 59.6 minutes. The mean recipient operative time was 605 ± 120 minutes. For patients, the mean duration of intensive care unit stay was 3.2 ± 2.3 days and the mean duration of postoperative hospitalization, 29.5 ± 23 days. The mean follow-up time was 305 ± 71.4 days. The surgical data are summarized in Table 1.

Eighty-seven postoperative complications in 24 of 30 (80%) patients who underwent RLDLT were evaluated by a modified 5-tier Clavien classification system (Table 2). Briefly, 43 (48.7%) postoperative complications were minor (grades I–II) and 44 (51.3%), major (grades III–V). Twenty-five (28.7%) complications were classified as grade I; 18 (20%), grade II; 14 (16%), grade IIIa; 14 (16%), grade IIIb; 7 (8%), grade IVa and 9 (10.3%), grade V. The most common postoperative complications, which occurred in 21 (24.1%) donors; were abdominal wound problems: Superficial wound seroma, infection, abscess, or dehiscence/hernia. Biliary complications the second most common complication in our series, occurred in 19 (21.8%) recipients; 7 biliary leaks required no intervention (grade I), whereas 7 leaks and 1 stricture required endoscopic retrograde cholangiopancreatography (grade

Table 1. Demographic and Surgical Data for Patients With Acute Liver Failure

Characteristics	Number Percent (%) or Mean ± SD
Age	32.2 ± 13.05
Gender	
Men	13 (43.3)
Women	17 (56.7)
The etiologies of ALF	
Acute hepatitis B	11 (36.6)
Hepatitis A	4 (13.3)
Drug intoxication	4 (13.3)
Pregnancy	2 (6.7)
Hepatitis B with pregnancy	1 (3.3)
Mushroom intoxication	1 (3.3)
Unknown etiologies	7 (23.3)
MELD scores	34.13 ± 8.72
GRWR	1.3 ± 0.3%
Intervals between indication for transplant and OLT (h)	19.7 ± 23.6
Cold ischemia time (min)	154.35 ± 59.6
Mean a recipient operation time (min)	605 ± 120
Intensive care unit stay (d)	3.2 ± 2.3
Duration of postoperative hospitalization (d)	29.5 ± 23
Follow-up times (d)	305 ± 71.4

Abbreviations: ALF, acute liver failure; GRWR, graft-to-recipient weight ratio; MELD, Model for End-Stage Liver Disease; OLT, liver transplantation; SD, standard deviation.

IIIa), and 2 leaks and 2 strictures required hepaticojejunostomy and T-tube choledochostomy (grade IIIb). Pulmonary complications, observed in 18 (20%) recipients, were the third most common problem. Reoperation was required in 14 of 30 (47%) recipients (grades IIIb–IVa). Nine deaths occurred owing to pulmonary ($n = 2$), cardiac ($n = 1$), septic ($n = 2$), or encephalopathic ($n = 4$) complications. The most common causes of death were brain edema and refractory intracranial hypertension. Biliary stenoses were primarily treated using percutaneous transhepatic dilatations with insertion of a drain in the radiology department. Hepatic artery thrombosis (HAT), which occurred in 3 patients, required retransplantation. All portal vein and hepatic vein stenoses were successfully treated by percutaneous angioplasty in the radiology department. Among the 4 patients with portal vein thrombosis, 3 presented with PVT during the first 2 weeks after transplantation. All of them underwent thrombectomy with revision of the portal vein anastomosis.

Donor Outcomes

The mean age of the 30 living donors was 33.8 ± 10.8 years. No mortality occurred among the donors in our series. The postoperative complete recovery rate without a complication was 76.4% ($n = 26$). Six (17.6%) donors experienced grade I (minor) and 2 (5.6%), grade II (no lasting disability) complications according to the modified Clavien classification.[12] All complications improved spontaneously or with conservative management. Donor recoveries were uneventful; all of them were alive and well with normal liver function at the final follow-up examination.

DISCUSSION

ALF is a life-threatening clinical condition with an high mortality rate (40%–80%), despite improvements in intensive care management.[13] The poor outcomes and high mortality rate among ALF patients are due to multifactorial causes.[6] Patients may be referred too late, or the decision to place them on the transplant list may be delayed owing to the lack of specific criteria to predict spontaneous recovery. These delays are compounded by the wait for a suitable organ. The lack of donor livers and other transplant-related problems lead to the death of many patients during the waiting period.[4,14] Therefore, early recognition and prompt transfer of potential transplant candidates to tertiary centers with intensive care and OLT expertise are vital.

Mortality from ALF has been reduced through improved specific treatment for certain etiologic types of ALF, introduction of OLT, and progress in intensive care medicine. Early identification of the underlying etiology of ALF is crucial because several causes of ALF, such as paracetamol (*N*-acetylcysteine), *Amanita phalloides* poisoning (penicillin and silibinin), fulminant hepatitis B (lamivudine), herpes simplex virus (acyclovir), and pregnancy (delivery), are susceptible to specific treatments and prognoses vary considerably among etiologies.[1,15] In the East and in developing countries, ALF is caused mainly by viral infections, primarily hepatitis B, but also hepatitis A and E, as well as other nonhepatotropic viruses.[3,16] By contrast, >65% of ALF cases in the West and developed countries are currently considered to be due predominantly to drug-induced liver injuries, including those related to intrinsic hepatotoxins such as paracetamol (acetaminophen).[17–19] The etiologies of ALF among patients in this study were acute hepatitis B in 11 (36.6%) patients, hepatitis A in 4 (13.3%) patients, drug intoxication in 4 (13.3%) patients, pregnancy in 2 (6.7%) patients, hepatitis B with pregnancy in 1 (3.3%) patient, mushroom intoxication in 1 (3.3%) patient, and unknown etiology in 7 (23.3%) patients.

The interval between disease onset and development of irreversible clinical deterioration and death is short in patients with ALF. The prognosis of these patients has uniformly been poor; the survival rate for spontaneous (transplant-free) recovery is <20%.[4,20–22] Currently, the overall short-term survival rate after transplantation is >65%; thus, emergency OLT clearly has a significant impact on survival.[4] A prolonged intensive care unit stay while awaiting an organ increases the risk of complications of coagulopathy, metabolic disturbances, renal failure, cerebral edema, and infection. Thus, the optimal timing of transplantation is crucial for patients with ALF.

In come countries with critical shortages of deceased donors because of religious, cultural, or legislative impediments, LDLT has become an essential alternative for transplantation.[23] The number of deceased donors per 1

Table 2. Postoperative Complications of Donors According to Clavien's Modified 5-Tier Classification

Postoperative Complications	*n* (%)	Grade I	Grade II	Grade IIIa	Grade IIIb	Grade IVa	Grade V
Abdominal wound	21 (24.1)						
Superficial wound serous fluid collection		2					
Superficial wound infection and abscess		9	4	1	2		
Abdominal wound dehiscence/hernia					3		
Biliary	19 (21.8)						
Bile leak/biloma		7		7	2		
Biliary strictures				1	2		
Pulmonary	18 (20)						
Pneumonia			6				
Pleural effusion		2		5			
Transient atelectasis		4					
Pulmonary hemorrhage		1					
Thoracostomy					2		
Respiratory failure							2
Vascular	14 (16)						
Hepatic artery trombosis						3	
Portal vein trombosis						4	
Middle hepatic vein trombosis			1				
Intra-abdominal bleeding requiring blood transfusion			3				
Intra-abdominal bleeding requiring relaparotomy					3		
Cardiac failure							1
Neurologic	10 (11)						
Delirium			2				
Epilepsy			2				
Encephalopaty							4
Sepsis	2 (2.2)						2
Total	87	25 (28.7%)	18 (20%)	14 (16%)	14 (16%)	7 (8%)	9 (10.3%)

million people is between 10 and 35 in Western countries, but <5 in Eastern countries. In the United States, 66% of ALF cases listed for urgent transplantation receive a deceased donor graft within 3 days, whereas only 19% of patients with ALF in Turkey receive a graft from a deceased donor.[14,17,24] RLDLT is the best treatment for adult patients with ALF in regions with extremely limited liver supplies from deceased donors, such as most of the Middle East, Asia, and Turkey.[14,24,25]

Given the rapid progression of ALF and the shortage of deceased donors, RLDLT provides many advantages over cadaveric transplantation, including timely supply of high-quality grafts with short ischemia times.[4,14,26] In this study, patients who underwent RLDLT had a significantly short interval between transplant decision and performance and short graft cold ischemia times. Nine patient deaths occurred after RLDLT in our study, 4 (44.4%) of which were owing to postoperative persistent encephalopathy. A prolonged waiting time on the nationwide list for a deceased-donor graft for a patient with urgent ALF may increase the grade of encephalopathy, leading to death during the postoperative period.[26,27]

The most common postoperative complications were incisional problems in 21 (24.1%) donors, representing a surprisingly higher incidence than that reported in the literature.[28,29] This discrepancy could be due to the detailed prospective surveillance and recording of abdominal wound problems, including infection, serous fluid collections, dehiscence, and hernia. Biliary complications, occurring in 19 (21.8%) donors, were the second most common postoperative complications.

HAT can cause devastating complications, including bile leakage, hepatic necrosis, graft loss, and sepsis.[30] Additionally, HAT has a mortality rate of 50%. Several factors have been suggested to cause HAT, including technical problems, anatomic variations, hypercoagulable states, severe intraoperative hypotension, long cold ischemic times, occlusion of hepatic artery outflow due to hepatic congestion, and systemic infection.[31] Only 3 recipients in this study underwent urgent retransplantation owing to the early development of HAT.

Kilic et al[14] reported a 79%, survival rate at 3 years after LDLT among patients with ALF. Two remarkable recent Japanese studies by Ikegami et al[26] and Mogazy et al[32] reported 10-year survivals of infants, children, and adults following LDLT of 67.2% and 68.2%, respectively. The authors concluded that LDLT can be performed effectively with the expectation of a high long-term survival rate for

patients with ALF. The 70% survival of patients undergoing RLDLT in our series can be explained by the opportunity provided by living donors to obtain significantly quicker access to liver grafts with short ischemia times.

Living donor selection crucially affects safety and recipient outcomes. The benefit of RLDLT remains controversial owing to concerns regarding donor safety during the emergency hepatectomy and the possibility of coercion in an urgent setting.[33,34] Living donor morbidity rates of around 30%, including minor and major complications are prevalent.[35] Although the selection and evaluation of a living liver donor for a patient with ALF is a complex process under such highly urgent conditions, no mortality, major morbidity, liver impairment, or reoperation was observed in our study. However, about 23.6% of donors suffered from minor complications, which improved spontaneously or upon conservative management.

In conclusion, the growing gap between the number of patients a waiting OLT and the availability of organs is a crucial problem. The interval between the onset of ALF and death is short; thus, RLDLT should be considered to be a life-saving procedure, requiring rapid acquisition of a liver graft and a short ischemia times.

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