Acute liver failure and liver transplantation

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Summary   **Acute liver failure (ALF) is defined by the presence of coagulopathy (International Normalized Ratio ≥ 1.5) and hepatic encephalopathy due to severe liver damage in patients without pre-existing liver disease. Although the mortality due to ALF without liver transplantation is over 80%, the survival rates of patients have considerably improved with the advent of liver transplantation, up to 60% to 90% in the last two decades. Recent large studies in Western countries reported 1, 5, and 10-year patient survival rates after liver transplantation for ALF of approximately 80%, 70%, and 65%, respectively. Living donor liver transplantation (LDLT), which has mainly evolved in Asian countries where organ availability from deceased donors is extremely scarce, has also improved the survival rate of ALF patients in these regions. According to recent reports, the overall survival rate of adult ALF patients who underwent LDLT ranges from 60% to 90%. Although there is still controversy regarding the graft type, optimal graft volume, and ethical issues, LDLT has become an established treatment option for ALF in areas where the use of deceased donor organs is severely restricted.**

Keywords: Acute liver failure, treatment, liver transplantation, living donor liver transplantation (LDLT), optimal graft volume

1. Introduction

Acute liver failure (ALF), sometimes called "fulminant hepatic failure" or "acute hepatic necrosis", is defined by the presence of coagulopathy (International Normalized Ratio ≥ 1.5) and hepatic encephalopathy due to severe liver damage in patients without pre-existing liver disease (*1-4*). The clinical symptoms are complicated, and include cerebral edema, coagulopathy, renal failure, metabolic disturbance, hemodynamic instability, and susceptibility to infection. Until recently, ALF has had a high mortality rate (widely reported to be > 80%) (*5*), but with the improved recognition of this entity, more aggressive medical therapy, intensive care, and especially the advent of orthotopic liver transplantation (OLT) as a radical treatment option, the

survival rate has considerably improved (*2,6-10*).

Here we review ALF with a focus on OLT for adult ALF patients, to describe the importance of OLT in the treatment of this critical disease entity. Additionally, living donor liver transplantation (LDLT) for ALF is separately reviewed.

2. Overview of acute liver failure

2.1. *Definitions*

In 1970, ALF was classically defined as fulminant hepatic failure in patients with no prior liver disease in which rapidly deteriorating hepatocellular function ensued with associated encephalopathy within 8 weeks of the initial presentation (*11*). The syndrome was redefined by O'Gradey *et al.* in 1993, who used the term ALF to describe a clinical syndrome in which encephalopathy occurs between 8 and 28 days after the onset of jaundice (*12*). They suggested further sub-classification comprising three distinct syndromes depending on the jaundice-to-encephalopathy time interval, thus categorizing liver failure as hyperacute

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(onset within 1 week), acute (between 8 days and 4 weeks), and subacute (between 29 days and 12 weeks). This sub-classification reflects not only the cause of the disease and probable complications, but also the differences in the survival rate for these groups, with the hyperacute group paradoxically having the best prognosis (*13*).

2.2. *Epidemiology and etiology*

ALF is rare and represents a syndrome, rather than a specific disease, with multiple causes that vary in course and outcome, making its precise incidence difficult to establish. Reports from developed countries suggest an overall incidence of between 1 and 6 per million people per year (*7,14,15*). A recent nationwide survey in Japan revealed an incidence of 0.9 per million people per year (*16*). It was once estimated to account for 0.1% of all deaths and 6% of all liver-related deaths in the United States (*17*).

The etiology of ALF varies widely depending on geographic location, patient profile, and year of the report. Whereas in a historical series from the 1980s, viral hepatitis was the most common etiology of ALF in the United States (*18*), the results of a recent multicenter study of ALF identified acetaminophen overdose as the most frequent cause in the United States (46% of cases) (*3*) as well as in European countries (*7*). On the other hand, in Africa and Asia, viral hepatitis remains the leading cause of ALF, and cases resulting from hepatitis E as well as hepatitis A and B are common (*16,19,20*). Table 1 shows the various etiologies in the United States, Europe, Japan, and other countries (*3,7,16,20-24*).

Identification of the cause of ALF is critically important because the etiology influences the prognosis and management (*25*), with outcome being much better for patients with ALF associated with acetaminophen, pregnancy, or hepatitis A (> 50-90%) than for those with seronegative hepatitis, idiosyncratic drug reactions, or Wilson's disease (< 10-20%) (*9*). On the other hand, the etiology of ALF remains indeterminate or unknown in approximately 14%, 33%, and 30% of cases in the United States, Europe, and Japan, respectively.

2.3. *Clinical features and their management*

Acute liver failure frequently causes multiple organ failure, while the initial presenting symptoms are usually non-specific, and include fatigue, malaise, anorexia, nausea, abdominal pain, fever, and jaundice (*26*). These symptoms finally lead to the development of encephalopathy and/or coma, although the rates of progression vary case by case, which necessitates urgent decision making regarding the use of the only effective treatment for this disease entity; emergent liver transplantation (*27,28*).

2.3.1. *Encephalopathy and cerebral edema*

The most lethal complication associated with ALF is the development of encephalopathy and cerebral edema, the mechanism and the actual percentage of which are still poorly understood (*29*). Recent clinical and experimental studies suggest an important role for the increased concentrations of circulating neurotoxins, especially, ammonia (*30*), with reports of a relation between the development of high grades of encephalopathy and arterial ammonia concentration (*31,32*). Cerebral edema occurs in nearly 80% of patients who progress to Grade 4 hepatic encephalopathy, leading to intracranial hypertension with subsequent irreversible ischemic brain damage or brainstem herniation, and accounting for up to 50% of ALF mortality (*33,34*). Intracranial pressure (ICP) should be monitored directly and more aggressively managed in patients who are deemed candidates for liver transplantation (*35,36*). Cerebral perfusion pressure, defined as systemic blood pressure minus ICP, must be maintained above 40 mmHg. Classical treatments to reduce ICP comprise sedation (*37*), hypertonic saline (*38*), and mannitol (*39*). In patients with increased ICP resistant to standard medical therapy, mild to moderate hypothermia (32-33°C) is also effective as a bridge to liver transplantation (*40*).

Table 1. Etiologies of acute liver failure worldwide

Contries and regions	Drug-induced (%)		Viral (%)			Unknown (%)	Other (%)
	Acetaminophen	Non-acetaminophen	HAV	HBV	HEV		
USA 1998-2007 (*3*)	46	11	3	7		14	19
Europe 2004-2009 (*7*)	14	12	19			33	22
UK 1999-2008 (*21*)	57	11	2	5	1	17	7
Germany 1996-2005 (*22*)	15	14	4	18		21	28
Japan 2004-2009 (*16*)	15		3	40		30	12
Korea 2000-2009 (*23*)	29		15	29		10	17
India 1989-1996 (*24*)	0	1	2	15	44	31	7
Sudan 2003-2004 (*20*)	0	8	0	22	5	38	27

Abbreviations: HAV, hepatitis A virus; HBV, hepatitis B virus; HEV, hepatitis E virus.

High-flow hemodiafiltration, using a high-performance polysulfone membrane coupled with plasma exchange with 40 to 50 units of fresh frozen plasma (FFP) per session is also useful for improving coma status or protecting against irreversible brain damage in patients scheduled for liver transplantation (*41*).

2.3.2. *Coagulopathy*

Because the liver plays a central role in the synthesis of almost all of the coagulation factors, severe coagulopathy is always encountered in ALF patients. Coagulopathy occurs not only due to the decreased synthesis of clotting factors, but also to an increase in peripheral consumption and at least some degree of disseminated intravascular coagulation and thrombocytopenia (*42*), which sometimes results in spontaneous hemorrhage, *i.e.*, from the gastrointestinal tract or cerebrovascular system (*43,44*). In contrast, there are abnormalities in both the coagulation and fibrinolytic pathways and recent data suggest the defects are balanced, that is, there is a relative preservation of hemostasis unless the platelet count is extremely low (*45,46*). Theoretically, prophylactic treatment with FFP in the absence of bleeding is unadvised for two reasons; first, the decrease in prothrombin time after FFP administration decreases the accuracy with which prognosis can be judged and second, FFP administration results in a volume load that might deteriorate renal function and increase ICP (*25,47*). In clinical practice, however, FFP infusion and platelet transfusion are sometimes inevitable, especially before invasive procedures, and correction of coagulopathy should be determined on a case by case basis (*28*).

2.3.3. *Renal failure and metabolic abnormalities*

Many factors encountered in ALF patients, such as the direct toxic effect of an ingested agent, volume depletion, and systemic hypoperfusion, co-existing sepsis, and hepatorenal syndrome can cause acute renal failure (*48*). Acute renal failure complicates ALF in 40% to 50% of cases and is significantly associated with a poor prognosis (*49-51*). When dialytic support is required, continuous hemodialysis is preferable to intermittent support to maintain the hemodynamic stability and decrease the cerebral perfusion pressure (*52*). Hypoglycemia due to decreased glycogenolysis and gluconeogenesis, and metabolic acidosis are often encountered as a result of massive liver necrosis (*53*).

2.3.4. *Cardiopulmonary and hemodynamic complications*

Cardiopulmonary complications and hemodynamic instability are conspicuous clinical sequelae of ALF, characterized by vasodilation, low systemic vascular resistance, and hypotension, with a compensatory increase in cardiac output (*48*). This hemodynamic status results in lower cerebral perfusion pressure, worsened encephalopathy, and pulmonary edema, which often preclude liver transplantation (*27*). Treatment goals are to perform volume resuscitation, provide supportive care with vasopressors, and increase oxygenation by mechanical ventilation (*25,28*).

2.3.5. *Infection*

The milieu of inflammation and necrosis of the liver predispose ALF patients to the development of infection, which means that patients with ALF are functionally immunosuppressed. Bacterial or fungal infection, particularly of the respiratory and urinary tracts, is common (occurring in up to 80% of patients), which worsens encephalopathy (*54*), and is the cause of death in 10% to 37% of cases (*55-58*). Bacteremia is observed in 20% to 80% of ALF patients (*2*). Additionally, patients with ALF are at substantial risk for sepsis caused by reticuloendothelial dysfunction and decreased opsonization (*59*). The mortality rate of patients with sepsis and septic shock is 59% and 98%, respectively (*60*). The empiric use of antibiotics, however, is controversial. Prophylactic antibiotics decrease the number of infections, but they do not alter the overall outcome, and may result in frequent fungal infections (*56*). Fungal infection, particularly *Candida albicans*, develops in up to one-third of ALF patients, and is a poor prognostic sign associated with high mortality, thereby precluding liver transplantation (*55,58*). Serial blood cultures for bacteria and fungi should be performed, and the administration of anti-infectives (both antibacterial and antifungal) is recommended for patients with significant isolates on surveillance cultures, refractory hypotension, or clinical evidence of systemic inflammatory response syndrome (*28*).

2.4. *Prognostic scores and indication for liver transplantation*

The most commonly used criteria to absolutely exclude ALF patients from liver transplantation, although these vary by transplant center, include age older than 70 years; certain malignancies outside of the liver; severe cardiac, lung, or multiple organ failure; severe infection; uncontrolled septic shock; and brain death (*61*).

The essentials for selecting patients for liver transplantation are the accurate identification of those in need, as well as those who will benefit from liver transplantation. Generally, there are two approaches to listing patients with ALF for liver transplantation. The first is to use some set of indicators of a poor prognosis without liver transplantation, and the second is to list all patients with encephalopathy and make the decision at the time a donor organ becomes available (*9*).

It is critical to promptly and accurately identify those patients most likely to benefit from emergent liver

Table 2. Prognostic scoring systems for acute liver failure

Variables	King's College Criteria non-Acetaminophen	King's College Criteria Acetaminophen	Clichy	MELD	APACHE II	Japanese guideline
Age	×		×		×	×
Etiology	×					
Encephalopathy		×	×		×	×
Arterial pH		×			×	
Onset of encephalopathy	×					×
Factor V			×			
PT-INR	×	×		×		×
Serum creatinine		×		×	×	
Serum bilirubin	×			×		×
Direct/indirect bilirubin ratio						×
Serum sodium and potassium					×	
White blood cell count					×	
Hematocrit					×	
Serum alanine aminotransferase						
Serum cholinesterase						
Vital signs (BT, BP, HR, RR)					×	
Oxygenation					×	

Abbreviations: APACHE, acute physiology and chronic health evaluation; BT, body temperature; BP, blood pressure; HR, heart rate; MELD, model for end-stage liver disease; PT-INR, prothrombin time-international normalized ratio; RR, respiratory ratio.

transplantation, as overall only 15% to 20% of ALF patients survive spontaneously (*5,62,63*). The risks of emergent transplantation in the context of deteriorating multiple organ failure must be balanced against the possibility of survival with continued medical supportive care alone. In addition, early recognition of irreversible ALF is important so that transplantation can be performed before the complications of ALF contraindicate transplantation. Because of the current organ scarcity, short-term risks of surgery, and requirement of lifelong immunosuppression, it is equally important to recognize reversible ALF so as not to perform unnecessary transplantations (*64*).

Many prognostic scoring systems have been reported worldwide (*50,65-70*). The major prognostic models listed in Table 2 are extracted from our previous report (*71*). Based on separate cohorts examining the accuracy of these models, the King's College Criteria are superior and the use of this prognostic model is prevalent worldwide (*62,72*). Two meta-analysis have been performed on the King's College Criteria. One included 18 studies with 1105 patients and yielded an overall specificity of 93% and sensitivity of 88% (*73*). The other meta-analysis included 14 studies with 1960 patients and yielded a specificity of 95% and a sensitivity of 58% (*74*). Three studies evaluated MELD score, which has been introduced and widely validated for the prediction of prognosis of chronic liver disease, in comparison with the King's College Criteria (*66,75,76*). One of the studies found that the MELD score was superior to the King's College Criteria (*66*). A recently described modification of the MELD score replaced bilirubin with cytokeratin 18 (a marker of cell injury), which yielded peak sensitivity and specificity of 81% and 82%, respectively, in 68 consecutive patients with ALF due to various etiologies (*77*). None of the currently available prognostic scoring systems, however, consistently demonstrates reliable accuracy in predicting the outcome of ALF and the subsequent need for liver transplantation. Therefore, the American Association for the Study of Liver Diseases recommends that none of these systems be relied on independently, and that all ALF patients with encephalopathy be considered for transplantation (*25*).

Among the factors listed in Table 2, the most important factors for predicting survival from ALF are the degree of encephalopathy, patient age, and the cause of ALF (*1*). Other factors reported to be associated with the prognosis of ALF include severity of systemic inflammatory response syndrome (*54,60,78*), serum alpha fetoprotein levels (*79*), serum phosphate levels (*80,81*), findings from computed tomography scans of the liver (*82-84*), 99mTc-GSA (*85*), cytokine levels (*86*), and serum lactate levels (*87-89*).

3. Liver transplantation for acute liver failure

Liver transplantation, the only proven therapy for ALF, has revolutionized the management of ALF. ALF accounted for 8% of indications for liver transplantation in Europe during 1988-2009 (*7*), and 7% in the US during 1999-2008 (90). With the advent of OLT as a treatment option, survival rates of ALF patients have improved considerably, up to 60% to 92% in large centers over the last two decades (*3,7,8,63*), which is remarkable given that the rate was below 20% before the OLT era (*5*). Although the survival rate of OLT for ALF patients was previously lower than that for other diseases (*91,92*), a recent report demonstrated comparable results of OLT for ALF and chronic liver diseases (*3*). Even in Western countries where OLT

with deceased donors is aggressively performed for ALF patients, death without transplantation occurs in 20% to 30% of cases (*3,93*). According to a multicenter study, even when patients with ALF are managed in large-volume centers, the OLT performance rate ranges between 41% to 72%, and the median wait time for a graft is 5 days (*94*). This is due to the rapid progression of ALF and persistent organ shortages.

Current results of OLT for ALF are satisfactory considering the natural history of this disease entity, the multi-organ involvement, the emergent context, and the lack of other effective treatments. To date the 1-year and 5-year patient survival rates documented in several studies range between 74% and 81%, and 61% and 76%, respectively (*7,63,93,95-98*), and two studies reported 10-year patient survival rates of 69% and 63% (*7,97*).

Multiple factors influence the outcome after liver transplantation. In some centers, the etiology of the underlying disease correlates with outcome. The best results were achieved for Wilson's disease and the worst for idiosyncratic drug reactions (*15,93*). Recipient age has a considerable impact on the outcome of liver transplantation for ALF, with postoperative mortality more than doubled in those over 50 years of age (*93,95*). Studies over United Network for Organ Sharing (UNOS) database (*98*) and European Liver Transplant Registry (ELTR) database (*7*) found that age over 50 is an independent risk factor for impaired outcome. The third main factor that determines outcome is the quality of the graft used. Impaired outcomes occur in recipients receiving size-reduced (*7,93,99*), ABO-incompatible (*7,93,99*), or steatotic grafts (*63,93*). Impaired graft function is poorly tolerated in acutely sick recipients and might predispose to the development of sepsis – the main cause of postoperative death. In earlier reports of emergent liver transplantation for ALF, graft quality was sacrificed to avoid waiting list mortality, which resulted in the primary non-function rates as high as 13% (*96*). Higher risk grafts, such as severely steatotic or partial grafts, result in worse survival in ALF. The use of ABO-incompatible grafts is most frequently reported for liver transplantation for ALF, which ranges from 13% to 29% and is associated with worse outcomes, including impaired patient/graft survival and complications (*63,96,100-103*).

Four risk factors were identified following an analysis of 1457 recipients who underwent liver transplantation for ALF in the US, a BMI > 30, serum creatinine > 2 mg/dL, recipient age over 50 years, and a history of life-support (*98*). A recent large study from ELTR among 4903 recipients who underwent liver transplantation for ALF found that recipient age > 50 years, ABO-incompatible transplant, acetaminophen-related ALF, ALF due to other known causes, and reduced-size graft were independent risk factors for patient/graft survival (*7*).

4. Living donor liver transplantation for acute liver failure patients

Organ scarcity is serious in Asia, where the deceased donor liver transplantation (DDLT) rate remains below 5 per million population (*104*). According to a recent report in Japan (*16*), only 24% of ALF patients underwent liver transplantation, and death without transplantation occurred around 40%, and more than 98% of liver transplants are from living donors, although organ procurement from brain-dead donors was legalized in 1997. Recently, the Intractable Liver Diseases Study Group of Japan reported that the overall 1-year, 5-year, and 10-year survival rates of ALF patients after LDLT were 79%, 74%, and 73%, respectively, in Japan (*105*).

LDLT for ALF was initially performed only in children, but since the first report of successful LDLT for adult ALF patients by Kato and colleagues (*106*), LDLT has become widely accepted as the alternative treatment of choice for adult ALF patients, mainly in Asian countries, but also in Western countries (*8*). Controversy remains regarding LDLT itself in regions where organs from deceased donors are fairly available, especially under urgent situations, but LDLT seems to have become an established treatment for ALF patients in Asia.

Although it has been suggested that the results of emergent LDLT are inferior to those of elective transplantation (*107*), there are as yet no conclusive data indicating that emergent LDLT is an ineffective or inferior treatment compared to emergent DDLT or elective liver transplants. Compared with cadaveric liver grafts, live donor grafts offer distinct advantages in that patients can receive a graft relatively early and graft function is excellent because the cold ischemia time is short if an adequate graft size is obtained (*108*). Large-volume centers report that outcomes of LDLT and DDLT are comparable for ALF patients (*23,109-116*). The timely availability of a liver graft in LDLT should be emphasized, because in the LDLT series for ALF reviewed here there has never been a neurologic death secondary to severe hepatic encephalopathy, except for two cases of the Seoul group (*110*), in contrast to the relatively high incidence of recipient death due to encephalopathy in the DDLT setting (*117*). Yet, beyond these results, many ALF patients without an appropriate donor have died, and, in the future, an increased prevalence of DDLT donors is expected in Asian countries (*16,105*). Considering the burden on live donors, LDLT will never replace DDLT where cadaveric organs are fairly available, but the addition of LDLT to a DDLT program may further improve the management of ALF, even in Western countries (*108*).

4.1. *Donor and graft selection*

LDLT should be considered only in situations in which

the risk to the donor is justified by the expectation of an acceptable outcome in the recipient. The potential live organ donor should be an adult who is mentally competent, willing to donate, free from coercion, medically and psychosocially suitable, and fully informed of the risks, benefits, and alternative treatments available to the recipient (*118*). Apart from the medical workup of the donor and volumetric/anatomic evaluation of the graft, ethical matters should be especially emphasized in urgent LDLT situations, such as for ALF, because donors do not have adequate time for contemplation and reflection, and most donors are likely to be close relatives who are influenced by the imminent death of the patient (*119*). Ethical issues include ensuring donor safety, avoiding donor coercion, and determining whether adequate informed consent can be obtained in this highly charged emergent setting. Donor safety, of course, is the primary measure of success. The ethical justification for LDLT cannot be based on the absence of donor complications and deaths because that is an unattainable goal. Therefore, its justification is dependent on continuous demonstration of overwhelming recipient benefit and reasonable donor safety (*108,120*).

Most countries consider 18 or 20 years to be the minimum age for independent decision-making regarding organ donation, but the upper age limit of the live donor differs by center, from 55 to 65 years (*107,110-112*). Similarly, the politics regarding the requisite relationship between the donor and recipient vary widely around the world according to different political and cultural standards. The relation to the recipient is usually limited to within the second or third degree of consanguinity (*121*); some countries, however, require no familial relation between the donor and recipient (*122*).

Selection of the graft type and appropriate graft size are critical problems in LDLT for adult ALF patients, in terms of both recipients and donors. It has been postulated that, because ALF is not associated with pre-existing portal hypertension, patients with ALF may tolerate smaller grafts than patients with chronic liver disease. In favor of the recipients outcome, to minimize the problem of a small-for-size graft, many centers have adopted the use of right liver grafts (*123*), although complications are much more common in those donating a right liver than a left liver (*124,125*). Generally, the lower limit of a live donor graft is set at 35% to 40% of the recipient standard liver volume (SLV) or at 0.8% to 1.0% of a graft-to-recipient weight ratio (GRWR).

The estimated risk of mortality and morbidity currently associated with live donor hepatectomy is 0.4% and 35%, respectively (*126*). Although surgeons should always try to decrease both morbidity and mortality, the present level of donor risk is considered acceptable in public opinion (*127*).

4.2. *Reports from high-volume LDLT centers*

Recently, Yamashiki *et al.* (*105*) performed a Japanese nationwide survey on 209 recipients who underwent LDLT for ALF. LDLT was performed a median of 4 days after the onset of encephalopathy. The right liver was utilized in 105 cases (50%), while the left liver was used in 99 cases (47%). The 1-year, 5-year, and 10-year survival rates were 79%, 74%, and 73%, respectively. Prognostic factors associated with patient survival were older recipient, older donor, and ABO-incompatible transplant.

The Kyoto group (*107*) reported 34 LDLT for ALF patients, including 15 adults. Among the 15 adult recipients, 3 received auxiliary partial orthotopic liver transplants (APOLT), 8 received a right liver graft, and 4 received a left liver graft. The minimum GRWR was 0.8%, but the optimal estimated GRWR was 1.0%. If the GRWR of the left liver was less than 0.8%, APOLT was considered. The median time from referral to transplant was 2.0 days (range 0-7 days). The overall 1-year and 3-year survival rate of this population, including 3 APOLT cases and the pediatric cases, was 59%.

The Kyushu group (*111*) primarily chose the left liver graft if it was over 35% of the recipient SLV. The right liver graft without the middle hepatic vein was otherwise chosen when the remnant liver volume was greater than 35% of the total liver volume of the donor. LDLT was performed in 42 ALF patients, including 3 pediatric cases and 39 adult cases (31 with left liver and 8 with right liver). The left liver grafts weighed 442 g (range 260-750 g), representing 42% (range 23-64%) of the SLV of recipients, and the right liver grafts weighed 605 g (range 505-735 g), representing 51% (range 37-57) of the SLV of recipients. The mean interval from onset to LDLT was 5 days. The overall 1-year, 5-year, and 10-year patient survival rates were 80%, 68%, and 68%, respectively.

The Tokyo group (*112*) utilized a right liver graft, a left liver graft, and a right lateral sector graft, with a lower limit of 40% of the recipient SLV, provided that the remnant liver volume of the donor over 30% of the total liver volume. LDLT was performed in 36 ALF patients, including 4 pediatric patients, with 18 right liver grafts, 16 left liver grafts, and 2 right lateral sector grafts. The cold ischemic time was 1.9 h (range 0.3-4.2 h). The weight of the grafts was 503 g (range 276-777 g), which corresponded to 46% (range 22-75%) of the recipient SLV. The overall 1-year and 5-year patient survival rates were 94% and 87%, respectively.

The Hong Kong group (*109*) emphasized the advantage of right liver grafts for ALF patients. Although they reported successful LDLT for an ALF patient with a minimum graft volume (25% of the estimated SLV, GRWR of 0.6%), this case suffered from massive ascites and required a long hospital stay (*128*). Based on their experience with this small-for-

size graft in an ALF case, they reported that the graft should be the donor's right lobe larger than 40% of the recipient SLV, and that the remnant donor's left liver should be greater than 30% of the total liver volume. LDLT was performed in 16 adult patients with ALF with extended right liver grafts from a family member. The median time from listing to transplant was 2 days (range 0.6-9 days) for ALF patients. The median cold ischemia time was 2.2 h (range 1.3-3.7 h). The grafts weighed 615 g (range 430-950) and represented 48% (range 39-89%) of the estimated SLV of the recipients. The overall 1-year survival rate was 88%.

The Seoul group (*23,110,129*) used a left liver graft, right liver graft (without middle hepatic vein), and a dual graft to achieve a GRWR of at least 0.8, provided that the remnant left liver of the donor was over 30% of the total liver volume. The dual graft comprised two left liver grafts or a combination of right and left hemiliver grafts. LDLT was performed in 124 patients with ALF (median age 40 (range 28-49)), including 100 cases with a right liver graft, 16 cases with dual grafts, and 8 cases with a left liver graft. The median GRWR was 1.0 (range 0.9-1.2). The median interval from admission to LDLT was 4 days (range 2-7 days). The overall 1-year and 5-year patient survival rates were 79% and 75%, respectively.

The US A2ALL study group recently reported the results of LDLT for ALF (*130*). Of 1201 LDLT candidates, LDLT was indicated for ALF in only 14 cases (1%). Among those, 10 finally received LDLT, 3 received DDLT, and 1 spontaneously recovered and was removed from the waiting list. The overall survival rate for LDLT was 70%.

5. Conclusion

The advent of liver transplantation has dramatically improved the outcome of patients with ALF, but ALF remains both a challenging and still-too-common cause of mortality. Although numerous medical therapies have been investigated, liver transplantation is the only proven effective treatment for ALF patients. LDLT has remarkably improved the overall survival rate of ALF patients living in regions where organ donation from brain-dead donors is extremely scarce, achieving an outcome comparable to that of DDLT. LDLT might also be valuable to increase the donor pool in Western countries.

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