Acute Liver Failure Graft and Patient Survival

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Overview

Emergency liver transplantation (LT) for acute liver failure (ALF) is a life-saving procedure, which improves the outcomes of patients. It is generally accepted that LT in the urgent scenario has inferior patient and graft survival rates in comparison with LT in non-urgent cases. Nevertheless, the outcomes after LT for ALF improved over the time from 60% to 80% for the short-term survival and from 61% to 76% for 5-year survival. This is probably due to an earlier referral of patients with ALF, a better management of the pre-, peri- and post-transplant phases, with also an improvement in the surgical procedure and a better management of the long-term immunosuppression. Not surprisingly, after the first year, the decrease in survival is less marked compared to elective LT indication, as the patients are younger, often in good condition before the onset of the ALF and have a much lower risk of recurrent disease that affects the graft function. The aetiology of the ALF influences the outcome. According to the European Liver Transplant Registry (ELTR), patients transplanted for viral hepatitis have a higher incidence of death or graft loss due to disease recurrence but decreased over time while the rate of "social" problems, resulting from suicide or lack of compliance, as cause of death or graft failure was 10 times higher in patients transplanted for paracetamol overdose. Overall, infections were the major cause of death, with no differences among

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aetiologies. The clinical severity of the patient before LT have an impact on the outcomes. Renal replacement therapy (RRT) or the need of vasopressor affects graft and patient survival. Quality of the graft has an impact on the survival rate. The use of living donor liver transplantation (LDLT) has improved the outcome of ALF patients, with results comparable to those of deceased donor liver transplantation (DDLT). The use of ABO-incompatible graft in order to reduce waiting time on the list remains an open issue. ABO mismatched was found as an independent risk factor for 3- and 12-month graft loss and death, however good results have also been reported in some centres. A specific immunosuppression protocol is the key factor for the safe use of these grafts.

Tips and Key Points

- Assessing ALF patient clinical severity by acceptable scores is a key step. If spontaneous recovery is unlikely and the patient is deteriorating, the option of urgent LT needs to be considered, as LT is a life-saving procedure in this scenario.
- The outcome of emergency LT for ALF in terms of patient and graft survival is less favourable comparing those for LT for CLD. In the first year post- LT. Long-term outcomes are comparable.
- Prognostic factors for LT outcomes are clinical severity before LT—degree of encephalopathy, sepsis, vasopressor use and need of RRT pre-LT; recipient age and body mass index (BMI); male recipient; donor age; graft quality and aetiology.
- In order to increase the donor pool and reduce the waiting time, LDLT is a valid option, with recent reports showing non-inferior results compared to DDLT.
- In selective patients, auxiliary orthotopic liver transplantation and ABO-mismatched LT may be considered. These types of LTs require special surgical techniques and immunosuppression protocols. Their use is recommended only in a highly qualified centre.

27.1 Introduction

Liver transplantation is a necessary life-saving procedure for most of the patients presenting with ALF. Since the availability of emergency LT, the outcomes of ALF significantly improved [1].

Over the years, outcomes of LT in the setting of ALF improved, although they have not yet reached those of elective LT for chronic liver disease (CLD) [2].

Graft and patient survival are affected by several factors such as ALF aetiology, recipient severity and graft quality. The timing of LT is important to avoid the onset of intracranial hypertension. Therefore, LDLT and ABO-mismatched donor have been used in order to reduce the time on the waiting list. Outcomes of emergency LDLT are comparable to the ones of DDLT, while the use of ABO-incompatible grafts needs to improve with specific immunosuppression protocols.

27.2 Short-Term Outcomes

The highest mortality rate of patients transplanted for ALF is in the first year post-LT (77% of overall deaths), with the majority of cases occurring within the first 3 months (86% of first year death) mostly due to infections, sepsis and multiorgan failure (MOF) [3, 4]. Neurological complications are the second most common cause of mortality (13%) due to cerebral oedema, cerebral herniation and haemorrhagic stroke probably representing patients who did not recover neurological function post-transplantation [4]. In recent years, neurological complications have declined due to lower number of ALF patients developing intracranial hypertension [1].

Other causes of mortality include cardiac events, primary graft non-function, rejection and intraoperative deaths.

The overall mortality of LT in this setting is higher than that of LT for CLD [3, 5]. Data from the UK and USA reported 90-day mortality of 9.4% and 8% for patients transplanted for CLD vs.24.9% and 18.2% for patients transplanted for ALF [5].

Data analysed from the European Liver Transplant Registry (ELTR) and American (United Network for Organ Sharing (UNOS)) LT registries reported overall 1-year patient survival following LT for ALF of 74%–78%; the overall graft survival at 1 year was 63% [3, 5].

27.3 Long-Term Outcomes

The management of these severely ill patients improved over the time with a consequent improvement in the long-term results (Table 27.1). In 1995, a large series from the Paul Brousse Hospital reported a 5-year patient survival rate of 61% [6]. In 2003, a report from the University of California Los Angeles reported a 5-year patient survival rate of 67% [7]. The group of Birmingham described the results of 110 patients transplanted for seronegative ALF. Survival rate at 5 years was 73%. Interestingly, the majority of deaths occurred in the first 2 months and the most common causes of death were sepsis and multiorgan failure [8]. Improved results came out from a study published in 2009 by Chan and colleagues: 5- and 10-year patient survival rates were 76% and 69%, respectively, and the graft survival rates

Table 27.1 Patient survival in acute liver failure transplant recipients according to the time from the transplant

		Patient survival			
	60 days	1 year	5 years	10 years	20 years
Bismuth et al. (1995)		68%	61%		
Farmer et al. (2003)		73%	67%		
Wigg et al. (2005)	83%	81%	73%		
Chan et al. (2009)		80%	76%	69%	
Yamashiki et al. (2012)		79%	74%	73%	
Germani et al. (2012)		74%	68%	63%	
Sars et al. (2018)		71%	63%	52%	40%

were 65% and 59%. In long-term follow-up, five patients died from rejection due to noncompliance (3.4 years), a ruptured abdominal aortic aneurysm (4.9 years), recurrent hepatitis B (5.6 years), metastatic prostate cancer (9.8 years) and chronic rejection (11.8 years). The long-term patient survival was significantly associated with pre-transplant cerebral oedema and the use of an extended criteria graft at univariate analysis; however when nationally shared grafts were included in the definition of extended criteria donor (ECD), it was no longer statistically significant [9]. The report from the European Liver Transplantation Registry (ELTR), which included 4903 patients transplanted for ALF from January 1988 to June 2009, showed that overall patient 5- and 10-year survival rates were 68% and 63%, respectively. Overall graft 5- and 10-year survival rates were 57% and 50%. Interestingly, the re-transplantation rate was 13%, decreasing from 20% in 1988–1993 to 6% in 2004–2009 ($p < 0.001$). This study clearly showed an improvement in survival over the time (Fig. 27.1): 5-year patient survival rate between 2004 and 2009 was 72%, significantly higher than for patients transplanted between 1999 and 2003, 70% ($p = 0.01$) or between 1994 and 1998, 65% ($p < 0.001$). Graft 5-year survival rate was also significantly better in the recent era, being 63% between 2004 and 2009 compared to 61% between 1999 and 2003 ($p = 0.004$) and 53% between 1994 and 1998 ($p < 0.001$). Infections were the major cause of death, with no difference among ALF aetiologies. Furthermore, there was a change in the causes of death according to the different LT eras: the incidence of both acute and chronic rejection, cerebrovascular causes and disease recurrence had fallen progressively. At multivariate Cox regression analysis, variables independently associated with death or graft loss were: recipient age >50 years (RR 1.26, 95% CI 1.10–1.44, $p < 0.001$), incompatible donor-recipient group matching (RR 2.04, 95% CI 1.85–2.70, $p < 0.001$), paracetamol-related ALF (RR 1.24, 95% CI 1.03–1.51, $p = 0.027$), ALF due to other known causes (RR 1.20, 95% CI 1.05–1.38, $p = 0.007$) and reduced

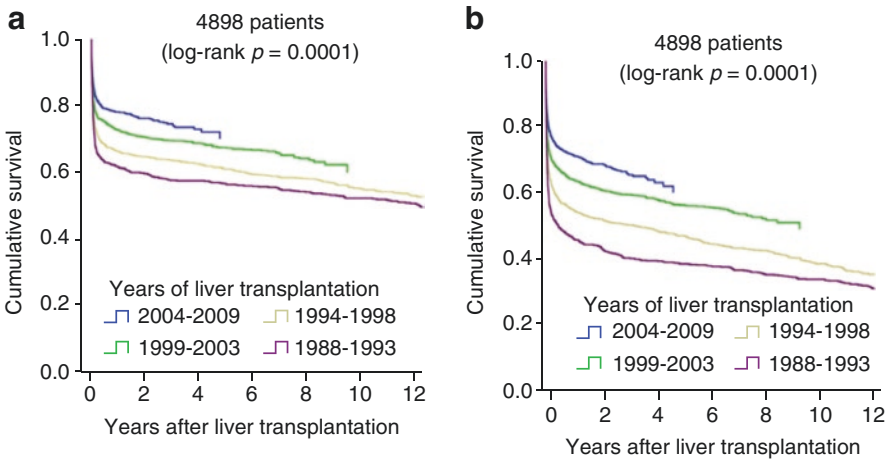

Fig. 27.1 Patient (**a**) and graft (**b**) survival after liver transplantation for ALF according to different eras. Adapted from Germani et al. J Hepatol 2012; 57: 288–296

graft size (split, reduced or partial for living) (RR 1.43, 95% CI 1.15–1.78, $p < 0.001$) [3]. These data were confirmed in a recent single centre experience from Scandinavia. A cohort of 78 patients who underwent LT for ALF between 1984 and 2014 was analysed. Patients were also divided in two eras: 1984–1999 ($n = 40$) and 2000–2014 ($n = 38$). Five- and 10- and 20-year survival rates for the overall population were 63%, 52% and 40%, respectively. The survival rates for the 2000–2014 cohort were 76% and 71% at 5 and 10 years, respectively. The same improvement was noted in graft survival. Overall 5-, 10- and 20-year graft survival rates were 59%, 48% and 29%. The corresponding graft survival rates for the late cohort were 79%, 71% and 66%, respectively [10]. Data from Japan showed the experience with Living Donor Liver Recipients (LDLT). The authors reported the experience of 209 patients who underwent LDLT for ALF. The 5- and 10-year survival rates were 74% and 73%, respectively. Survival rate did not differ according to ALF aetiology. The long-term mortality was significantly associated with patient and donor age [11].

Several studies tried to assess the different factors influencing the outcome of patients transplanted for ALF. Survival post-LT is influenced by several factors concerning the recipient, donor and the type of transplantation, but so far, no single factor was found to be the best predictor of survival.

27.3.1 Aetiology of ALF

It has been demonstrated that the aetiology of ALF can influence the outcomes after LT. It was reported that patients transplanted for acetaminophen and viral-related ALF have better post-transplant outcomes than those patients transplanted for autoimmune hepatitis and drug-induced liver injury ALF [12]. In the ELTR report, there

was no statistically significant difference in graft and patient overall survival according to aetiology of ALF, however, at multivariate analysis paracetamol-related ALF and ALF due to other known causes (excluding virus and other drugs) were independently associated with death or graft loss [13]. In patients transplanted for acetaminophen-ALF, outcomes are related to the high incidence of psychological problems [3], which affect survival in LT as many of them make other suicidal attempts after LT. For these patients, a close psychological surveillance is important. Concerning viral-ALF, a recent report found that patients who underwent LT for HAV-ALF were compared to patients transplanted for HBV-ALF. HAV-ALF patients had a lower graft survival at 1 and 5 years (65.5% vs. 88% and 65.5% and 84%, $p = 0.48$) as well as a lower patient survival at 1 and 5 years (69% vs. 88% and 69% and 84%, $p = 0.09$). At multivariate analysis, acute pancreatitis and HAV recurrence were found as independent risk factors of graft and patient survival [14]. However, this lower survival in HAV-infected patients was not confirmed by other teams and HAV recurrence was not described by others [12].

27.3.2 The Recipient

Patient survival post-LT has increased progressively over the years since the late 1980s to nowadays (55.6% in 1984–1988 vs. 86% in 2004–2008) [1]. This may not only be due to better surgical transplant techniques but also due to earlier referral to dedicated centres, advances in intensive care and better patient selection for LT. Patient selection and timing of LT are essential for patient survival and LT outcome. The clinical severity of the patient with ALF (i.e. grade of hepatic encephalopathy and coma, renal failure, sepsis, respiratory failure, use of vasopressors) before LT is a key factor for patient and graft survival after LT. Hence, the importance of rapid clinical and prognostic assessment of ALF patient according to different score systems (Clichy criteria, King's College criteria, SOFA (sequential organ failure assessment) and APACHE II (acute physiology and chronic health evaluation II) scores) is paramount.

In the Paul Brousse experience, grade 3 coma at admission to hospital and at the time of LT was a predictive factor of neurological complications and higher mortality rate—83% survival in patients with grade 1–2 coma vs. 56% in patients with grade 3 coma [6]. A randomized multicentre control trial held in France evaluating the use of albumin dialysis with molecular adsorbent recirculating system (MARS) in ALF patients was unable to conclusively demonstrate an advantage of MARS over conventional therapy, with a similar rate of neurological complications in both groups. Moreover, there was no significant difference in the 6- and 12-month patient survival rates, though the probability of being transplanted was higher in the MARS patients [15].

Data from the UK Transplant Registry showed that renal failure with use of renal replacement therapy before LT was a predictor of mortality and graft failure at 1- and 3 years post-LT [16].

Different data from UNOS, ELTR and the UK registries showed that the recipient age was an independent prognostic factor: patients over 45–50 years old have worse prognosis with 47% survival rate vs. 80% in the younger cohort [17]. Those

registries also found recipient BMI >30 kg/m, male sex, paracetamol-induced ALF and use of vasopressors to be independent risk factors.

27.3.3 The Graft

The quality of liver graft in terms of liver function, hepatic steatosis, ischaemic time, hypoperfusion before donor death and hepatic volume is a crucial determinant of LT success.

The ELTR found donor age above 60 years to be a risk factor for mortality and graft loss at 3 and 12 months post-LT [3]. The King's College hospital registry of 310 patients also found donor age above 60 years to be related to 3-month mortality [17]. In these cohorts, the use of steatotic grafts and partial or small grafts was in correlation with lower rates of graft survival. In the Paul Brousse experience of 116 patients transplanted for ALF, graft steatosis (30–60% steatosis) and use of reduced size or partial grafts were predictive of lower patient and graft survival [6].

27.3.4 Living Donor Liver Transplantation

LDLT significantly improved the outcome in ALF. Given the shortage of available organs, the option of LDLT has become valid in selected CLD patients. Is there a place to consider LDLT in the setting of ALF? In contrast to previous studies describing the association between partial graft and mortality, recent reports suggest non-inferior results of LDLT for ALF compared to DDLT. Data collected from the Organ Procurement and Transplantation Network (OPTN) database assessed 2337 patients transplanted for ALF, of whom 21 (0.9%) underwent LDLT. They showed comparable patient and graft survival rates with 71% one-year and 71% five-year patient survival post-LDLT vs. 79% one-year and 71% five-year survival post-DDLT ($p = 0.764$). Graft survival rates at 1- and 5-year post-LDLT were 62% and 57%, respectively, vs. 74% and 66% post-DDLT ($p = 0.569$) [18]. A Korean series of 160 ALF patients of whom 124 had LDLT showed patient survival rates at 1- and 3 years of 79% and 75% post-LDLT vs. 78% and 74% post-DDLT ($p = 0.99$). Similarly, there was no significant difference in graft survival rates, with 1- and 3-year survival rates of 77% and 72%, respectively, post-LDLT vs. 75% and 71% post-DDLT [19]. A cohort of 209 patients who underwent LDLT for ALF in Japan showed similar results—patient survival rates at 1, 5 and 10 years after LT were 79%, 74% and 73%, respectively. In this cohort, the patient age was associated with short- and long-term mortality after LT, whereas ABO incompatibility affected short-term mortality and donor age affected long-term mortality [11]. A recent report from India [20] evaluated 61 LDLT recipients for ALF between 2011 and 2018: 5-year actuarial survival rate was 66% with a median follow-up of 35 months. On multivariate analysis, post-operative worsening of cerebral oedema, systemic inflammatory response syndrome (SIRS), preoperative culture positivity and longer anhepatic phase duration predicted poor outcome.

27.3.5 Auxiliary Liver Transplantation

Facing the need for an emergency transplantation and shortage of organs, auxiliary LT (ALT), meaning the implantation of partial or whole liver graft while retaining the native liver (part or all of it), has been used as an alternative to LT in ALF. ALT allows potential post-transplant native liver regeneration and withdrawal of immunosuppression [21]. The regenerative capacity of the native liver is better in children and younger adults (<40 years). In case of ALF induced by acetaminophen overdose, hepatitis B and E and mushroom poisoning, the liver has an excellent regenerative potential. Histological predictors of regeneration are diffuse pattern or map-like necrosis and at least 25%–40% remaining recipient liver mass. [22, 23]

Several series reported comparable 1-year survival rate post-ALT versus post-DDLT ranging between 62% and 66%. However, considering the technical complexity of the surgery, the higher rates of complications like primary non-function (PNF), vascular thrombosis, biliary leaks and strictures, neurological sequelae made this option less favourable [21, 24]. More recent series reported higher survival and native liver regeneration rates in preadolescent children with ALF with 85%–100% one-year survival and 65%–76.9% weaned off immunosuppression [25, 26].

This technique should be proposed mainly in young patients, with ALF with high regeneration potential, absence of severe grade of coma and when surgeons are confident in this technique. This will also require a follow-up of the volumes and of liver functions of the graft and of the native liver using Hida (hepatobiliary iminodiacetic acid) scintigraphy, volumetry computed tomography (CT) scan.

27.3.6 ABO-Incompatible Graft

With 1-year survival rate of 30%–60%, LT across ABO remains a controversial issue [27]. The ELTR data showed double rate of graft loss at 3 months in ABO-mismatched grafts used during emergency transplantation, with ABO mismatched being an independent risk factor for 3- and 12-month graft loss and death [3]. The Paul Brousse team reported ABO incompatibility as an independent predictive factor for lower graft survival [6]. In some centres, the use of specific immunosuppression protocols led to better results. For example, the University of Alberta Hospital reported 14 patients treated with quadruple immunosuppressive regimen without splenectomy; graft survival rate at 1 year was 64% of ABO-incompatible grafts and 86% for one-year patient survival [28]. These protocols allow LT over ABO to be a valid option in selected patients with ALF. However, they require maximum expertise with close monitoring and adjustment of immunosuppression, as infection remains the major cause of morbidity and mortality. A meta-analysis published in 2017 included 21 retrospective studies with 1494 patients who had ABO-I and 6753 ABO-C (living and cadaveric donors). There was no difference in terms of patient survival between the two groups. On the other hand, the rate of graft lost was higher in the ABO-I group with an odds ratio (OR) of 0.66 at 1 year post- LT and 0.8 at 10 years post-LT. Additionally, antibody-mediated rejection, chronic rejection,

cytomegalovirus (CMV) infection, biliary and hepatic artery complications were significantly more prevalent in the ABO-I group [29]. A cohort of 235 patients having ABO-I LDLT vs. 1301 ABO-C LDLT in a single centre in South Korea, who used a desensitization protocol with Rituximab and total plasma exchange in the ABO-I group, showed comparable 1- and 3-year patient and graft survival rates between the two groups [30]. Another series of 47 ABO-I LDLT compared to that of 94 ABO-C LDLT from another hospital in South Korea showed comparable rates of 3-month postoperative infections, acute rejection, bile ducts and vascular complications. Patient survival at 1, 2 and 3 years was similar between the two groups [31].

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