ORIGINAL ARTICLE

Emergency versus elective living-donor liver transplantation: a comparison of a single center analysis

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Abstract

Purpose We studied the risk factors for postoperative mortality between patients who underwent emergency or elective living-donor liver transplantation (LDLT).

Methods Forty-seven patients underwent LDLT in our institute, 16 for emergencies and 31 as elective procedures. The emergency LDLT status was applied to cases in which the time period between referral to our institution and transplantation did not exceed 10 days, and in which liver failure was accompanied by the presence of any degree of hepatic encephalopathy.

Results With regard to preoperative factors, age ($P = 0.03$), the model for end-stage liver disease score ($P = 0.001$), preoperative tracheal intubation ($P = 0.001$), ratio between arterial oxygen tension and fractional inspired oxygen (PaO_2/FiO_2 ratio) ($P = 0.03$), steroid therapy use ($P = 0.001$), lymphocyte count ($P = 0.02$), and cases requiring hemodiafiltration ($P = 0.001$) differed significantly between the two groups. Postoperative pneumonia occurred more frequently in emergency LDLT patients than in elective LDLT patients ($P = 0.006$). Invasive pulmonary aspergillosis (IPA) was the main cause of postoperative death in emergency LDLT patients, and, in a univariate analysis, a preoperative status of high serum $(1 \rightarrow 3)$-β-D-glucan (>20 pg/ml, $P = 0.001$), advanced age (>52 years, $P = 0.02$), and a low PaO_2/FiO_2 ratio (<320, $P = 0.01$) were identified as factors predictive of IPA.

Conclusion Careful perioperative management, including preoperative investigation of aspergillosis and empiric antibiotic therapy, should be considered for emergency LDLT patients who fulfill IPA risk factors.

Keywords Emergency living donor liver transplantation · Postoperative pneumonia · Invasive pulmonary aspergillosis

Introduction

Liver transplantation (LT) is now accepted as a reliable treatment for patients with end-stage liver disease [1, 2]. Compared to liver transplantation from a deceased donor, living-donor liver transplantation (LDLT) may reduce the waiting time, particularly for patients suffering from hepatic encephalopathy [3]. The survival outcome of LDLT for patients with hepatic encephalopathy is controversial [4, 5]. LDLT using a right-lobe graft was shown to improve the overall survival rates of these patients [6, 7]. However, most of the previously reported causes of death of these patients were neurological damage and infections [8]. In this article, we reviewed the clinical outcomes of emergency LDLT in our institution to clarify the risk factors for postoperative mortality that may lead to improved survival rates for patients with emergency LDLT; namely, for those with hepatic encephalopathy irrespective of the presence of either acute liver failure or acute on chronic liver failure (ACLF).

Patients and methods

Forty-seven patients underwent LDLT at Yokohama City University Graduate School of Medicine, Japan, including

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one case of retransplantation. Sixteen patients underwent LDLT for emergency status and 31 for elective status. In this study, the emergency LT status was applied to cases in which the time period between referral to our institution and transplantation did not exceed 10 days, and in which liver failure was accompanied by the presence of any degree of hepatic encephalopathy. Hepatic encephalopathy was graded from 1 to 5 in accordance with the criteria described by the Japan Study Group for Fulminant Hepatitis: [9] grade 1 patients exhibit euphoria or depression, grade 2 exhibit drowsiness or confusion, grade 3 show somnolence but the ability to be roused, grade 4 are in a coma with response to painful stimuli, and grade 5 patients are in a deep coma with no response to painful stimuli.

The emergency indications included acute liver failure ($n = 9$) and ACLF ($n = 7$). The former was defined by the presence of hepatic encephalopathy as a consequence of severe liver damage without preexisting liver disease [10] and the latter as chronic end-stage liver disease [11]. The primary disease underlying acute liver failure was fulminant hepatitis, the etiology of which included unknown origins ($n = 5$), autoimmune hepatitis (AIH) ($n = 3$), and hepatitis B virus (HBV) ($n = 1$). The etiology of ACLF included HBV ($n = 4$), primary biliary cirrhosis (PBC) ($n = 1$), AIH ($n = 1$), and alcoholism ($n = 1$). The indications for elective LDLT in the 31 patients included hepatocellular carcinoma ($n = 10$), PBC ($n = 7$), HBV cirrhosis ($n = 6$), hepatitis C virus (HCV) cirrhosis ($n = 3$), AIH ($n = 1$), alcoholic cirrhosis ($n = 1$), and other diseases ($n = 3$).

Indications for emergency LDLT

We referred to the criteria of Chiba University, Japan, to determine the indications for three levels of emergency LDLT: [4] (1) subacute type (between 11 days and 8 weeks), (2) acute type with liver atrophy, and (3) acute type with no liver atrophy. The national guidelines were referred to for level 3 [4]; in other words, when conservative therapy was not found to be an effective treatment for liver failure, then LDLT was considered.

Preoperative management

Hemodiafiltration (HDF) was performed to treat hepatorenal syndrome, and, if hepatic encephalopathy above grade 2 was also present, high flow dialysate continuous hemodiafiltration (HFCHDF) [12, 13] was commenced to prevent irreversible brain damage. Plasma exchange (PE) was carried out to treat coagulopathy, with 0.1 l fresh frozen plasma/kg body weight given per PE session.

Chest and abdominal computed tomography (CT) were performed to evaluate the presence of lung disease and the degree of liver atrophy. Mechanical ventilation was performed if the arterial oxygen tension (PaO_2) was less than 60 mmHg. The degree of brain edema was evaluated using cranial CT, and abnormal electrical activity of the brain was examined by electroencephalography (EEG). To avoid any incidental bleeding that might occur while applying this invasive technique, we did not monitor intracranial pressure. In ten ABO-incompatible cases, rituximab was administered, and PE was performed in two or three preoperative sessions to reduce the anti-donor blood type antibody titer [14].

Recipient operation

During the recipient operation, the whole liver was removed, and the branches of the vascular and biliary tree were divided and preserved for reconstruction. All LT procedures were performed using the piggyback technique without a venovenous bypass. A temporary portacaval shunt was placed during the anhepatic phase of the transplant in patients in whom circulatory instability was evident from the portal clamping test. A splenectomy was performed in ABO-incompatible cases, in cases of pancytopenia caused by splenomegaly, in patients with HCV infection as the primary disease, and when high portal vein pressure was diagnosed after liver graft reperfusion (>20 mmHg).

In ABO-incompatible cases, hepatic artery infusion (HAI) or portal vein infusion (PVI) was started immediately after liver graft reperfusion. HAI consisted of prostaglandin E_1 (PGE_1, 0.01 µg/kg/min) and methylprednisolone (initial dose 60–125 mg/day); PVI consisted of PGE_1 (0.01 µg/kg/min), methylprednisolone (initial dose 62.5 mg/day), and gabexate mesilate (1000 mg/day) or nafamostat mesilate (150 mg/day). HAI or PVI continued for 2–3 weeks [15]. A Witzel tube jejunostomy was placed in the proximal jejunum with an 8 Fr enteral tube.

Postoperative management

All patients were treated with tacrolimus and steroids as immunosuppressants. Mycophenolate mofetil was frequently added to reduce the risk of renal dysfunction induced by tacrolimus. The whole-blood trough level of tacrolimus was adjusted to 10–12 ng/ml during the first postoperative week and tapered thereafter. Methylprednisolone (10 mg/kg) was administered twice intraoperatively, then tapered from 1 mg/kg/day on postoperative day 1–0.3 mg/kg/day at the end of the first postoperative month. If liver function stabilized, then steroids were discontinued from 2 months after LDLT. Steroid pulse therapy was performed if severe or moderate acute cellular rejection was diagnosed by liver biopsy.

Postoperative prophylactic antibiotic treatment included flomoxef sodium for 5 days and antifungal micafungin sodium for 7 days in all patients. Sulfamethoxazole/trimethoprim against *Pneumocystis carinii* was administered if a splenectomy was performed. Doppler echography was used three times daily during the patient's ICU stay to monitor the blood flow of the reconstructed portal vein, hepatic artery, and hepatic vein, and once daily during regular hospitalization.

The intratracheal tube was extubated after surgery according to the patient's good general and respiratory conditions. If patients did not meet these criteria by about 7 days after LT, a tracheostomy was considered. The patients were started on an enteral diet when contrast medium that had been administered intraoperatively reached the ileocecum.

The clinical and demographic parameters and surgical outcomes of the 16 emergency LDLT patients were compared with those of the 31 patients who underwent elective LDLT during the same period. The postoperative morbidities and survival rates were compared between the two groups, and the predictive factors for postoperative mortality among patients with emergency LDLT were also investigated.

Statistical analysis

Quantitative variables were given as the mean ± standard deviation and categorical variables as values and percentages. Chi-square testing was carried out for univariate analysis of categorical variables, and the significance level was set at a *P* value <0.05. The statistical software package, SPSS II for Windows (SPSS), was used for the analysis. To determine the cutoff levels of continuous variables, the receiver operating characteristic curve was used.

Results

Patient characteristics in emergency and elective LDLT

The patient characteristics from each group are summarized in Table 1. Preoperative factors including age (emergency, elective = 42.3 ± 14.4, 51.3 ± 8.0, respectively; $P = 0.03$), the model for end-stage liver disease (MELD) score (27.4 ± 7.6, 15.1 ± 6.6; $P = 0.001$), the percentage of cases requiring tracheal intubation (43.7, 0%; $P = 0.001$), the ratio between arterial oxygen tension and fractional inspired oxygen (PaO_2/FiO_2 ratio) (335.2 ± 110.2, 405.6 ± 73.7; $P = 0.03$), the percentage of cases requiring HDF (81.2, 0%; $P = 0.001$), steroid therapy in the 1 month before LDLT (68.7, 16.1%; $P = 0.001$), and the lymphocyte count (806 ± 856.3, 960 ± 533.5; $P = 0.02$) were significantly different between the two groups. Other variables

Table 1 Characteristics of the study population

Factor	Emergent LDLT ($n = 16$)	Elective LDLT ($n = 31$)	P value
Preoperative factors			
Females (%)	9 (56.2)	14 (45.1)	0.47
Age (years)	42.3 ± 14.4	51.3 ± 8.0	0.03
MELD score	27.4 ± 7.6	15.1 ± 6.6	0.001
ABO incompatibility	2 (12.5)	8 (25.8)	0.29
Tracheal intubation (performed)	7 (43.7)	0 (0)	0.001
PaO_2/FiO_2 ratio	335.2 ± 110.2	405.6 ± 73.7	0.03
HDF	13 (81.2)	0 (0)	0.001
Steroid (1 month)	11 (68.7)	5 (16.1)	0.001
Lymphocyte count	806 ± 856.3	960 ± 533.5	0.02
Intraoperative factors			
Duration of operation (min)	1085.4 ± 807.6	929.2 ± 164.3	0.45
e-Blood loss (ml)	6375.0 ± 8048.7	6257.1 ± 4926.8	0.95
Warm ischemic time (min)	61.3 ± 18.4	64.7 ± 18.6	0.55
Cold ischemic time (min)	137.4 ± 71.8	185.6 ± 96.2	0.06
Splenectomy (performed)	5 (31.2)	15 (48.3)	0.26
Right lobe graft	11 (68.7)	22 (70.9)	0.87
Postoperative factors			
Duration of admission (days)	93.6 ± 53.1	57.3 ± 38.4	0.02

Data are presented as number of patients (percentages in parentheses) or mean ± SD

LDLT living donor liver transplantation, *MELD* model for end-stage liver disease, *PaO₂/FiO₂ ratio* ratio between arterial oxygen tension and fractional inspired oxygen, *HDF* hemodiafiltration, *e-Blood loss* estimated blood loss

including gender and ABO incompatibility did not differ significantly between the two groups. Concerning intraoperative factors, the two groups were similar in the duration of surgery, estimated volume of blood loss, warm ischemic time, cold ischemic time, and rates of splenectomy and of using a right lobe graft. Of the postoperative factors, the duration of admission for emergency LDLT was significantly longer than that for elective LDLT [93.6 ± 53.1, 57.3 ± 38.4 days, respectively ($P = 0.02$)].

Postoperative short-term outcomes

A total of 14 types of complications occurred (Table 2). Twelve patients in the emergency LDLT group encountered a total of 24 complications and 20 patients in the

Table 2 Postoperative complications

Complication	Emergent LDLT	Elective LDLT	P value
Total number of complications	24	32	
Surgery- and liver graft-related	6 (37.5)	15 (48.3)	0.47
Biliary stricture	2 (12.5)	3 (9.6)	0.77
Biliary leakage	1 (6.2)	5 (16.1)	0.33
Hepatic artery stenosis	0 (0)	1 (3.2)	0.46
Hepatic vein stenosis	0 (0)	2 (6.4)	0.29
Primary nonfunction	1 (6.2)	0 (0)	0.15
Intraabdominal bleeding	1 (6.2)	0 (0)	0.15
Acute cellular rejection	1 (6.2)	4 (12.9)	0.48
Central nervous system-related	4 (25.0)	3 (9.6)	0.16
Cerebral hemorrhage	2 (12.5)	1 (3.2)	0.21
Central pontine myelinolysis	1 (6.2)	0 (0)	0.15
Tacrolimus-related convulsion	1 (6.2)	2 (6.4)	0.97
Respiratory system-related	6 (37.5)	5 (16.1)	0.47
Pneumonia	5 (31.2)	1 (3.2)	0.006
Others	1 (6.2)	4 (12.9)	0.48
Others	8 (50.0)	9 (29.0)	0.15
Cytomegalovirus infection	7 (43.7)	9 (29.0)	0.31
Acute cardiac infarction	1 (6.2)	0 (0)	0.15

Data are presented as number of patients (percentages in parentheses)

LDLT living donor liver transplantation

Table 3 Causes of hospital mortality

Cause	Emergent LDLT ($n = 16$)	Elective LDLT ($n = 31$)	P value
Hospital mortality (all)	4 (25.0)	1 (3.2)	0.02
Cause of hospital mortality			
Pneumonia	3 (18.7)	0 (0)	0.01
Cerebral hemorrhage	0 (0)	1 (3.2)	0.46
Primary nonfunction	1 (6.2)	0 (0)	0.15

Data are presented as number of patients (percentages in parentheses)

LDLT living donor liver transplantation

elective LDLT group encountered a total of 32 complications. There was no significant difference in the frequency of postoperative complications between the two groups, including surgery and liver graft, and the central nervous system complications. Regarding preoperative hepatic coma, of 16 emergency LDLT patients, 6 patients had grade 2 encephalopathy, 5 had grade 3, and 5 had grade 4. All emergency LDLT patients who survived the perioperative period recovered without any degree of hepatic encephalopathy. Postoperative pneumonia occurred more frequently in emergency LDLT patients ($n = 5$, 31.2%) than in elective LDLT patients ($n = 1$, 3.2%; $P = 0.006$). A tracheotomy was also performed more frequently in emergency LDLT patients ($n = 9$, 56.2%) than in elective LDLT patients ($n = 7$, 22.5%; $P = 0.02$).

Hospital mortality occurred in four patients in the emergency LDLT group (25%) and in one patient in the elective LDLT group (3.2%; $P = 0.02$) (Table 3). The causes of death were pneumonia ($n = 3$) and primary nonfunction ($n = 1$) in the emergency LDLT group and cerebral hemorrhage ($n = 1$) in the elective LDLT group.

Characteristics of pneumonia after LDLT

The incidence and causes of pneumonia after LDLT were investigated (Table 4). Six patients with postoperative pneumonia, five of whom were in the emergency LDLT group, required a respirator. Among the six patients who suffered from pneumonia, three (50%) were ABO incompatible, and all these patients underwent a splenectomy; the corresponding rates were similar among patients without pneumonia (41.4 and 17.0%, respectively). The pneumonia-causing pathogens were shown to be *Aspergillus* spp. ($n = 3$), methicillin-resistant *Staphylococcus aureus* (MRSA) ($n = 1$), and *Pseudomonas aeruginosa* ($n = 1$) in emergency LDLT patients and *Enterococcus faecalis* in the elective LDLT patient.

Aspergillus spp. were the most common pneumonia pathogen, and in all three cases of infection, the pathogenesis developed as invasive pulmonary aspergillosis (IPA). IPA was defined as any LDLT recipient meeting the criteria for proven or probable IPA as described in a report from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Co-operative Group and the National Institute of Allergy and Infectious Disease Mycoses Study Group [16].

One IPA case was diagnosed from a resected lung specimen [17] and another at autopsy. The mean age of infected patients was 52.3 years, and the mean time from surgery to the initial IPA diagnosis was 7.6 ± 12.4 days. Although one IPA case has survived for 57.5 months after LDLT [17], the other two patients died 3.1 and 3.6 months, respectively, after LDLT.

The predictive factors for IPA were investigated by a univariate analysis among patients who had undergone an emergency LDLT, which was the only group in which IPA was encountered. The predictive preoperative factors were shown to be mature age (>52 years, $P = 0.02$), serum $(1 \rightarrow 3)$-β-D-glucan levels above 20 pg/ml ($P = 0.001$), and a PaO_2/FiO_2 ratio of less than 320 ($P = 0.01$).

Long-term outcomes

The overall cumulative 3- and 5-year patient survival rates after emergency LDLT were 73.6 and 73.6%, respectively,

Table 4 Respiratory management of post-LDLT pneumonia

Case	LDLT	Age/gender	Primary disease	ABO	MELD	Splenectomy performed	Initial diagnosis of pneumonia (days after LDLT)	Pneumonia pathogen	Final diagnosis of IPA	Outcome	Months after LDLT
1	Emergent	47/M	HBV-LC	Incompatible	31.9	(+)	1	*Ps. aeruginosa*	–	Survived	29.9
2	Emergent	52/F	HBV-LC	Incompatible	23.7	(+)	0	MRSA	–	Died	2.4
3	Emergent	52/F	FHF	Identical	18.9	(−)	22	*A. fumigatus*	Proven	Died	3.1
4	Emergent	52/F	PBC	Identical	36.5	(−)	1	*A. terreus*	Probable	Died	3.6
5	Emergent	53/F	FHF	Compatible	20.2	(−)	0	*A. fumigatus*	Proven	Survived	57.5
6	Elective	66/M	HCC	Incompatible	9.0	(+)	5	*E. faecalis*	–	Survived	26.3

M male, *F* female, *HBV-LC* hepatitis B virus-liver cirrhosis, *FHF* fulminant hepatic failure, *PBC* primary biliary cirrhosis, *HCC* hepatocellular carcinoma, *MELD* model for end-stage liver disease, *LDLT* living donor liver transplantation, *Ps. aeruginosa Pseudomonous aeruginosa*, *MRSA* methicillin-resistant *Staphylococcus aureus*, *A. fumigatus Aspergillus fumigatus*, *A. terreus Aspergillus terreus*, *E. faecalis Enterococcus faecalis*, *IPA* invasive pulmonary aspergillosis
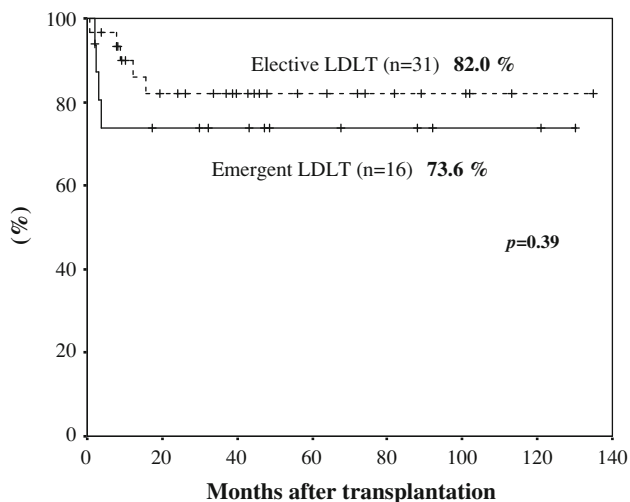
Fig. 1 The patient survival rate of the emergency and elective LDLT patients. *LDLT* living donor liver transplantation

and those of elective LDLT patients were 82.0 and 82.0%, respectively. The patient survival rate of the emergency LDLT group was therefore inferior to that of the elective LDLT group, although the difference was not significant ($P = 0.39$; Fig. 1).

Discussion

LDLT is a timely and lifesaving procedure for fulminant hepatitis [5], but the long-term survival outcome is controversial. The complications of emergency LDLT were reported to be acute cellular rejection [5, 8], surgical complications [4], or opportunistic infection [5]. Our study showed that the frequency of surgical complications was not

significantly different between the emergency LDLT and elective LDLT groups, but the rate of postoperative pneumonia was significantly higher in the former group. Thus, avoidance of respiratory complications is crucial for increasing the survival rates of the emergency LDLT group.

The present study showed that the MELD score was higher in emergency LDLT patients than in elective LDLT patients. In addition, the preoperative lymphocyte count was significantly lower in patients who underwent an emergency LDLT, and they received more frequent preoperative immunosuppressive therapy than elective LDLT patients. Thus, emergency LDLT patients appear to suffer from more preoperative immunosuppressive conditions. Furthermore, emergency LDLT patients received tracheal intubation therapy at a higher frequency than elective LDLT patients and had a higher occurrence of postoperative respiratory infections.

IPA was shown to be the most frequent cause of postoperative infection in this study. Therefore, it is important that associated risk factors should be recognized at an early stage to enable empirical therapy to commence. Generally, most cases of IPA in LT recipients occur during the early period [18]. The frequency at which aspergillosis develops in the first 100 days after transplantation has previously been shown to range from 75 to 90% [19]. In this study, as all three patients developed IPA within 30 days after LDLT, it is conceivable that *Aspergillus* infection was already present during the preoperative period. Therefore, the risk factors for IPA were evaluated from the point of view of preoperative factors in this study.

Several risk factors for IPA have previously been reported, including dialysis requirements [20], increased immunosuppression [21], retransplantation [22], and

preoperative steroid administration [21]. The presence of the *Aspergillus* antigen was also found to be useful for the detection of IPA [22], but false-positive reactions with fungus-derived antibiotics or other fungal genera are a matter of concern [23]. The polymerase chain reaction (PCR) assay of bronchoalveolar lavage fluid is an accurate test for detection of *Aspergillus* spp. DNA, but it does not differentiate between infection and colonization [24]. Therefore, the results must be considered cautiously in conjunction with diagnostic procedures.

In this study, a preoperative high $(1 \rightarrow 3)$-β-D-glucan serum level (>20 pg/ml), advanced age (>52 years), and a low PaO_2/FiO_2 ratio (<320) in emergency LDLT patients were found to be potential predictive factors for IPA. Serum $(1 \rightarrow 3)$-β-D-glucan detection is quick and straightforward, with results being obtainable within a day. Moreover, in a previous study, plasma $(1 \rightarrow 3)$-β-D-glucan elevation was detected earlier than a positive fungal culture in half of recorded fungemic episodes [25]. Aging is known to be related to immunodeficiency [26] as a result of dysfunction of T cells. The pathogenesis of low preoperative PaO_2/FiO_2 ratios could be multifactorial, including atelectasis caused by pleural effusion, adult respiratory distress syndrome (ARDS), and hepatopulmonary syndrome (HPS), and these easily lead to pulmonary infection [27].

We showed that IPA occurred only in emergency LDLT patients, i.e., those with severe immunosuppression. Such patients should be considered a high-risk group for the development of IPA, requiring more careful management, including empiric antibiotic therapy. The preoperative administration of voriconazole [28] should be considered, whereas the administration of systemic immunosuppressants, such as tacrolimus and steroids, should be reduced as much as possible [16]. Although the perioperative improvement of nutrition is also necessary [29], preoperative ingestion was shown to be fundamentally difficult because emergency LDLT patients often experience a hepatic coma. Therefore, preoperative enteral nutrition using a nasointestinal feeding tube may be effective. Strict postoperative management can ensure the survival of some IPA patients, as reported in the present study. Thus, the rate of IPA complications can be controlled, and the prognosis of emergency LDLT patients might be further improved.

In conclusion, immunosuppression was stronger and the risk of postoperative pneumonia was higher in emergency LDLT patients compared with elective LDLT patients. IPA was the most frequent cause of hospital death in emergency LDLT patients, with preoperative high $(1 \rightarrow 3)$-β-D-glucan serum levels, advanced age, and low PaO_2/FiO_2 ratios found to be predictive factors. Empiric antibiotic therapy should be considered for emergency LDLT patients who fulfill these factors to improve their outcomes and survival rates.

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