

Living-donor liver transplantation for moderate or severe porto-pulmonary hypertension accompanied by pulmonary arterial hypertension: a single-centre experience over two decades in Japan

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Authors' contributions

E. Ogawa, T. Hori, H. Doi and H. Segawa collected the data. E. Ogawa and T. Hori performed this research. H. Doi and H. Segawa provided academic contributions based on their specialized experiences. S. Uemoto supervised this research.

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Abbreviations: Acute cellular rejection, ACR; Abernethy malformation, AM; acute volume challenge test, AVCT; body surface area, BSA; blood volume, BV; congenital biliary atresia, CBA; cardiac index, CI; cardiac output, CO; deceased-donor liver transplantation, DDLT; endothelin-1, ET-1; graft-to-recipient weight ratio, GRWR; hepato-pulmonary syndrome, HPS; intensive care unit, ICU; living-donor liver transplantation, LDLT; liver needle biopsy, LNB; nitric oxide, NO; orthotopic liver transplantation, OLT; Model for End-stage Liver Disease, MELD; mean arterial pressure, mAP; mean pulmonary arterial pressure, mPAP; Paediatric End-stage Liver Disease, PELD; pulmonary arterial hypertension, PAH; pulmonary capillary wedge pressure, PCWP; prostaglandin I₂, PGI₂; postoperative day, POD; porto-pulmonary hypertension, PPHTN; pulmonary vascular resistance, PVR; right ventricle, RV; steroid pulse therapy, SPT; total peripheral resistance, TPR; United Network for Organ Sharing, UNOS.

Abstract

Background. Candidates for orthotopic liver transplantation (OLT) often have porto-pulmonary hypertension (PPHTN) with pulmonary arterial hypertension (PAH). Poor outcomes of PPHTN contraindicate OLT. There are no guidelines for living-donor liver transplantation (LDLT) in PPHTN patients.

Methods. We present our experiences of LDLT in six patients with moderate or severe PPHTN, along with our institutional guidelines. Three had liver cirrhosis and three were non-cirrhotic. Catheterization-studies were undertaken before, during and after LDLT, and the mean pulmonary arterial pressure (mPAP), cardiac output (CO), pulmonary vascular resistance and total peripheral resistance (TPR) were monitored.

Results. The results showed significant differences in CO and TPR between cirrhotic and non-cirrhotic patients before, during and after LDLT. Cirrhotic patients showed systemic hyperdynamic state. Two cirrhotic patients showed poor responses to pre-transplant treatment and continued to have increased PAH and poor clinical courses after LDLT. LDLT has an advantage of flexible timing of LT. Currently in our institution, PPHTN patients with mPAP <40 mmHg were registered for LDLT after treatment and catheterization. However, LDLT was performed when mPAP was ≤ 35 mmHg, leading to improved outcomes.

Conclusion. PPHTN patients with well-controlled PAH, or secondary PAH resulting from porto-systemic shunts, may be appropriate candidates for LDLT after careful considerations.

Introduction

Advanced liver disease results in cardiopulmonary disorders, including porto-pulmonary hypertension (PPHTN) and hepato-pulmonary syndrome (HPS). In addition, eventration of the diaphragm because of intractable ascites, or easily-broken ribs because of vitamin D deficiency, often disrupt ventilation. Hepatic failure and pulmonary arterial hypertension (PAH) may also be accompanied by congenital diseases such as Alagille syndrome. In immunocompromised patients with end-stage liver disease, such problems with the cardiopulmonary circulation result in increased mortality.

Previous studies show that (depending on the institutional definition) the frequency of cardiopulmonary disorders in patients with liver cirrhosis ranges between 5.3-8.4% [1,2]. Although PPHTN in patients with advanced liver disease was initially defined as PAH due to portal hypertension, the current definition of PPHTN includes secondary PAH due to porto-systemic shunts, as seen in patients with Abernethy malformation (AM). In other words, the presence of portal hypertension may not always be necessary for a diagnosis of PAH [3,4]. However, HPS is defined as liver disease with abnormal pulmonary gas exchange and evidence of intrapulmonary vascular dilatation that results in a right-to-left intrapulmonary shunt. Therefore, PPHTN and HPS should be considered as different pathological states.

Several studies define the diagnostic criteria for PPHTN in association with portal hypertension as follows: (i) mean pulmonary arterial pressure (mPAP) >25 mmHg and pulmonary capillary wedge pressure (PCWP) <15 mmHg; (ii) pulmonary vascular resistance (PVR) >120 dynes $\cdot$ s $\cdot$ cm $^{-5}$; and (iii) the exclusion of other causes, such as congenital cardiac disorders [5–11]. In paediatric patients, an mPAP of >20 mmHg is indicative of PPHTN.

Previous studies show that 38-41% of PPHTN patients die within 15 months of diagnosis and that 50% of untreated PPHTN patients die within 6 months of diagnosis [3,12]. PPHTN causes right ventricular dysfunction, and 36% of PPHTN patients die during the early postoperative period after orthotopic liver transplantation (OLT) because of right ventricular dysfunction, acute respiratory distress syndrome, and cardiovascular collapse [13]. This, coupled with poor outcomes after OLT, led many physicians to believe that OLT was contraindicated in PPHTN patients with moderate (mPAP $\geq$ 35 mmHg) or severe (mPAP $>$ 50 mmHg) PAH [10,14,15]. However, some reports suggest that the outcome for OLT in PPHTN patients with mild PAH (mPAP $<$ 35 mmHg) has improved [13,16,17]. Successful OLT in PPHTN patients needs to be established, and some studies have focused on this [10,13,17-26]. However, the actual strategy for OLT in PPHTN patients with PAH is still unclear, especially with respect to living-donor liver transplantation (LDLT).

Though deceased-donor liver transplantations (DDLTs) make up the majority of OLTs in the United States and Europe, almost all OLTs performed in Japan are LDLTs. The indications for OLT as a treatment for end-stage liver disease are almost identical for DDLT and LDLT; however, each OLT has its own particular characteristics. For LDLT, donor selection and graft volume are more limited, but shorter cold ischemic times and more flexibility in the timing of OLT are an advantage. In this retrospective study, we focused on PPHTN patients who underwent LDLT in our institution within the last two-decades. To our knowledge, this is the first study of the long-term experiences in a single centre performing LDLT in PPHTN patients with PAH. Based on our retrospective evaluations, we discuss the outcomes of LDLT in PPHTN patients with PAH, with the aim of establishing strategies for the successful use of LDLT as a treatment for this condition.

Patients and Methods

Patients

A total of 1421 recipients, who underwent LDLT at Kyoto University Hospital between 1990 and 2010, were enrolled in the study. The median of follow-up period was 6.9 years (range: 1 day (patient died) to 20.5 years).

In our institution, all recipients were received cardiac survey by Doppler ultrasound beforehand. Patients received advanced investigations including catheterization-study, if any abnormalities were detected or suspected. Patients with mild PAH, such as those with Alagille syndrome and suspicious cases identified during the survey, underwent LDLT without any intensive preoperative therapy for PPHTN. Six patients (3 male and 3 female; median age 8.3 years, range: 5.0-21.0 years) with moderate or severe PAH underwent LDLT. The median body surface area (BSA) was 0.93 m² (range: 0.67-1.67 m²). The primary disease was congenital biliary atresia (CBA) in four cases and AM (one each of type Ib and II) in two cases (Table 1). The two cases of AM have been documented in detail elsewhere [27,28]. The protocol used in this study was approved by the Ethics Review Committee for Clinical Studies of Kyoto University Graduate School of Medicine (Approved No.: E976).

Important parameters for the catheter studies before, during and after LDLT

Cardiac catheter studies were performed before OLT if required. All six patients in this study received detailed catheterization-studies both before and after LDLT. Swan-Ganz catheters were used routinely both during OLT and in the intensive care unit (ICU) and cardiac parameters were

closely monitored throughout the perioperative period.

mPAP (mmHg), mean arterial pressure (mAP, mmHg), cardiac output (CO, L/min) and PCWP (mmHg) values were collected retrospectively. The cardiac index (CI, L/min/m²) was calculated as: CO/BSA. The PVR (dynes·s·cm⁻⁵) was calculated using the following formula: $PVR = (mPAP - PCWP) \times 80 / CO$ (13,17). Previous studies show that the total peripheral resistance (TPR) and/or systemic vascular resistance (peripheral vascular resistance) reflects the peculiar systemic haemodynamics in cirrhotic patients [29–32]. TPR (dynes·s·cm⁻⁵) was calculated using the following formula: $TPR = mAP \times 80 / CO$ [30,33].

In our institution, to evaluate the function of the right ventricle (RV), acute volume challenge test (AVCT) was performed during catheter study before LDLT. Normal saline of 10ml/kg body weight was injected for 6 to 7 minutes via cardiac catheter.

We also evaluated the temporal changes in each of the parameters: (i) Upon initial diagnosis of PAH (cardiac catheterization-study); (ii) after the induction of treatment (cardiac catheterization-study); (iii) during LDLT (via Swan-Ganz catheter after the induction of anaesthesia); (iv) after LDLT in the ICU (after weaning from respiratory ventilation); (v) up until discharge or the first cardiac investigation after discharge (catheterization-study); and (vi) the latest cardiac investigation after LDLT (catheterization-study).

Immunosuppression

Immunosuppression after LDLT was comprised tacrolimus and methylprednisolone. The trough level of tacrolimus was maintained at 8-15 ng/ml during early post-operative period, based on the clinical findings in each case. Methylprednisolone was given intravenously (1 mg/kg) once daily from postoperative days (POD) 1 to 3 followed by 0.5 mg/kg once daily for

the next 3 days. On POD 7, 0.3 mg/kg of methylprednisolone was given intravenously. Steroids were switched to oral prednisolone 0.3 mg/kg once daily on POD 8 and this dose was reduced to 0.1 mg/kg 4 weeks after LDLT. Thereafter, the immunosuppression was controlled according to each clinical course.

Histopathological analysis of native livers and liver needle biopsy (LNB) results

Native livers were assessed macroscopically and microscopically by at least two experienced histopathologists. If necessary, LNB was performed after LDLT. Five of the six PAH cases underwent LNB. Liver tissues were fixed in neutral-buffered formalin, embedded in paraffin and sliced into sections (4- μ m thick). The histopathological findings were assessed after standard haematoxylin and eosin staining, and hepatic fibrosis was reconfirmed by Masson trichrome and reticulin staining. Liver fibrosis was scored using a five-grade scale (F0–F4) according to the METAVIR scoring system [34]: F0, no fibrosis; F1, portal fibrosis without septa; F2, portal fibrosis with rare septa; F3, numerous septa without cirrhosis; F4, cirrhosis.

Statistical analysis

Results were expressed as the median and the range. Survival rates were calculated using the Kaplan-Meier method, and the log-rank test was used for between-group comparisons. The differences between unpaired continuous or discontinuous variables between two groups were analysed by Student's *t* test. For individually, temporally, and repeatedly measured data, the differences in changes over time between groups were analysed by repeated measures ANOVA. Statistical calculations were performed using SPSS Software, Version 17.0 (SPSS Inc., Chicago, IL 60606, USA). A *p* value of < 0.05 was considered to be statistically significant.

Results

Profiles before LDLT

All patients had a confirmed history of respiratory disturbances such as hypoxemia, lip cyanosis, and puffing when breathing. The standard deviations in height and body weight were 0 (range: 0.8–0.5) and -0.1 (range: -0.9–0.3), respectively. Four of five recipients (aged < 20 years) had a history of reduced growth. The United Network for Organ Sharing (UNOS) status was estimated to be III in five cases and IIB in one case. The median Model for End-stage Liver Disease (MELD) or Paediatric End-stage Liver Disease (PELD) score was 4.5 points (range: 0–13 points). Grafts in five cases were from the father and in one case from the mother. Human leukocyte antigen typing indicated no barriers to LDLT. The ABO blood groups were identical in four cases, and compatible in two cases. The pre-transplant profiles are summarized in Table 1.

Surgical treatments before LDLT

Overall, 5/6 patients had undergone surgery before LDLT. All of the CBA cases had undergone Kasai's operation. Two of these cases received additional surgery after Kasai's operation; one for a distal spleno-renal shunt due to portal hypertension (Case 1), and another underwent seven re-boring operations (Case 3). One patient with AM type II underwent ligation of a porto-systemic shunt 4.2 years before LDLT (Case 5). Surgery performed prior to LT is outlined in Table 1.

Treatment for PAH prior to LDLT

The interval from initial diagnosis of PAH to LDLT was 0.96 years (range: 0.8-11.9 years). Continuous intravenous prostaglandin I₂ (PGI₂) was given to all patients before LDLT, and oxygen was given in 5/6 cases.

Catheterization-studies before LDLT showed that 4/6 patients (Cases 3-6) had a positive reaction to the loading tests and/or a negative response to the AVCT, though two cases showed low reactivity against the loading tests and a positive response to the AVCT (Case 1 and 2). In Case 2, PGI₂ treatment was discontinued 8.8 years after LDLT owing to a catheter-related infection and deteriorations in quality of life and activities of daily living. Thereafter, PAH worsened temporarily. In retrospect, we feel that PGI₂ had a positive effect on reducing PAH in Case 2. The period of PGI₂ treatment prior to LDLT ranged from 6–9 months.

Currently, in our institution, we determine the time point after induction of anaesthesia at which LDLT should be performed. The cut-off level for mPAP (measured via a Swan-Ganz catheter) is 35 mmHg. If mPAP is >35 mmHg, we postpone LDLT and continue to manage the PAH. LDLT is performed when the mPAP after anaesthesia is controlled at ≤35 mmHg. Although LDLT was postponed in two cases in the present study (Cases 3 and 4), these patients received LDLT after further treatment for PAH. The mPAP and PVR values at the time of LDLT were 34.0 mmHg (range: 23-54 mmHg) and 244.4 dynes·s·cm⁻⁵ (range: 81.8-281.7 dynes·s·cm⁻⁵), respectively. The treatments for PAH prior to LDLT are summarized in Table 2.

Profiles during LDLT

The median operation time was 628 min (range: 484-931 min) and the median amount of intra-operative blood loss was 2965 ml (range: 420-3970 ml). Graft types were as follows: two extended lateral-segment grafts, two left-lobe grafts, one posterior-segment graft, and one right-

lobe graft without the middle hepatic vein. The median of body weight was 26.0 kg (range: 15.4-61.6 kg), and the median graft weight was 342.5 g (range: 280-790 g). The median graft-to-recipient weight ratio (GRWR) was 1.30 g (range: 0.95-2.24) (Table 1). A small-for-size graft is defined as a graft to GRWR <0.8 or a ratio of graft weight against standard liver volume <40%, and these grafts result in a high mortality and morbidity [35,36]. Our six cases in this study had appropriate graft size, though LDLT can not avoid inevitable insufficiency of allograft size. The median cold ischemic time was 73.5 min (range: 26–346 min) and the median warm ischemic time was 30.5 min (range: 22-61 min). The median anhepatic phase was 58.5 min (range: 42-75 min). Though side clamp of the inferior vena cava was performed during LDLT, total clamp did not be performed. Temporal portal-systemic shunt was made only in Case 1, though we currently do not use temporal portal-systemic shunt. From 2006, an intentional control of portal venous pressure <15 mmHg was performed during adult LDLT in our institution. Retrospectively, portal venous pressure was monitored only in Case 3.

Cirrhotic findings at LT

The Child-Pugh score was 6.5 points (range: 5-10 points). Imaging studies prior to LDLT showed that 3/6 cases (Cases 1,2 and 4) had cirrhosis. The CO, CI and TPR values were 5.88 L/min (range: 3.60-17.60 L/min), 5.49 L/min/m² (range: 3.33-17.40 L/min/m²) and 942.9 dynes·s·cm⁻⁵ (range: 327.3–1361.3 dynes·s·cm⁻⁵), respectively. Hepatic fibrosis in the native livers was assessed as follows: two at F3 and one each at F0, F1, F2 and F4 (Table 3).

Liver cirrhosis was apparent in three cases (Cases 1, 2 and 4); the other three cases (Cases 3, 5 and 6) did not seem to have signs of advanced liver cirrhosis. Statistical differences were found between cirrhotic and non-cirrhotic patients with regard to the Child-Pugh score ($p = 0.0023$),

TPR ($p = 0.0164$) and the F score ($p = 0.0249$). Although the CO and CI values were higher in cirrhotic recipients than in non-cirrhotic recipients (Table 3), these differences did not reach statistical significance.

Clinical course and outcome after LDLT

The length of hospital stay was 55.0 days (range: 51–97 days) and the follow-up LNBs were F0 and F1. One patient died on POD 12. The follow-up term in the surviving patients was 3.6 years (range: 1.8–9.9 years) (Table 4). The survival curves after LDLT showed no statistical differences in survival rates between LDLT recipients with or without PPHTN ($p = 0.8114$). The results of long term blood gas analyses after LDLT in 4/6 patients are shown in Table 4. Case 4 showed no respiratory discomfort after LDLT, so blood gas analysis was not performed in this case.

Catheter-related infections occurred in 5/6 cases (83.3 %) during PGI₂ therapy. In four cases (Cases 3–6), PGI₂ was successfully withdrawn after LDLT, and the patients were followed-up. In one case (Case 2), PGI₂ was stopped 8.8 years after LDLT without stable mPAP. The time of PGI₂ withdrawal after LDLT was 1.9 years (range: 0.9–8.8 years) in the surviving five cases (Table 2).

In one patient (Case 1), PAH became worse after LDLT regardless of intensive care, causing cardiac failure and death. In Case 2, PAH became worse 2 years after LDLT. A remnant from a spleno-renal shunt was detected, and we consider that this contributed to the increase in PAH. Splenectomy and ligation of the shunt were subsequently performed on POD 783. However, the resulting decrease in mPAP was not enough. Therefore, these two cases (Cases 1 and 2) were considered to be PPHTN recipients with a poor clinical course and outcome after LDLT (Table

4).

In case 4, surgical haemostasis was performed on POD 1 and 12 because of intraperitoneal bleeding after LDLT. In this case, a haemorrhagic tendency was observed. Acute cellular rejection (ACR), which was observed in four cases, was successfully treated by steroid pulse therapy (SPT). Drug-induced liver dysfunction was also successfully treated (Table 4).

Changes of cardiac and Swan-Ganz catheter parameters before, during and after LDLT

The changes in mPAP, CO, SVR and TPR, before, during and after LDLT are shown in Fig. 1. The *P* values between cirrhotic and non-cirrhotic patients relating to changes in mPAP, CO, PVR and TPR were 0.1478, 0.0495, 0.4269 and 0.0030, respectively. The changes in CO and TPR in cirrhotic and non-cirrhotic recipients were significantly different (Table 5). The two patients (Cases 1 and 2) with increased PAH after LDLT both had liver cirrhosis. The *p* values related to changes in mPAP, CO, PVR and TPR over time in recipients with or without a good clinical course were 0.0256, 0.7582, 0.3767 and 0.3789, respectively. The difference in mPAP between patients with or without a good clinical course after LDLT was statistically different (Table 5).

Discussion

The cirrhotic haemodynamic state is characterized by high CO or CI values, a large blood volume (BV), a reduced or normal central BV, a low TPR, mild tachycardia and low or normal aortic pressure [30,37-39]. In particular, TPR is considered to be the most reliable indicator of vascular alterations in cirrhotic patients [30–32]. The peculiar haemodynamics seen in cirrhosis are referred to as ‘hyperdynamic’, and are indicated by a large BV, high CO and a low TPR

[33,40]. Previous studies clearly show that a systemic haemodynamic state persists in cirrhotic recipients after OLT regardless of the restoration of portal pressure [33,37,41,42] and that optimal systemic haemodynamics are required for excellent outcomes after OLT [33,40,43]. Even subtle disorders in systemic haemodynamics during the early postoperative period after OLT may result in decreased splanchnic flow [33,40], subsequently disrupting liver regeneration [43]. The two cases (Cases 1 and 2) with persistently elevated PAH after LDLT both had liver cirrhosis. One patient died during the early postoperative period (Case 1). Because the cirrhotic hyperdynamic state is one of several possible reasons for PAH in this case, post-operative management on the dry-side may be effective in controlling mPAP. However, maintenance of a hyperdynamic state during the perioperative period is important for excellent OLT results in cirrhotic patients because the collateral vessels do not disappear immediately, even after restoration of portal pressure [33,40,43]. Small BVs result in decreased portal flow and subsequent graft loss. Thus, the postoperative management of cirrhotic patients after OLT involves a dilemma to maintain a low mPAP.

The aetiology of PPHTN is still unclear, although several mechanisms have been suggested. One hypothesis is that the cirrhotic hyperdynamic state itself causes mild increases in pulmonary arterial pressure and shear resistance in the pulmonary vessels. Another is that some vasoactive substances impact on the pulmonary vascular bed, as patients with portal hypertension show increased concentrations of vasoactive substances such as endothelin-1 (ET-1), angiotensin II, norepinephrine, vasopressin, nitric oxide (NO), leukotriene, endotoxin and serotonin [44–47]. These vasoactive substances, which are usually metabolized in the liver via the portal flow, are not defused in cirrhotic livers, or do not flow into the liver because of the formation of collateral vessels [45,48,49]. Subsequently, these substances flow directly into the right side of the heart.

This pathway may explain PPHTN in patients with porto-systemic shunts. In one case (Case 1), a distal spleno-renal shunt was performed to control the portal pressure. We do not recommend this type of surgical treatment for PPHTN patients because of the risk of PAH caused by vasoactive substances, as porto-systemic shunts may exacerbate PAH.

We performed LDLT in two patients with AM (Cases 5 and 6). Because of the mechanisms involved and the malignant potential of this condition [28], OLT may become the definitive treatment for PPHTN patients with porto-systemic shunts. We suggest that PPHTN patients with PAH due to porto-systemic shunts are good candidates for LDLT, although ligation of the porto-systemic shunts should be the initial treatment for patients with AM type II.

Several therapies for PAH have been documented. Because of advances in diagnosis and treatment over the last two decades, the median survival rates for PPHTN patients with PAH have improved from 68-81.1% at 1 year, to 48-61.1% at 3 years, and 34-57.9% at 5 years [50]. PPHTN requires the correct treatment. Many agents, such as oxygen, nitric oxide, phosphodiesterase 5 inhibitors and ET-1 receptor antagonists are effective for the treatment of PPHTN patients with PAH [5,51-53]. However, some agents have side effects, such as increasing the effects of immunosuppressant drugs, hepatocyte toxicity and enhancement of the cirrhotic hyperdynamic state [23,54,55]. Thus, some agents cannot be used after OLT. After the introduction of epoprostenol (a synthetic analogue of prostacyclin, PGI₂), the outcome for PPHTN patients with PAH improved [5,54]. Currently, PGI₂ is considered a key drug for the control of PAH [20,21]. However, PGI₂ also has problems, including central line placement, drug preparation/handling, intensive patient education and the inhibition of platelet aggregation [54]. Haemorrhagic tendency is one problem during the early postoperative period, and 1/6 cases (Case 4) required additional surgery after LDLT because of inhibited platelet coagulation caused

by continuous PGI₂ administration. However, PGI₂ is only active for a short time and is chemically unstable (although the compound has adequate stability for 24 h in carbonate buffer (pH 10.0) at 0 °C). Also, a mobile device is required for continuous infusion and a central venous catheter is needed to avoid painful the vein irritation caused by peripheral administration [56]. The incidence of catheter-related sepsis has been reported as 0.1-0.6 cases per patient-year [56,57]. Immunosuppression after LDLT carries a risk of infection (the rate of catheter-related infections in our patients was high). Thus, quality of life and activities of daily living may be disturbed. Indeed, we had to discontinue PGI₂ treatment in one case for these very reasons (Case 2). However, the effective control of moderate/severe PPHTN prior to OLT is associated with excellent outcomes [19], and we speculate that PGI₂ still play an important role before, during and after LDLT. PGI₂ therapy was successfully withdrawn in four cases after LDLT. We found no significant differences in PVR between PPHTN patients, regardless of clinical course. However, unstable mPAP appeared to be associated with clinical course. One possible explanation is that PGI₂ affected vasoconstriction and pulmonary vascular remodelling, even in PPHTN patients with unsatisfactory reductions in mPAP. In one case, PAH worsened 2 years after LDLT (Case 2) and a remnant from a spleno-renal shunt was detected. At that time, we considered that this shunt may have caused the increase in PAH. Therefore, ligation of the shunt and splenectomy were performed. However, the decrease in mPAP was still insufficient. One possible explanation is that organic consolidation within the pulmonary vessels had already occurred during the course of the disease. In this case, no signs of cardiac failure were detected 9.9 yr after LDLT, though a temporal increase in PAH was observed after withdrawal of PGI₂.

Previous studies show that only 29% of untreated PPHTN patients survive after OLT [10] and that patients with moderate/severe PPHTN (mPAP >35 mmHg and PVR >250 mmHg) have a

>90% risk of death after OLT [13]. Effective pharmacological control of moderate/severe PPHTN prior to OLT is associated with excellent survival rates [19].

Our results showed that two recipients of LDLT (Cases 1 and 2) had poor a response to treatment before LDLT, and their mPAP showed different courses after LDLT compared with the other four patients. The clinical course in these two cases were retrospectively consistent with the currently-documented criteria prior to OLT [13,16,17], and illustrate the importance of intensive pre-operative control of PAH for successful OLT [19]. The flowchart currently used in our institutional guidelines for LDLT in PPHTN patients is shown in Table 6. PGI₂ therapy was introduced when mPAP was >35 mmHg. Though we want to shorten the waiting times for LDLT, this therapy may be continued for 6-9 months prior to LDLT if necessary. Retrospectively, three cases (Cases 1-3) did not fulfil the criteria set out in previous studies (mPAP >35 mmHg and PVR >250 mmHg) [13,16,17], and two cases (Cases 1 and 2) did not conform to our own institutional guidelines. In PPHTN patients, the RV is well designed for volume transmission, but does not have the muscle power to deal with the increased work caused by an increased afterload unless the load develops very gradually to allow hypertrophy of the RV muscle. In the presence of decreased RV contractility, as seen in cases of cirrhotic cardiomyopathy, or dilatation from volume overload or increased afterload, the RV is even more sensitive to increases in work load and may become dysfunctional and fail. Right ventricular failure is commonly caused by acute increases in PVR. Once failure occurs, cardiac function declines at an accelerated pace. During OLT, temporal clamping of the inferior vena cava and hepatic vein, and the portal reflow after the anhepatic phase cause acute volume overload to the right-side of the heart, and this stress may result in right heart failure. After the restoration of portal reflow, vasoactive substances may stimulate the pulmonary artery and subsequently cause the paroxysms associated with pulmonary

hypertension. Our institution currently uses AVCT before LDLT to confirm RV function against acutely increased preloading. When mPAP is <40 mmHg, we perform AVCT. LDLT is considered if PAH is controllable and if cardiac function can be maintained during the clinical course. A decision is also based on the findings from catheter examinations and the level of brain natriuretic peptides. In our institution, cardiopulmonary variables during LDLT are checked using a Swan-Ganz catheter and LDLT may be postponed and internal treatments reconsidered if mPAP is >35 mmHg after the induction of general anaesthesia. This strategy seems to work well, even though LDLT was postponed in two cases. We suggest that a hasty decision to perform LDLT will lead to worse results in PPHTN patients, and that thoughtful decision making regarding the advantages of LDLT maybe the key to successful LDLT in PPHTN patients. This is because OLT is based on the advantages of LDLT, as the timing of LDLT is more flexible than that of DDLT.

Previous researchers documented that the mPAP value should be decreased as <35 mmHg, preoperatively [58,59]. General anesthesia involves invasive factors, and may affect mPAP values after the induction. Then, we agreed that preoperative mPAP <35 mmHg is an ideal. Actually, we still have some concerns about the patients with mPAP of 35-40 mmHg, to register as a LDLT recipient. Preoperative reactivity for pharmacological control of moderate/severe PPHTN is a key for excellent survival rates [19]. Though Case 4 preoperatively showed marginal mPAP (mPAP 35 mmHg at LDLT) in comparison with previous documents and actually received a postponement of LDLT, this case had well-kept RV function and favorite course after treatment induction. Case 6 (mPAP 35 mmHg at LDLT) survived for 9.9.years after LDLT. Our cut-off level for LDLT registration (mPAP <40 mmHg) may seem higher than that in other institutions. The timing of LDLT is more flexible, and paradoxically the criteria of mPAP ≤ 35 mmHg after

anesthesia induction seemed to work as a final check point before LDLT. Though our experiences are still not enough, we currently speculate that some patients with mPAP of 35-40 mmHg may have a potential as LDLT candidates.

Treatment of PPHTN should be considered because non-treated patients have terrible outcomes. However, the effect PPHTN treatment in candidates for OLT still requires well-designed prospective studies to establish formal guidelines [18]. Overall, we believe that, in some cases, PPHTN patients with PAH are potentially curable and that LDLT can achieve good results. PPHTN patients with well-controlled PAH, or secondary PAH due to porto-systemic shunts, may be appropriate candidates for LDLT after thoughtful consideration of the relevant factors, including clinical course, the results of catheterization-studies and Swan-Ganz monitoring, the response to therapeutic agents and the findings of imaging studies. Close follow-up after LDLT is also crucial to establish good results in PPHTN patients.

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Figure legend

Figure 1 Changes in mPAP, CO, PVR and TPR before, during and after LDLT

The mPAP, CO, PVR and TPR values are shown at each time point after LDLT. ●, Δ, ○ and ◇ represent Cases 1–4. (□) represents Cases 5 and 6 combined.

Red lines represent cirrhotic recipients (Cases 1, 2 and 4) and blue lines represent non-cirrhotic recipients (Cases 3, 5 and 6). The changes in CO and TPR between cirrhotic and non-cirrhotic recipients over time were significantly different.

Dotted lines represent recipients with a poor clinical course (Cases 1 and 2) and solid lines represent recipients with a good clinical course (Cases 3–6) after LDLT. The changes in mPAP over time between recipients with poor or good clinical courses after LDLT were significantly different.

Figure 1.

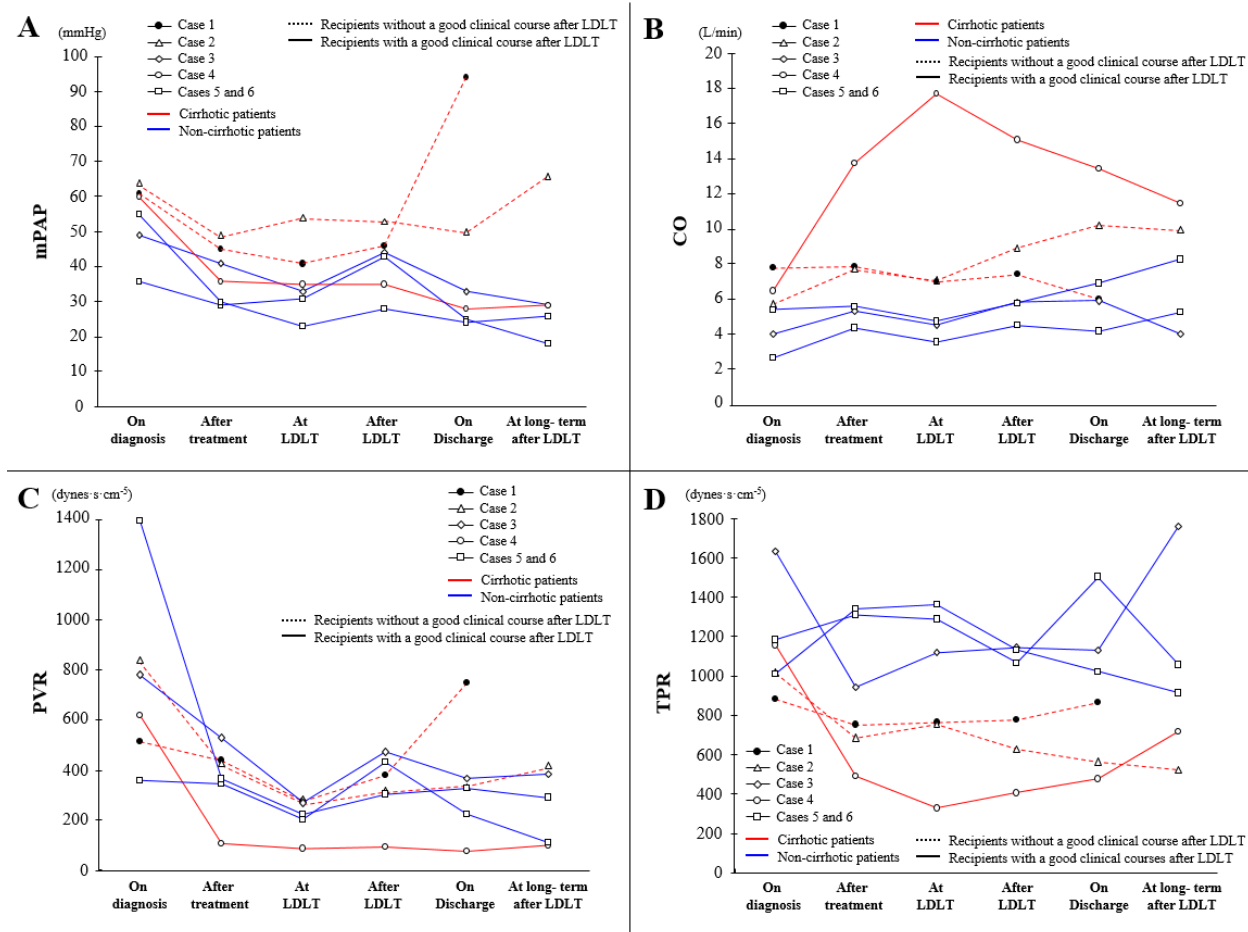


Table 1. Profiles of PPHTN patients with PAH before and during LDLT

Case	OLT	Age at LDLT (yrs)	Original diseases	Surgical treatments before LDLT	Respiratory disturbances [†]	Growth reduction ^{††}	UNOS status	MELD/PELD score (point)	ABO compatibility	GRWR
1	LDLT	17.9	CBA	Kasai's operation Distal spleno-renal shunt	+	-	III	13	Identical	1.28
2	LDLT	6.5	CBA	Kasai's operation	+	+	III	2	Identical	1.22
3	LDLT	21.0	CBA	Kasai's operation Subsequent reoperations (seven)	+	N/A	III	11	Identical	1.29
4	LDLT	9.2	CBA	Kasai's operation	+	+	IIB	3	Identical	0.95
5	LDLT	7.5	AM type II	Ligation of porto-systemic shunt	+	+	III	0	Compatible	1.57
6	LDLT	5.0	AM type Ib	-	+	+	III	6	Compatible	2.24

[†] Respiratory symptoms included hypoxemia, lip cyanosis and puffing when breathing

^{††} The values in patients of age < 20 yrs.

Abbreviations: AM, Abernethy malformation; CBA, congenital biliary atresia; GRWR, graft-to-recipient weight ratio; LDLT, living-donor liver transplantation; MELD, Model for End-Stage Liver Disease; N/A, not applicable; OLT, orthotopic liver transplantation; PAH, pulmonary arterial hypertension; PELD, pediatric end-stage liver disease; PPHTN, porto-pulmonary hypertension; UNOS, United Network for Organ Sharing.

Table 2. Treatments for PPHTN with PAH before and after LDLT

Case	Time up to LDLT [†] (yrs)	Treatments before LDLT ^{††}	Favorite reactivity against loading and challenging tests ^{†††}	Treatment term with PGI ₂ before LDLT (mo)	At LDLT			Catheter-related infection	Withdrawal of PGI ₂ after LDLT (yrs)	
					History of postponement	mPAP (mmHg)	PVR (dynes·s·cm ⁻⁵)			
1	11.9	PGI ₂ (20.0 ng/kg/min)	-	9	-	41	274.3	-	-	
2	1.1	PGI ₂ (6.0 ng/kg/min) O ₂	±	8	-	54	281.7	+	+	(8.8)
3	0.9	PGI ₂ (36.5 ng/kg/min) O ₂	+	9	+	33	266.7	+	+	(1.3)
4	0.8	PGI ₂ (20.5 ng/kg/min) O ₂	+	8	+	35	81.8	+	+	(1.9)
5	4.4	PGI ₂ (9.6 ng/kg/min) O ₂	+	6	-	31	201.7	+	+	(2.2)
6	1.7	PGI ₂ (1.9 ng/kg/min) O ₂	+	9	-	23	222.2	+	+	(0.9)

[†]Time from diagnosis to LDLT^{††}Medications at the time of LDLT^{†††}Positive reactivity against loading test (PGI₂, O₂ and NO) and negative reactivity against AVCT

Abbreviations: AVCT, acute volume challenge test; LDLT, living-donor liver transplantation; mPAP, mean pulmonary arterial pressure; PAH, pulmonary arterial hypertension; PGI₂, prostaglandin I₂; PPHTN, hypertension; PVR, pulmonary vascular resistance.

Table 3. Cirrhotic findings at LDLT

Case	Child-Pugh score (point)	Developed collaterals	Splenomegaly	CO (L/min)	CI (L/min/m ²)	TPR (dynes·s·cm ⁻⁵)	Hepatic fibrosis [†]
1	8	+	+	7.00	4.19	765.7	F3
2	9	+	+	7.10	8.88	754.9	F3
3	5	-	-	4.50	3.33	1120.0	F2
4	10	+	+	17.60	17.40	327.3	F4
5	5	-	-	4.76	5.60	1361.3	F1
6	5	-	-	3.60	5.37	1288.9	F0

[†]Histopathological assessment of removed native livers using the METAVIR score

Abbreviations: CI, cardiac index; CO, cardiac output; LDLT, living-donor liver transplantation; TPR, total peripheral resistance.

Table 4. Episodes during LDLT and clinical course and outcomes after LDLT

Case	Complications and treatments	Discharge (POD)	Blood gas analysis [†] (PaO ₂ , mmHg)	Histopathological analysis ^{††}	Outcome (d or yrs) ^{†††}
1	Confounded PAH, oversystemic PAH Cardiac failure	-	-	F0	Dead (12 d)
2	ACR (SPT) Sepsis Confounded PAH 2 years after LDLT The remnant of spleno-renal shunt (Splenectomy and the ligation of shunt at POD 783)	97	69.2	F1	Alive (9.9 yrs)
3	ACR (SPT)	51	-	F0	Alive (4.2 yrs)
4	Haemorrhagic tendency Intraperitoneal bleeding (Surgical haemostasis at PODs 1 and 12) ACR (SPT)	53	87.8	-	Alive (2.3 yrs)
5	Drug-induced liver dysfunction (the cessation of suspected drugs)	58	78.3	F0	Alive (3.6 yrs)
6	ACR (SPT)	55	100.5	F0	Alive (1.8 yrs)

[†]Long term blood gas analysis of PaO₂ levels after LDLT

^{††}Histopathological assessment in LNBs after LDLT using the METAVIR score.

The worst scores in each case are shown.

^{†††}Follow-up term

Abbreviations: ACR, acute cellular rejection; LDLT, living-donor liver transplantation; LNB, liver needle biopsy; SPT, steroid pulse therapy; PAH, pulmonary arterial hypertension; POD, post-operative day.

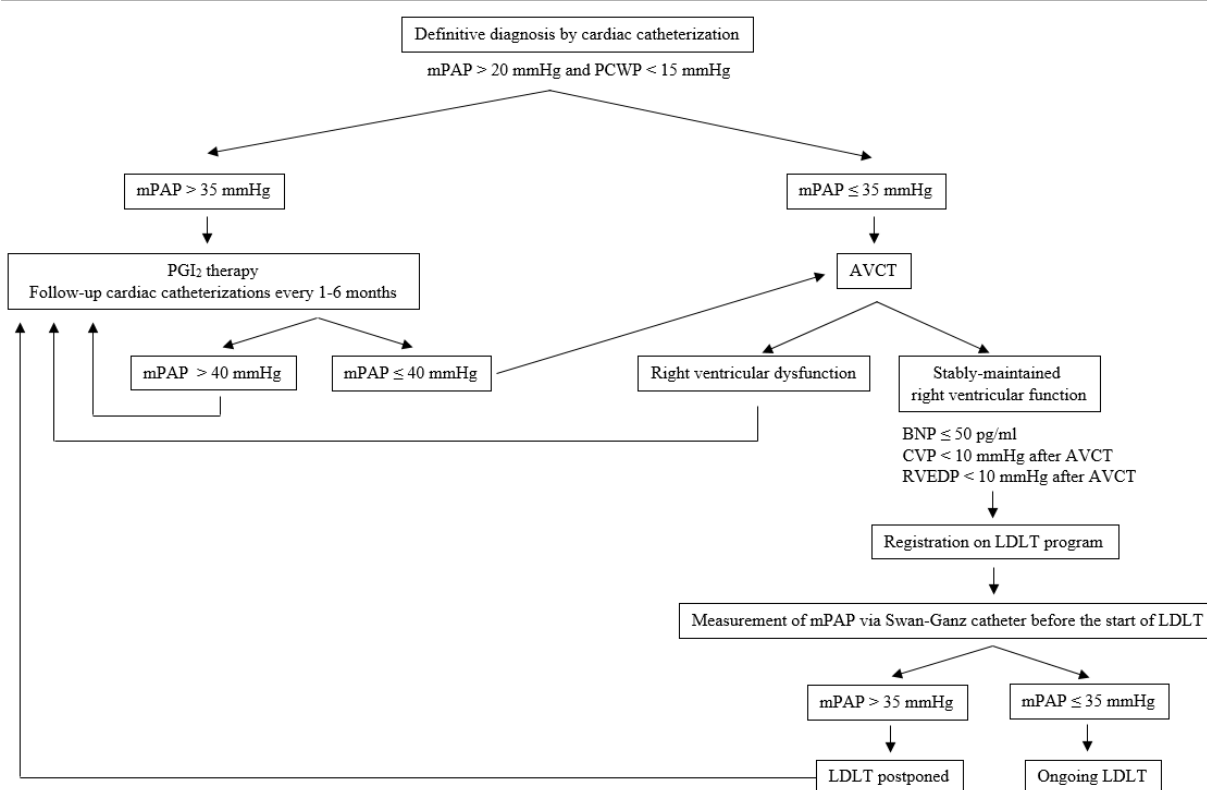
Table 5. Statistical differences in the changes over time between groups for each variable before, during and after LDLT

	Statistical differences between cirrhotic and non-cirrhotic patients [†] (Cases 1, 2 and 4 vs. Cases 3, 5 and 6)	Statistical differences between recipients with or without good clinical courses after LDLT [†] (Cases 1 and 2 vs. Cases 3-6)
mPAP	0.1478	0.0256 ^{††}
CO	0.0495 ^{††}	0.7582
PVR	0.4269	0.3767
TPR	0.0030 ^{††}	0.3789

[†]The statistical differences between groups in the changes over time of each variable were analyzed by repeated measures ANOVA.

^{††}*p* value < 0.05.

Abbreviations: CO, cardiac output; LDLT, living-donor liver transplantation; mPAP, mean pulmonary arterial pressure; PVR, pulmonary vascular resistance; TPR, total peripheral resistance.

Table 6. Flowchart of pre-transplant treatments for PPHTN patients with PAH

Abbreviations: AVCT, acute volume challenge test; BNP, Brain Natriuretic Peptide; CVP, central venous pressure; LDLT, living-donor liver transplantation; mPAP, mean pulmonary arterial pressure; PAH, pulmonary arterial hypertension; PCWP, pulmonary capillary wedge pressure; PGI₂, prostaglandin I₂; PPHTN, porto-pulmonary hypertension; RVEDP, right ventricle end diastolic pressures.

第 28 卷 第 9 号 1031 頁 ~ 1040 頁

Living-donor liver transplantation for congenital biliary atresia with porto-pulmonary hypertension and moderate or severe pulmonary arterial hypertension: Kyoto University experience

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Conflict of interest

None of the authors have financial conflicts of interest.

Authors' contributions

E. Ogawa collected the data. T. Hori and E. Ogawa performed this research. H. Doi and H. Segawa provided academic contributions based on their specialized experience. Prof. S. Uemoto supervised this research.

E. Ogawa, T. Hori, H. Doi, H. Segawa, S. Uemoto

Living-donor liver transplantation for congenital biliary atresia with porto-pulmonary hypertension and moderate or severe pulmonary arterial hypertension: Kyoto University experience

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Clin Transplant

Abstract

Porto-pulmonary hypertension with moderate or severe pulmonary arterial hypertension (PAH) is viewed as a contraindication to liver transplantation (LT) because of associated poor outcomes; however, patients with biliary atresia (BA) are generally good candidates for LT. Ten patients with moderate/severe PAH underwent living-donor LT (LDLT) at our institution; eight of these patients had BA and were the focus of this study. Preoperative therapies, including prostaglandin (PG)_{I₂}, were introduced. When mean pulmonary arterial pressure (mPAP) after treatment was <40 mmHg or initial mPAP without therapy was <35 mmHg, we performed an acute volume challenge test to evaluate right ventricular function. LDLT was performed, when mPAP after anaesthetic induction was confirmed at ≤ 35 mmHg. Six patients had favourable responses to preoperative treatment and catheter testing, but two patients showed poor responses. The two patients with poor responses had poor clinical courses with unstable mPAP after LDLT. The other six patients had successful courses with well-controlled mPAP, and PGI₂ was withdrawn or weaned following LDLT. Survival did not significantly differ between the eight BA recipients with moderate/severe PAH and 77 age-matched BA recipients without PAH from the same time period. LDLT has major benefits for BA patients with well-controlled PAH.

Keywords: congenital biliary atresia, living-donor liver transplantation, pulmonary arterial hypertension, porto-pulmonary hypertension, prostaglandin.

Introduction

Living-donor liver transplantation (LDLT) is widely performed for end-stage liver disease, especially in countries where deceased donors are scarce. Following Kasai's operation, patients with congenital biliary atresia (BA) can survive with native livers, but they continue to have abnormal liver function and signs of biliary cirrhosis (1,2). The clinical course and the survival of BA patients have greatly improved in the era of liver transplantation (LT) (1,2).

Advanced liver diseases result in cardiopulmonary disorders, including porto-pulmonary hypertension (PPHTN) and pulmonary arterial hypertension (PAH). In particular, cirrhosis is sometimes accompanied by cardiopulmonary disorders (3,4). Although PPHTN in patients with advanced liver disease used to be defined as PAH caused by portal hypertension, the current definition of PPHTN includes secondary PAH such as that due to Abernethy malformation (5,6). The current diagnostic criteria for PPHTN are defined as follows: (i) mean pulmonary arterial pressure (mPAP) >25 mmHg and pulmonary capillary wedge pressure <15 mmHg, (ii) pulmonary vascular resistance >120 dynes $\cdot$ s $\cdot$ cm $^{-5}$, and (iii) exclusion of congenital cardiac disorders (7-11). In paediatric patients, mPAP >20 mmHg is indicative of PPHTN with PAH. Previous studies have demonstrated that $\sim 40\%$ of PPHTN patients die within 15 months of diagnosis and that half of the untreated PPHTN patients die within 6 months of diagnosis (6,12). PPHTN causes right ventricular dysfunction, and 36% of PPHTN patients die during the early postoperative period after LT because of right ventricular dysfunction, acute respiratory distress syndrome, and cardiovascular collapse (13). Unfortunately, LT does not always result in the

reversal of PPHTN (14). These poor outcomes after LT have led many physicians to believe that LT is contraindicated in PPHTN patients with moderate (mPAP ≥ 35 mmHg) or severe (mPAP > 50 mmHg) PAH (10,15-17). Still, some reports suggest that LT outcomes in PPHTN patients with mild PAH (mPAP < 35 mmHg) have improved (13,18-20). Although several studies have focused on LT in PPHTN patients (10,13,18,20-25), the actual strategy for LT in PPHTN with moderate or severe PAH is still unclear.

Here, we present a retrospective study of BA patients with PPHTN and moderate or severe PAH who underwent LDLT at our institution, and we discuss the current status of LDLT for patients with moderate or severe PAH.

Patients and methods

Patients

A total of 1611 patients received LT at Kyoto University Hospital from 1990. Our institutional procedures for donor selection, donor surgery, and recipient surgery have been previously described in detail (26), as has our post-LDLT immunosuppressive regimen (5). Echocardiographic evaluation was routinely performed prior to LDLT, and patients identified as having mild or suspicious PAH underwent LDLT without any intensive therapy for PPHTN. Detailed cardiac catheter studies were performed before LDLT, if moderate or severe PAH was suspected.

Ten patients with moderate or severe PAH underwent LDLT during this period. The primary disease was congenital BA in eight cases and an Abernethy malformation (one each of type Ib and II) in two cases. The two cases with Abernethy malformation were previously reported in detail (27,28), and it is acknowledged that LDLT can drastically improve PAH due to

Abernethy malformation (5,29,30). Therefore, this study focused only on eight BA patients with moderate or severe PAH. These patients were aged 4–22 years and underwent LDLT from 2000 to 2012. This study was approved by the Ethics Review Committee for Clinical Studies of Kyoto University Graduate School of Medicine.

Treatment for moderate or severe PAH before LDLT, assessment of PAH, and registration for LDLT program

Current institutional guidelines for LDLT in patients with PPHTN and PAH have been described previously (5). In our patient population, internal treatment was considered first because of the known poor outcomes of untreated patients. Internal therapy, including prostaglandin (PG) I₂, was introduced if mPAP was >35 mmHg. Catheterization studies were repeated after treatment.

During LDLT, the temporary clamping and subsequent resumption of blood flow in the large vessels cause rapid changes in the volume loading of the right heart; this stress may result in right heart failure. Additionally, released vasoactive substances may stimulate the pulmonary artery. When indicated, our institution uses acute volume challenge test (AVCT) prior to LDLT to assess right ventricular function in the presence of acute increases in preload. The test involves the injection of normal saline (10 mL/kg body weight) over 6–7 minutes via a cardiac catheter (5). When mPAP after internal treatment is <40 mmHg or initial mPAP without therapy is <35 mmHg, we perform the AVCT during the catheter study (5).

LDLT is considered if PAH is controllable and cardiac function can be maintained during the patient's clinical course. At our institution, cardiopulmonary variables are monitored during LDLT using a Swan–Ganz catheter. LDLT may be postponed and internal treatments reconsidered if mPAP is >35 mmHg after the induction of stable general anaesthesia (5); this is

possible because LDLT carries the advantage of flexibility in its timing. LDLT is performed when mPAP after anaesthesia is controlled at ≤ 35 mmHg.

Investigations of mPAP before, during, and after LDLT

All eight patients underwent detailed catheterization studies before, during, and after LDLT. Swan–Ganz catheters were routinely placed during LDLT and in the intensive care unit (ICU), and cardiac parameters were closely monitored throughout the perioperative period. The mPAP values obtained before, during, and after LDLT were collected retrospectively. Temporal changes in mPAP were generally assessed at five time points: (i) at initial diagnosis of PAH (by cardiac catheterization study), (ii) after preoperative treatment (by cardiac catheterization study), (iii) at LDLT after anaesthetic induction (by Swan–Ganz catheter), (iv) during the ICU stay after weaning from mechanical ventilation (by Swan–Ganz catheter), and (v) at cardiac investigation after LDLT (by catheterization study).

Histopathological analysis of native livers and liver needle biopsy (LNB) results

All eight patients underwent LNB after LDLT. Liver specimens were assessed microscopically by at least two experienced histopathologists. Liver fibrosis was scored using a five-grade scale (F0–F4) according to the METAVIR scoring system (31): F0, no fibrosis; F1, portal fibrosis without septa; F2, portal fibrosis with rare septa; F3, numerous septa without cirrhosis; F4, cirrhosis.

Statistical analysis

Results were expressed as mean and standard deviation. Survival rates were calculated using the

Kaplan–Meier method; the log-rank test was used for between-group comparisons. Statistical calculations were performed using SPSS software (SPSS Inc., Chicago, IL, USA). A *p* value <0.05 was considered statistically significant.

Results

Profiles before LDLT

Pre-transplant data are summarized in Table 1. Age at LDLT ranged from 4.9 to 21.6 years. The mean Model for End-stage Liver Disease or Paediatric End-stage Liver Disease score was 7.6 ± 5.4 points. Grafts were from the father in five cases, from the mother in two cases, and from an elder brother in one case. The ABO blood groups were identical/compatible in seven cases, and incompatible in one. Lymphocyte cross-matching was negative in all cases.

Surgery for BA before LDLT

Surgery performed prior to LT is outlined in Table 1. All patients had undergone Kasai's or Suruga's operation before LDLT. Two of these cases underwent additional surgery after Kasai's operation; one underwent correction of a distal splenorenal shunt that developed because of portal hypertension, and another underwent seven reborings operations.

Treatment for PAH before LDLT

Pre-LDLT treatment for PAH and resulting changes in mPAP are summarized in Table 2. The interval from initial diagnosis of PAH to the performance of LDLT was 2.5 ± 3.9 years (range: 0.2–11.9 years). This interval was 1.1 ± 1.1 years for the six cases in which PAH was successfully treated, but 11.9 years passed before LDLT was performed in one of the cases with a

poor outcome. Continuous intravenous PGI₂ was administered to all patients before LDLT, and oxygen was given in five cases. The length of PGI₂ treatment prior to LDLT ranged from 3 to 11 months, with a mean of 7.3 ± 2.9 months. Catheterization studies performed before LDLT showed that six patients had favourable reactions to the loading tests and/or a negative response to the AVCT, but that two cases reacted poorly to the loading tests and had positive responses to the AVCT. Although LDLT was actually postponed in four cases (3, 4, 6 and 7), these patients all underwent LDLT after further treatment for PAH.

Profiles during LDLT

Intraoperative profiles are summarized in Table 3. The mean operation time and intraoperative blood loss were 781.9 ± 160.9 minutes and 2176.3 ± 1199.4 mL, respectively. Graft types were as follows: left-lobe graft ($n = 4$), right-lobe graft without the middle hepatic vein ($n = 3$), and posterior segment graft ($n = 1$). The mean cold and warm ischemic times were 135.1 ± 104.0 and 39.8 ± 12.8 minutes, respectively. The mean actual graft weight and graft-to-recipient weight ratio were 501.9 ± 209.0 g and 1.22 ± 0.35 , respectively.

Clinical courses and outcomes after LDLT

For surviving patients, the ICU and hospital stay lengths were 5.7 ± 3.1 and 91.4 ± 47.9 days, respectively. Postoperative complications and outcomes are summarized in Table 4. LNB revealed F0, F1 and F2 fibrosis. Case 1 died on postoperative day (POD) 12. The follow-up term in the surviving patients was 4.6 ± 3.9 years. A survival comparison was performed with age-matched patients who underwent LDLT at our institution during the same time period (age: 4–22 years; date: January 2000 through December 2012). Figure 1A shows the survival curves for the

LDLT recipients with PPHTN and PAH, including the two cases of Abernethy malformation ($n = 10$), and for the age- and time-matched LDLT recipients without PPHTN or PAH ($n = 151$). There was no significant difference between the groups ($p = 0.60121$). A survival comparison looking at age- and time-matched patients with BA was also performed. Figure 1B shows the survival curves for BA LDLT recipients with moderate or severe PAH ($n = 8$) and for BA LDLT recipients without PAH but of the same age and from the same era ($n = 77$; age: 4–22 years; date: January 2000 through December 2012). There was no significant difference between the groups ($p = 0.59864$).

Despite intensive care, one patient (Case 1) suffered worsening PAH after LDLT, ultimately leading to cardiac failure and death. In another patient (Case 2), PAH worsened 2 years after LDLT. A remnant from the patient's previously treated splenorenal shunt was detected and regarded to be contributing to the increase in PAH. Therefore, splenectomy and ligation of the shunt were performed on POD 783. However, the resulting decrease in mPAP was not sufficient, and PGI₂ treatment was continued. These two cases were considered as having poor clinical courses and outcomes after LDLT.

Changes in cardiac and Swan–Ganz catheter parameters before, during, and after LDLT

Changes in mPAP before, during, and after LDLT are shown in Figure 2. Post-LDLT changes in mPAP appeared to differ between patients with and without good clinical courses after LDLT. In Case 1, PAH was exacerbated after LDLT. In Case 2, PGI₂ treatment was continued for 8.8 years after LDLT and discontinued at that time owing to a catheter-related infection and deterioration in the patient's quality of life and activities of daily living. Thereafter, PAH temporarily worsened. PGI₂ treatment was resumed after a temporary discontinuation of 9 months. In

retrospect, we believe that PGI₂ had a positive effect in reducing PAH in this case (Case 2), although responses to preoperative PGI₂ therapy seemed to be insufficient. In the six successful cases (Cases 3–8), PGI₂ therapy was successfully withdrawn after LDLT or was at the weaning stage at the time of the study (Table 2). The mean time of PGI₂ withdrawal after LDLT was 0.9 ± 0.6 years in the successful cases (Table 2). Catheter-related infections occurred in four cases during PGI₂ therapy.

Discussion

BA is a rare disease with an unknown aetiology and unpredictable outcome, even when a timely diagnosis has been made and exemplary surgery has been performed (32). Currently, BA is the most common indication for LT during childhood (2,32,33). Our LDLT results in BA patients are comparable to those reported by others, and we are of the opinion that LT affords the best survival and quality-of-life for BA patients (2,32,34).

The aetiology of PPHTN with PAH is still unclear, although several mechanisms have been documented. One hypothesis is that the cirrhotic hyperdynamic state causes mild increases in PAP (34,35). Another is that certain vasoactive substances, such as endothelin-1, angiotensin II, norepinephrine, vasopressin, nitric oxide (NO), leukotriene, endotoxin and serotonin, directly affect the pulmonary vascular bed (35–40). These substances are usually metabolized in the liver via the portal blood flow. However, these substances are not degraded in cirrhotic livers, or they may not flow into the liver in these patients because of the development of collateral vessels (34–36,41). Subsequently, these substances flow directly into the right heart without hepatic metabolism (39), resulting in increased concentrations in cirrhotic patients (35–40). Paradoxically, we speculate that LT itself may be advantageous in the control of PPHTN with PAH, because

LDLT restores hepatic metabolism and leads to decreases in collateral vessels under normalized portal venous pressure.

The diagnosis and treatment of PPHTN with PAH have advanced during the past two decades, and survival rates have improved (42,43). At our institution, we view catheter studies as an important part of the pre-transplant treatment plan; consequently, catheter studies were repeated prior to LDLT in the studied patient population. Based on the catheter study results treatment plan were formulated, and therapeutic responses were evaluated. Many agents are currently available for the treatment of PAH (7,36,40,43,44), although some cannot be used after LT (35,45). Although oxygen, NO, phosphodiesterase inhibitors (sildenafil and tadalafil), endothelin receptor antagonists (bosentan and macitentan) and calcium channel blocker (amlodipine) are available for PAH treatment, their use may be associated with increased side effects when administered in conjunction with immunosuppressants after LT. Sildenafil remains a valuable option for the treatment of pulmonary hypertension in young infants (46), and we combined sildenafil administration with PGI₂ and O₂ in Case 6 prior to LDLT. In Case 5, we used a phosphodiesterase inhibitor with PGI₂ and O₂ prior to LDLT. This combination therapy appears to have been effective in the preoperative control of PAH in Cases 5 and 6.

PGI₂ has drastically improved outcomes (7,45,47), and is currently considered a key drug in the control of PAH (7,23,24,45,47). Epoprostenol is the first choice in our institution; we consider transitioning the patient from epoprostenol to treprostinil if indicated (48,49). However, the use of PGI₂ is associated with some difficulties, such as the placement of a central venous catheter, the preparation of the drug, and the handling of a mobile device, and it can inhibit platelet aggregation (45). Indeed, we observed a haemorrhagic tendency following continuous PGI₂ administration, and one patient (Case 4) required additional surgery to achieve complete

haemostasis. Because a mobile device and central venous catheter are required for continuous PGI₂ infusion (50), patients' quality of life and activities of daily living are disturbed during PGI₂ therapy. Although the incidence of catheter-related sepsis has been reported as only 0.1–0.6 cases per patient-year (50,51), immunosuppression after LDLT may increase risk of infection. For these reasons, we stopped PGI₂ treatment in one patient (Case 2), although we had to resume it to control PAH following the temporary discontinuation. However, PGI₂ was successfully withdrawn or weaned in six of seven surviving patients. Our results support the idea that PGI₂ therapy plays an important role before, during, and after LDLT (20,22–24). At our institution, catheter studies are performed at least every 3–6 months after LDLT, including the PGI₂ weaning/withdrawal period, although echocardiography is initially employed for monthly post-LDLT surveillance during the early years. The possibility of weaning or withdrawing PGI₂ is assessed using the results of these follow-up catheter studies.

Previous studies have shown that only 29% of untreated PPHTN patients survive after LT (10) and that patients with moderate or severe PAH have a >90% risk of death after LT (13). Two of our cases had poor responses to preoperative treatments for PAH (Cases 1 and 2), and their mPAPs showed different courses after LDLT compared with the six successfully treated cases. In these two cases, combined pre-surgical therapy as described above was insufficient, and the dose of PGI₂ was increased up to 20.0 ng/kg/min in Case 1. The clinical courses in these two cases were consistent with previous reports (13,18–20,22–24), and they did not fulfil the criteria established in previous studies (13,18,19) or meet our current institutional guidelines (mPAP ≤35 mmHg at LDLT) for the control of mPAP prior to LDLT (5). We suggest that unstable mPAP is associated with a poor clinical course after LDLT. Although we would like to shorten the waiting times for LDLT, continuous PGI₂ therapy was required for ~7 months before LDLT could be

performed in the studied patient population. Our results suggest that a hasty decision to perform LDLT can lead to worsened results in patients with PAH.

Although donor selection and graft volume are more limited when working with living donors, LDLT has some advantages, such as a shorter cold ischemic time and greater flexibility in its timing. To maximize this flexibility in LT timing, we made the decision to perform LDLT based on patients' mPAP after anaesthetic induction, using a 35 mmHg cut-off. Accordingly, LDLT was actually postponed in four cases, but these patients were able to undergo LDLT after additional PAH treatment.

Our mPAP cut-off of mPAP <40 mmHg for LDLT registration may seem high relative to the cut-offs used by other institutions, but it enabled us to use the flexibility in the timing of LDLT to our advantage. There was a difference between the cut-off level that we used for LDLT registration (i.e., mPAP <40 mmHg after PGI₂ therapy) and the value we required for actual performance of LDLT (i.e., mPAP ≤35 mmHg after anaesthetic induction). As documented by a previous report, well-designed prospective studies are still needed to establish formal guidelines for LT in candidates with PPHTN and PAH (21), and we strongly believe that a prospective study is needed to validate the use of a mPAP cut-off of <40 mmHg to guide LDLT performance in patients with well-controlled PAH.

LT may be effectively used in PPHTN patients; if rigorous screening, early identification of comorbid conditions, aggressive pre-transplant optimization and diligent postoperative care are practised (52). In our study, the patient who experienced the longest delay from initial diagnosis to performance of LDLT suffered a poor outcome. We speculate that LDLT itself may be advantageous in the control of moderate to severe PAH from the viewpoint of enhancing the hepatic metabolism of vasoactive substance. We believe that LDLT provides a major benefit to

BA patients and that LDLT can even achieve curability for BA patients with well-controlled PAH.

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Figure legends

Figure 1. Survival comparisons with age- and time-matched patients (4–22 years; January 2000 to December 2012) who underwent LDLT at our institution. (A) Survival curves for recipients with moderate/severe PAH ($n = 10$) and for age- and time-matched recipients without PAH ($n = 151$). (B) Survival curves for BA LDLT recipients with moderate/severe PAH ($n = 8$) and for age- and time-matched BA recipients without PAH ($n = 77$).

Figure 2. Changes in mPAP before and after LDLT, and withdrawal of PGI₂ after LDLT. Changes in mPAP before and after LDLT, with the timing of PGI₂ withdrawal indicated, for the two recipients with a poor disease course (A) and for the six recipients with a good disease course (B).

Figure 1.

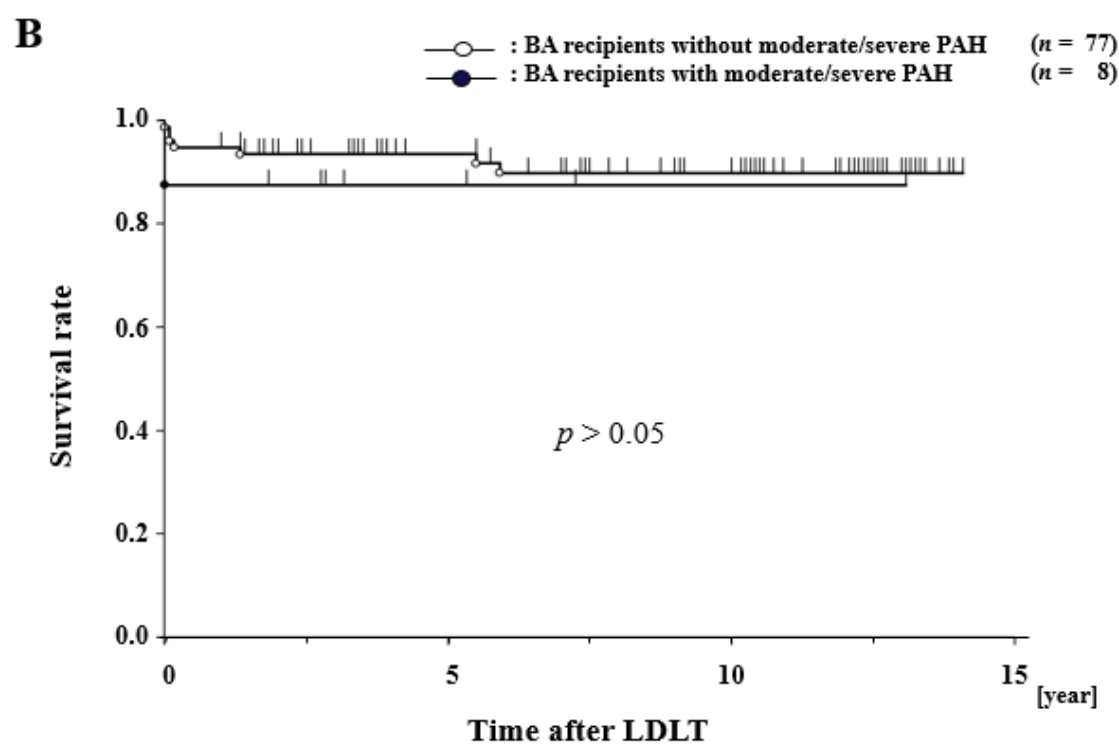
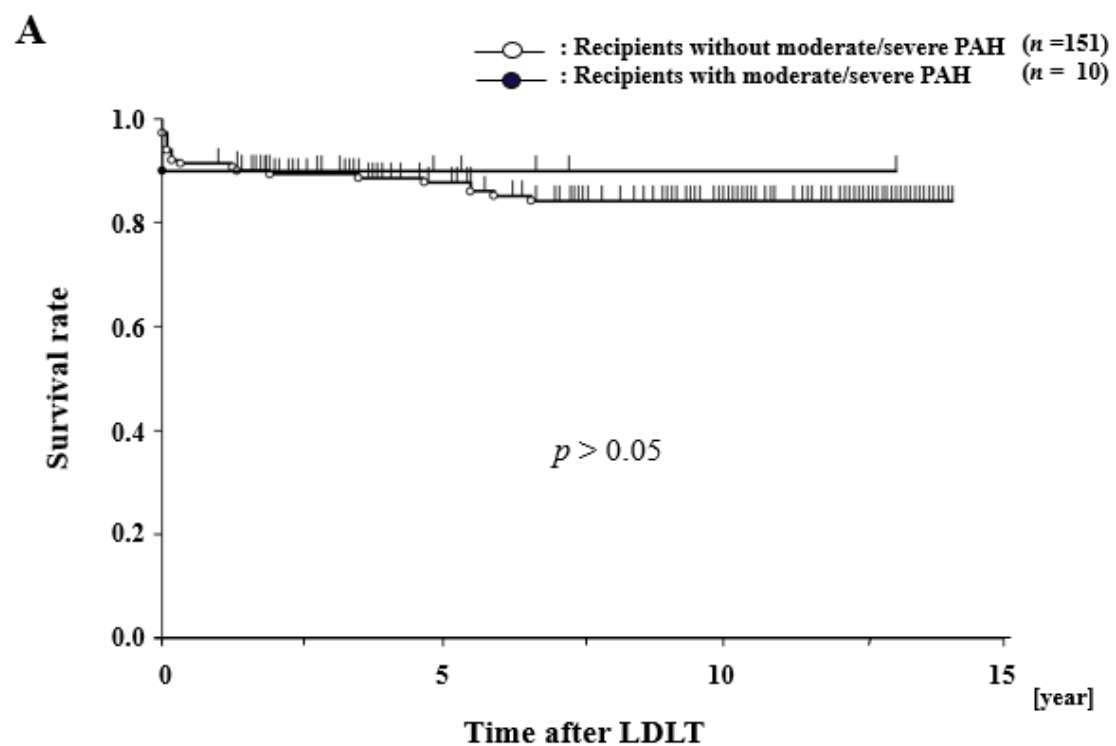


Figure 2.

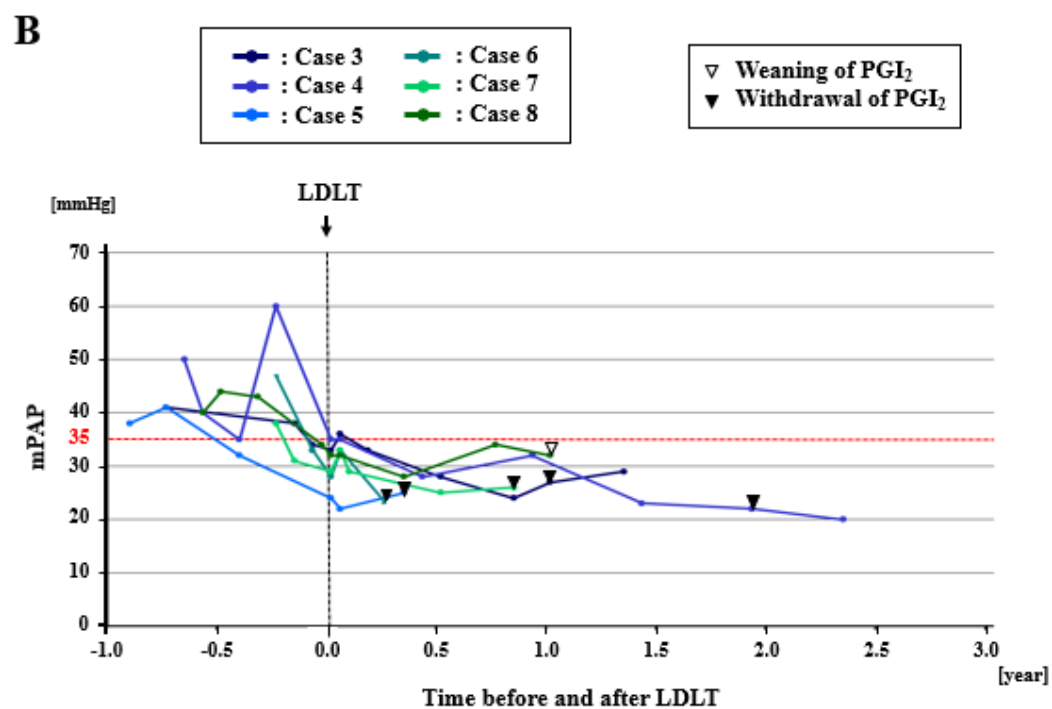
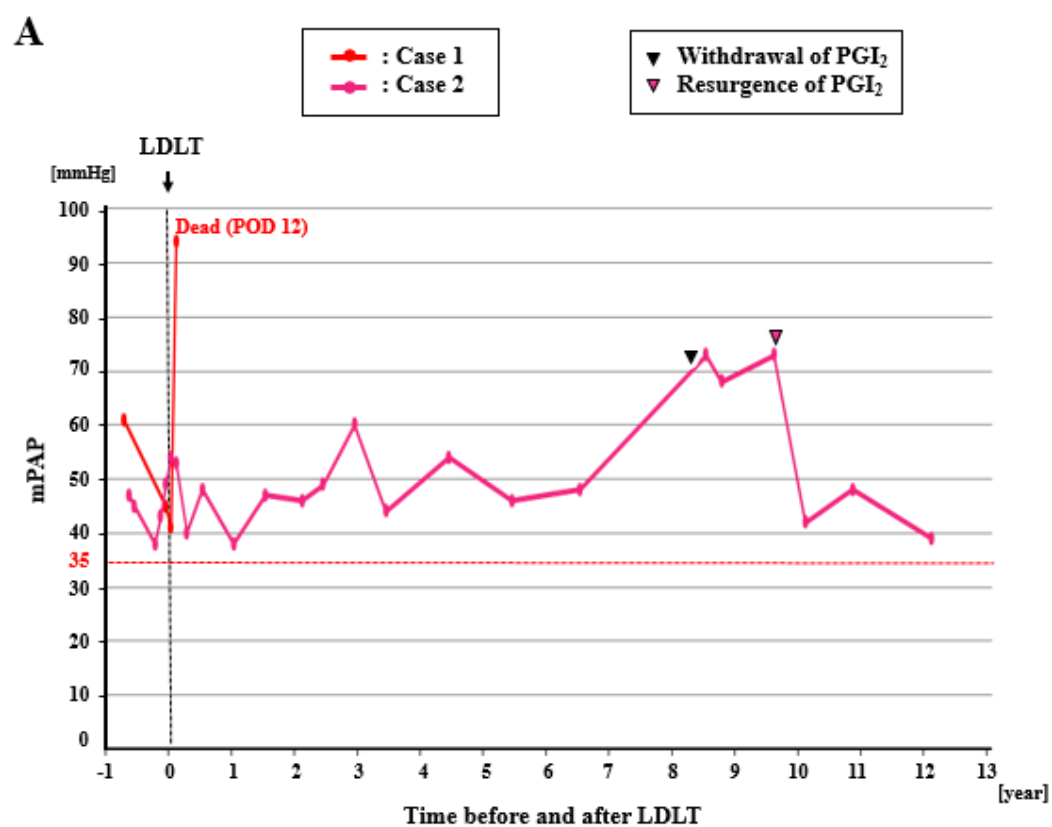


Table 1. Profiles before LDLT

Case	Age at LDLT [year]	Surgical treatments before LDLT	Other anamnesis	MELD/PELD score [point]	ABO compatibility
1	17.9	Kasai's operation Distal <u>spleno</u> -renal shunt	<u>Hepatoplumony</u> syndrome	13	Identical
2	6.5	Kasai's operation	-	2	Identical
3	21.0	Kasai's operation and <u>rebor</u> ing Splenectomy Bile drainage EIS/EVL	-	11	Identical
4	9.2	Kasai's operation	Bronchial asthma	3	Identical
5	18.9	Suruga's operation Subsequent stoma closure EIS	-	11	Identical
6	19.3	Kasai's operation	Juvenile nonspecific arthritis	14	Incompatible
7	4.9	Kasai's operation	-	0	Compatible
8	21.6	Kasai's operation EVL PSE	Defect of IVC <u>Malrotation</u>	7	Identical

Abbreviations: LDLT, living-donor liver transplantation; MELD, Model for End-Stage Liver Disease; PELD, pediatric end-stage liver disease; EIS, endoscopic injection sclerotherapy; EVL, endoscopic variceal ligation; PSE, partial splenic embolization.

Table 2. Treatments for moderate/severe PAH before and after LDLT

Case	Treatments before LDLT	Favorite reactivity for preoperative treatments or challenge test †	Treatment term with PGI ₂ before LDLT [month]	Improvement of <u>mPAP</u> before LDLT (Changes of <u>mPAP</u> [mmHg])	Withdrawal of PGI ₂ after LDLT (Withdrawal point [year])
1	PGI ₂ , O ₂	-	9	+ (61 → 41)	-
2	PGI ₂ , O ₂	±	8	- (47 → 54)	-
3	PGI ₂ , O ₂	+	9	+ (49 → 33)	+ (1.0)
4	PGI ₂ , O ₂	+	8	+ (50 → 35)	+ (1.9)
5	PGI ₂	+	11	+ (38 → 24)	+ (0.4)
6	PGI ₂	+	3	+ (47 → 28)	+ (0.3)
7	PGI ₂	+	3	+ (38 → 29)	+ (0.8)
8	PGI ₂ , O ₂	+	7	+ (40 → 32)	Weaning stage

† Acute volume challenge test

Abbreviations: PAH, pulmonary arterial hypertension; LDLT, living-donor liver transplantation; PGI₂, prostaglandin I₂; mPAP, mean pulmonary arterial pressure.

Table 3. Profiles during LDLT

Case	Operative time [minute]	Blood loss [ml]	CIT [minute]	WIT [minute]	GRWR
1	931	2900	346	31	1.28
2	484	1520	95	30	1.22
3	918	3030	87	46	1.29
4	678	3970	26	61	0.95
5	959	1630	158	56	0.98
6	836	2833	215	31	1.23
7	721	290	106	32	1.96
8	728	1237	48	31	0.82

Abbreviations: LDLT, living-donor liver transplantation; CIT, cold ischemic time;
WIT, warm ischemic time; GRWR, graft-to-recipient weight ratio.

Table 4. Clinical course and outcomes after LDLT

Case	Complications (Treatments)	Histopathological analysis by LNB [†]	Outcome (Follow-up term)
1	Confounded PAH Oversystemic PAH Cardiac failure	F 0	Dead (12 days)
2	ACR (SPT) Sepsis (Antibiotics) Confounded PAH at 2 years after LDLT (PGI ₂) The remnant of spleno-renal shunt (Splenectomy and the ligation of shunt at POD 783)	F 2	Alive (12.4 years)
3	ACR (SPT)	F 0	Alive (6.6 years)
4	Haemorrhagic tendency and intraperitoneal bleeding (Surgical haemostasis at PODs 1 and 12) ACR (SPT)	F 1	Alive (4.8 years)
5	Hepatic vein stenosis and massive ascites (Hepatic vein balloon dilatations at PODs 98 and 124) Cholangitis (Antibiotics)	F 1	Alive (2.6 years)
6	Acute respiratory distress syndrome (Intensive care) Cholangitis (Antibiotics)	F 0	Alive (2.4 years)
7	ACR (SPT) Cholangitis (Antibiotics)	F 0	Alive (2.3 years)
8	ACR(SPT)	F 0	Alive (1.3 years)

[†] Histopathological assessment in LNBs after LDLT using the METAVIR score. The worst scores in each case are shown.

Abbreviations: LDLT, living-donor liver transplantation; LNB, liver needle biopsy; PAH, pulmonary arterial hypertension; ACR, acute cellular rejection; SPT, steroid pulse therapy; PGI₂, prostaglandin I₂; POD, post-operative day.