Pediatric Living Donor Liver Transplantation

28

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Key Points

- The advantages of obtaining a liver graft from living donors include the preoperative control of graft steatosis by diet and exercise, as well as short ischemic time.
- The outcome of ABO-incompatible living donor liver transplantation is largely dependent on patient age.
- Potential LDLT donors for Alagille syndrome recipients must be cautiously evaluated to rule out unsuspected bile duct paucity by magnetic resonance cholangiopancreatography.
- The modified-reduced left lateral segment grafts, including hyper-reduced grafts and monosegmental grafts, have the potential to allow these children to undergo transplantation safely without the associated complications of large-for-size grafts.
- In recipient operation, the collateral vessels must be carefully devascularized to obtain sufficient portal venous front flow.
- If the native portal vein is sclerotic with insufficient front flow, portal venous anastomosis by using interpositional vein graft is indicated.

Research Needed in the Field

- Long-term outcomes of living donors, especially "quality of life" after donor operation
- Long-term outcomes of recipients undergoing living donor liver transplants, especially growth and development
- Long-term outcomes of the recipients receiving technical variant grafts, especially modified-reduced left lateral segments grafts
- Long-term patency of portal venous anastomosis by using interpositional vein graft
- Immunological benefits of living donors, such as haplo-identical HLA matching
- Significance of preformed or de novo donor-specific antibody and the treatment of antibody-mediated rejection
- Possibility of withdrawal of immunosuppressants related to immunological tolerance

28.1 Introduction

The concept of living donor liver transplantation (LDLT), using a part of the liver from a healthy individual to treat another sick individual, is likely as far back as the mid-twentieth century. When deceased whole liver transplantation became a universal standard procedure in the 1980s, transplantation medicine in turn began to face the inevitable issue of organ shortage so far. Deceased organ shortage in the pediatric population soon led to the technical innovations of reduced-size and split-liver transplantation [1, 2]. The emergence of LDLT as a special extension to the concept of split-liver transplantation, i.e., the sharing of a liver between a donor and a recipient, seemed to be a natural consequence of these changes. Difference of these two procedures is that no mortality/morbidity is allowed in living donors. There are also many anatomical, physiological, and surgical similarities between split-liver transplantation and LDLT.

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When the first cases of LDLT in children were tried and successful in 1988, no one imagined that this treatment modality would be passed onto the adult patients and spread all over the world. Graft selection has been extended from left lateral segment to the left lobe, right lobe, and some modification of the left lateral segment to save infants. The process has always been accompanied by caseless controversies about the donor safety. Today the role of the LDLT is increasing rapidly even in countries where deceased donor transplantation program is working nicely, especially pediatric liver transplantation program.

Living donor liver transplantation (LDLT) was introduced in Japan in 1989 as a lifesaving procedure for a patient with biliary atresia due to the absolute scarcity of organs available for deceased donor transplantation [3]. The shortage of deceased organ donors led to the development of unique technical, physiological, and logistical innovations in LDLT [4, 5]. Experience with technical improvements in living donor surgery has led to the generalization of pediatric LDLT, and even adult LDLT, with excellent patient and graft survival outcomes [6]. These techniques have expanded the potential donor pool and decreased waiting list mortality in the setting of pediatric liver transplantation (LT) [7]. Living donor candidates are strictly limited to relatives up to the third civil degree or spouses of the recipient who show a strong voluntary will to donate.

The number of LDLTs performed in Japan showed an initial increase to a maximum of 562 in 2005 followed by a decrease and return to the status quo of approximately 400–450 annually (Fig. 28.1). During these 25 years (November 1989 to December 2015), 7862 LDLTs were performed in Japan; 2897 were children less than 18 years of age (36.8%). The annual number of pediatric LDLT cases has been 120–140 over the past 5 years. During the same study period, 45 deceased LTs, including 20 split-liver transplantations in pediatric patients, were performed [8].

There have been technical and immunological refinements in the Japanese pediatric LDLT program, such as resolving graft size matching and overcoming blood type mismatches. The Kyoto group reported that the use of small-for-size grafts, defined as grafts with a graft-to-recipient body weight ratio (GRWR) less than 0.8%, is associated with small-for-size syndrome, the development of massive ascites, renal insufficiency, persistent cholestasis, coagulopathy, and infectious complications in patients with lower grafts and reduced patient survival, especially in adolescents, most likely due to enhanced parenchymal cell injury and reduced metabolic and synthetic graft capacity [9]. Meanwhile, large-for-size grafts are used in neonatal and infantile LDLT. The main problems associated with large-for-size grafts include the small size of the recipient's abdominal cavity, size discrepancies between vascular calibers, and insufficient blood supply to the graft. Further reducing the left lateral segment (LLS) increases the possibility of supplying an adequate graft size, while reduced or hyper-reduced LLS has been introduced to mitigate the problems of large-for-size grafts

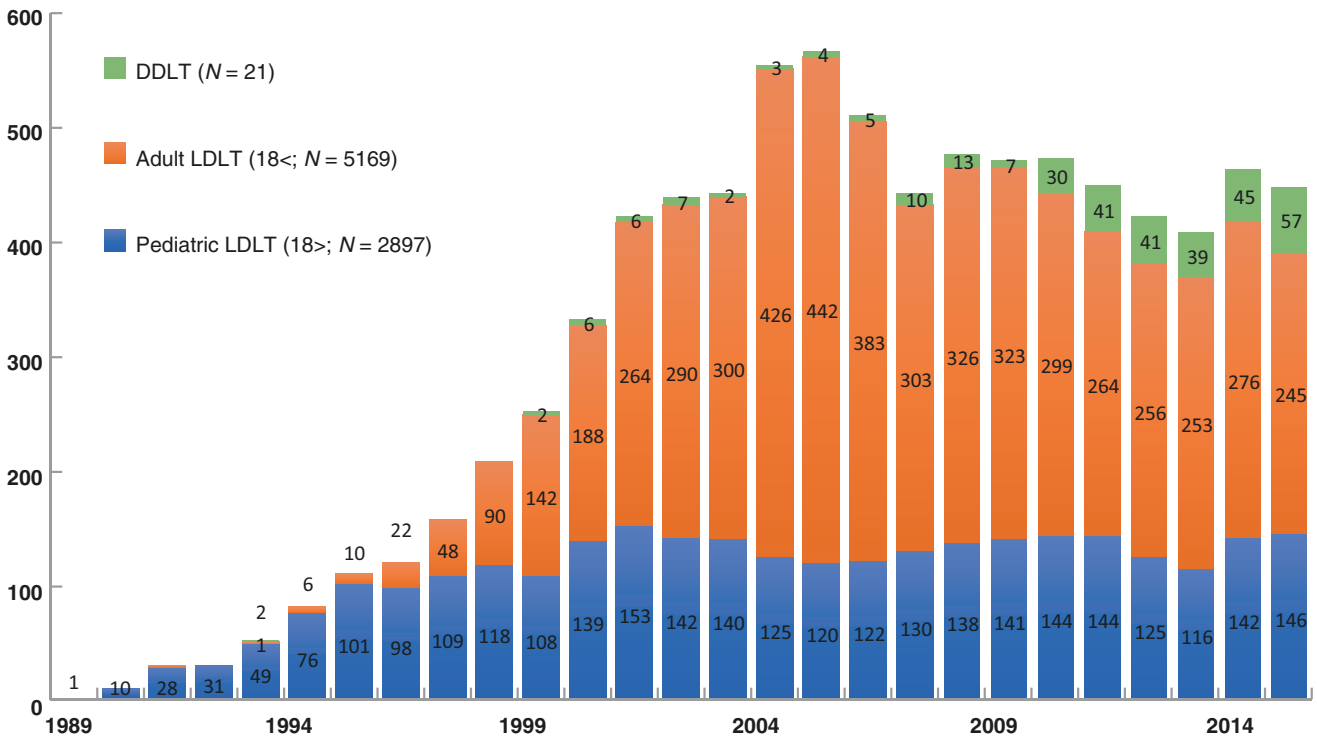


Fig. 28.1 Liver transplantation in Japan (1989~2015; $n = 7862$)

with GRWRs estimated to be over 4.0% especially in the neonatal acute liver failure patients [10].

28.1.1 Blood Type Combination in LDLT

ABO-incompatible LDLT was introduced in Japan to overcome the potential donor shortage. ABO-incompatible grafts were used in nearly 13% of the recipients included in the Japanese LDLT series. It has been reported that, despite the application of preoperative plasma exchange, splenectomy, and enhanced immunosuppression, the 5-year graft survival rate is less than 70% in the pediatric population. A Japanese LDLT series reported that ABO-incompatible liver transplantations were performed with relative safety in infants less than 2 years of age, although the long-term results were not satisfactory in children over 2 years of age [11, 12] (Fig. 28.2). Patients over 10 years of age remain at considerable risk for early fatal outcomes due to complications such as hepatic necrosis and late ischemic cholangitis. New strategies to prevent antibody-mediated rejection are required. New strategies for preventing antibody-mediated rejection using rituximab prophylaxis have been routinely applied since 2005 to overcome the ABO-blood barrier. The current immunosuppression protocol for ABO-incompatible LDLT in NCCHD consists of rituximab infusion (375 mg/m^2) 4 weeks prior to planned LDLT, pre-LDLT plasma exchange (targeted at recipient isoagglutinin titer ≤1:8), and mycophenolate mofetil as an additional immunosuppressant (Fig. 28.3). Significant improvements in the graft survival, however, were obtained in more recent transplants within 5 years with a 5-year graft survival rate of 88.9% (Fig. 28.4).

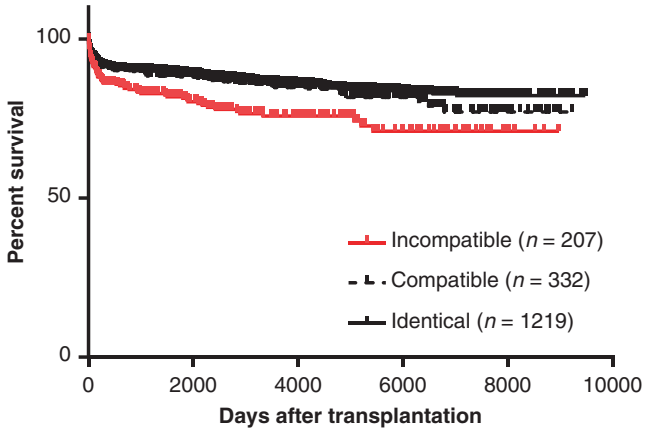


Fig. 28.2 Graft survival after pediatric living donor live transplantation in Japan

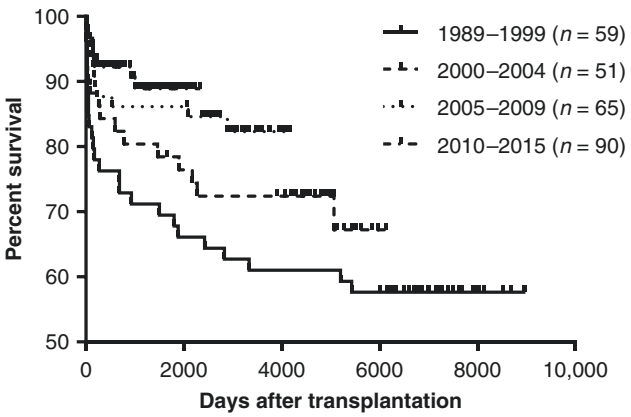


Fig. 28.4 Graft survival in ABO-I LDLT according to LDLT era

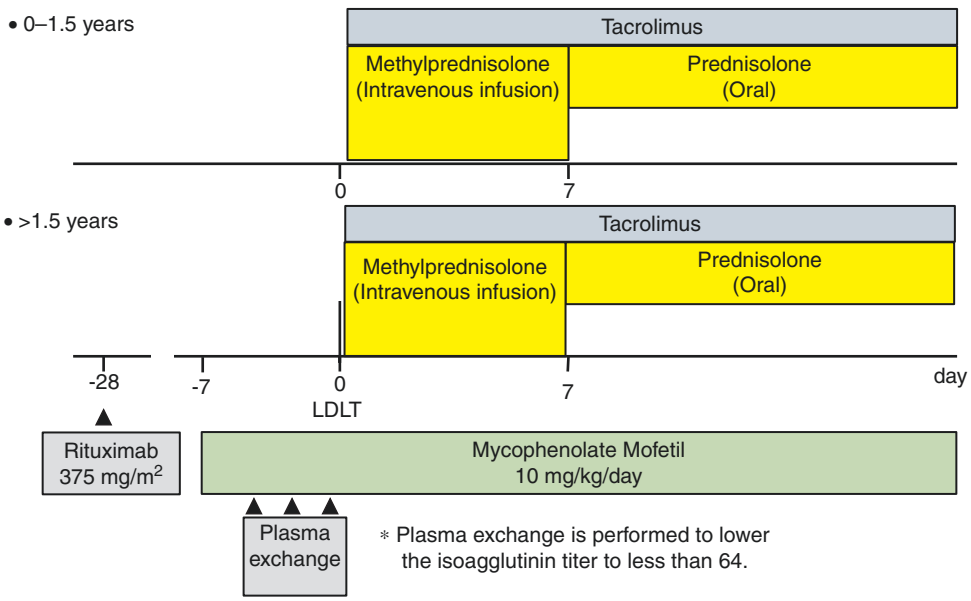


Fig. 28.3 Immunosuppressive strategy for ABO-I LTx in NCCHD

28.1.2 Indication of LDLT

The indications for LT include cholestatic liver disease, metabolic liver disease, acute liver failure, neoplastic disease, vascular disease, graft failure, and other indications. Specific diseases and preoperative patient conditions might be associated with transplantation outcomes [13, 14]. During the past two decades, medical and surgical innovations have established pediatric LDLT to be the optimal therapy for patients suffering from acute and chronic liver disease. This has allowed expansion of the indications for LT to assess patient severity and body weight in association with various diseases. The profiles of current pediatric LT recipients differ significantly from those of earlier eras [15] (Fig. 28.5). If we reviewed the outcomes of 270 pediatric LDLT recipients with metabolic disorders, the 1-, 5-, 10-, and 15-year patient and graft survival rates of the patients with metabolic disorders undergoing LDLT were 91.2%, 87.9%, 87.0%, and 79.3% and 91.2%, 87.9%, 86.1%, and 74.4%, respectively (Fig. 28.6). There are increasing incidence of urea cycle disorders and decreasing in Wilson's disease in JLTS series (Fig. 28.7).

28.1.3 Intraoperative Findings of Specific Liver Disease

There are many textbooks illustrating the indication of various liver diseases in children; however, few have been reported regarding actual intraoperative findings of specific

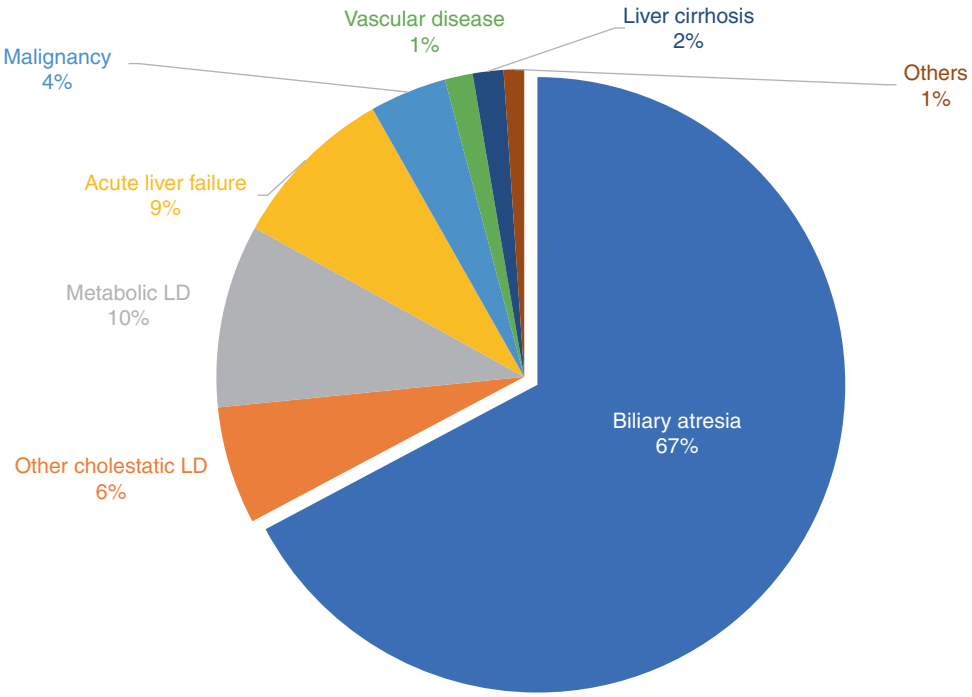


Fig. 28.5 Indication of pediatric living donor liver transplantation in Japan (1989~2015: $n = 2897$)

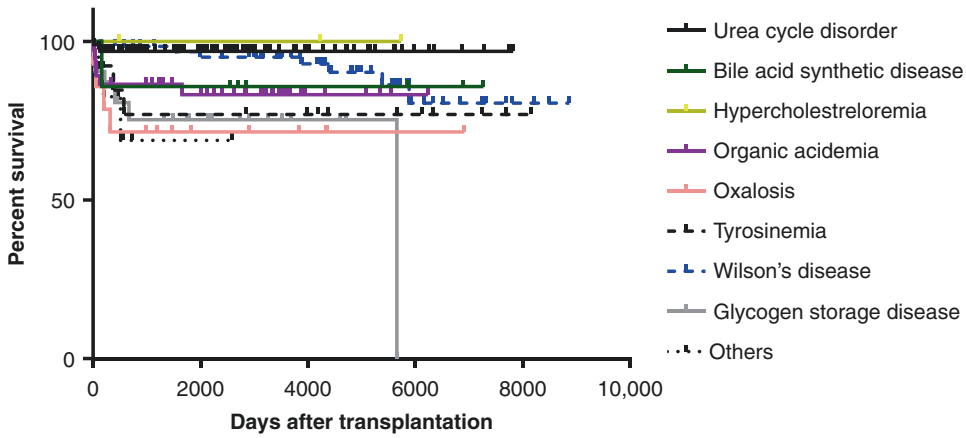


Fig. 28.6 Graft survival in metabolic LD in Japan

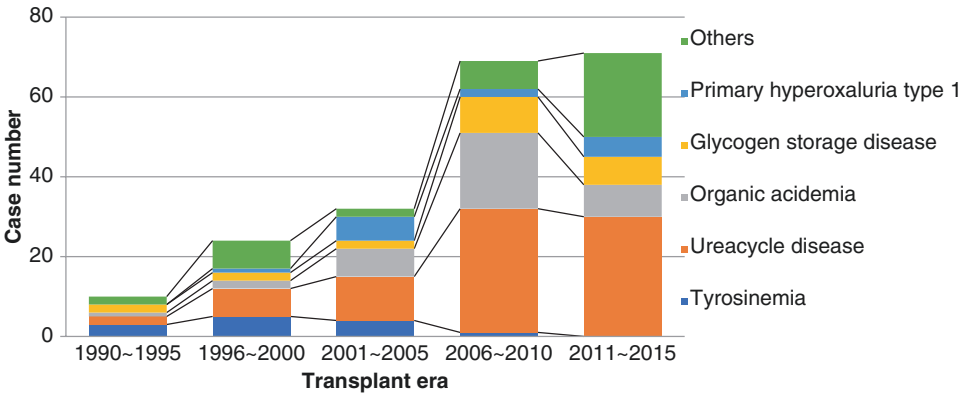
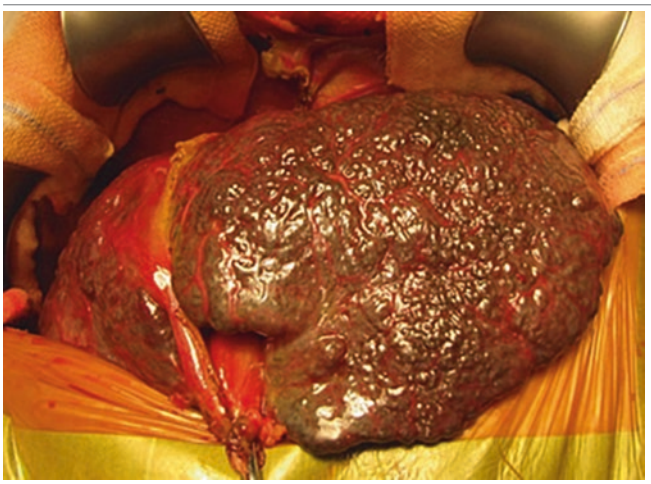


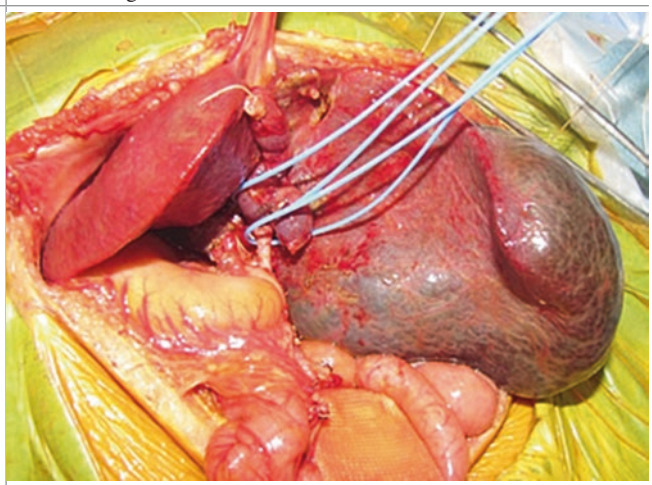
Fig. 28.7 Metabolic disorders according to transplant era ($N = 270$)

liver diseases. The following figure shows intraoperative findings of specific liver disease indicating living donor liver transplantation in the National Center for Child Health and Development, Tokyo, Japan.

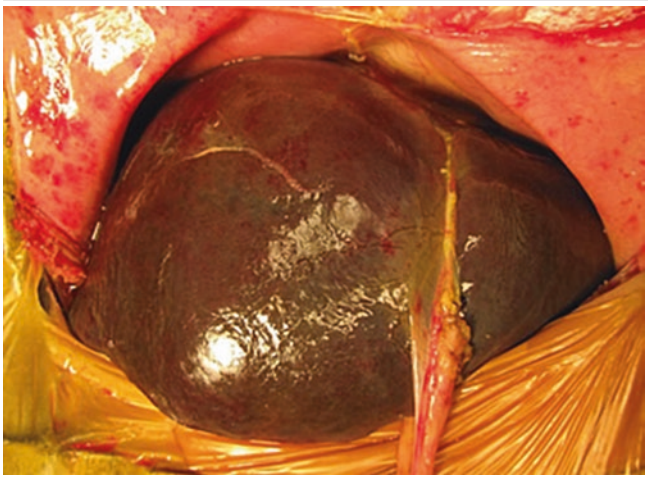
(a) Biliary atresia



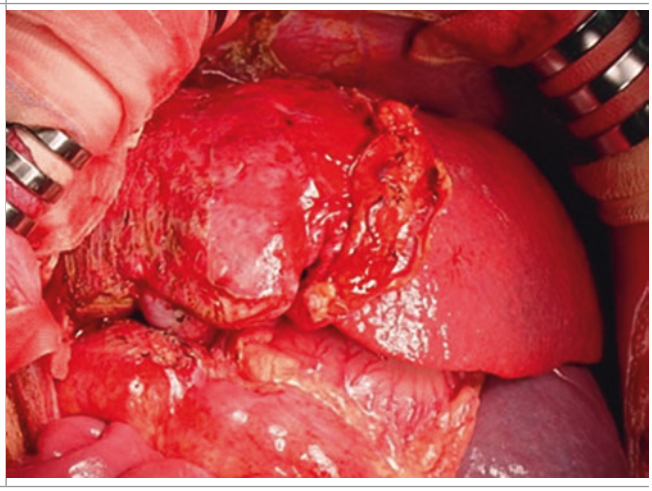
(b) Biliary atresia with situs inversus, absence of inferior vena cava, preduodenal portal vein, and poly splenia. The stomach in the right side



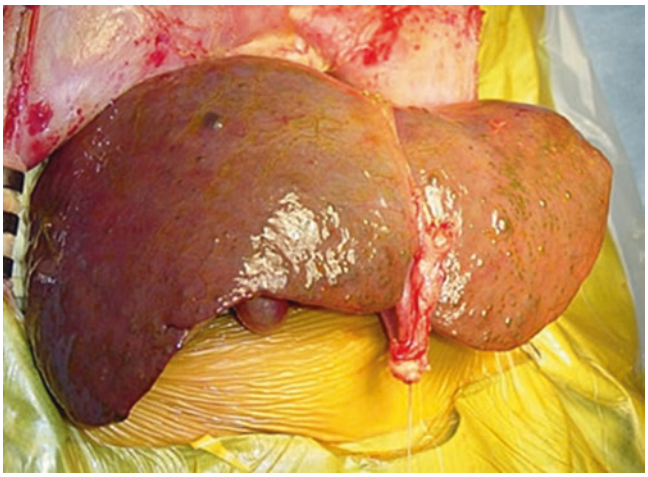
(c) Alagille syndrome



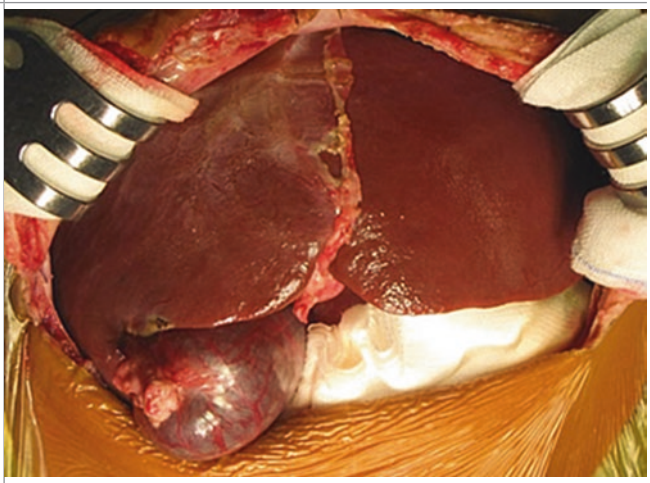
(d) Budd-Chiari syndrome



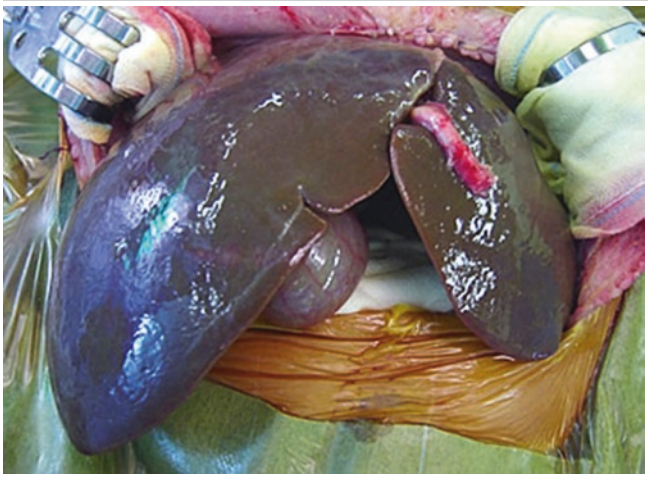
(e) Oxysterol 7α-hydroxylase deficiency



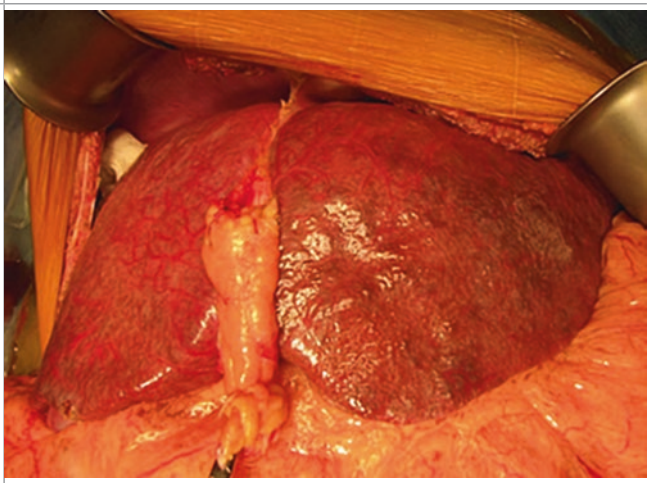
(f) Primary familial cholestasis type I



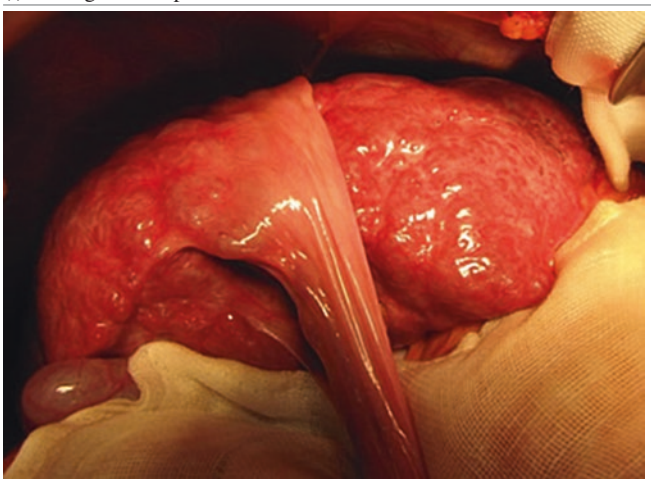
(g) Primary familial cholestasis type II: Looks like horseshoe crab



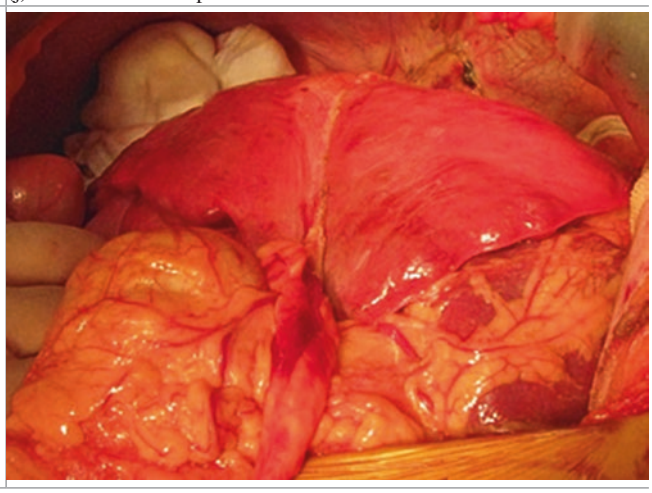
(h) Caroli disease



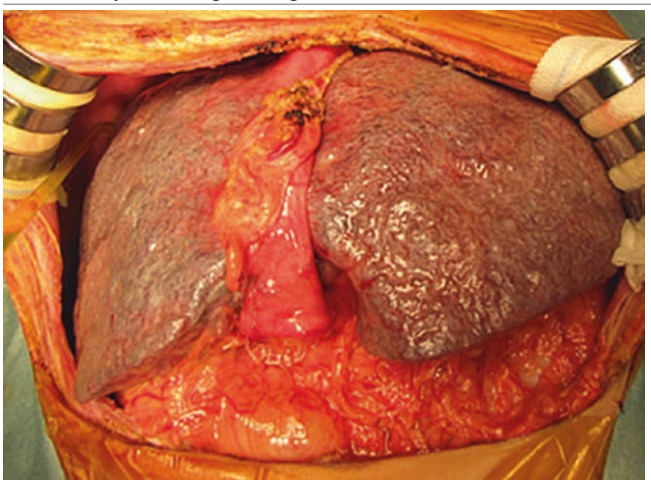
(i) Congenital hepatic fibrosis



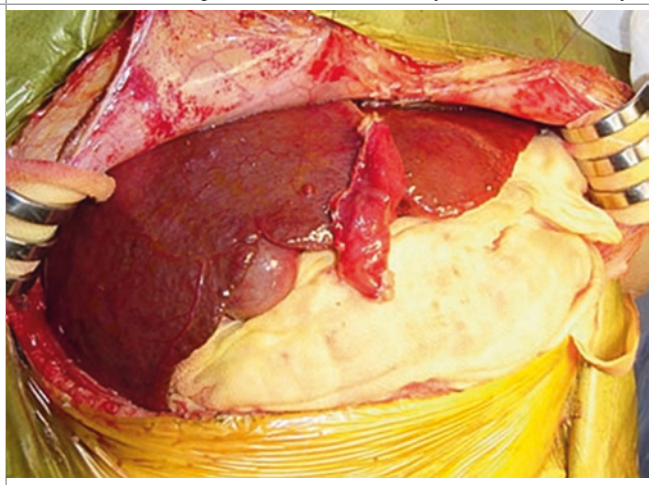
(j) Autoimmune hepatitis



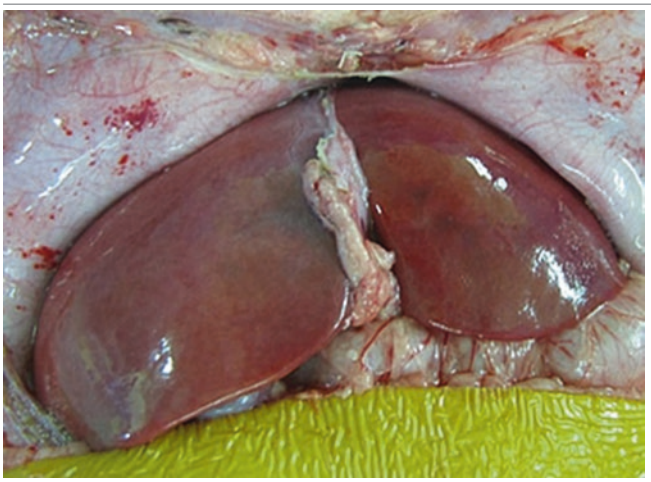
(k) Primary sclerosing cholangitis



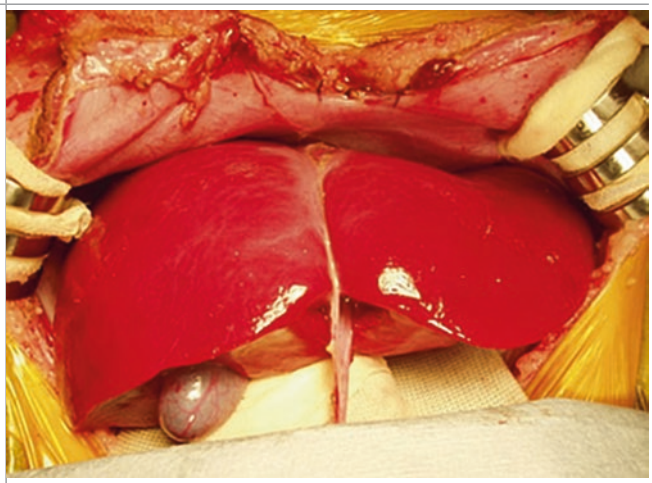
(l) Neonatal intrahepatic cholestasis caused by citrulline deficiency



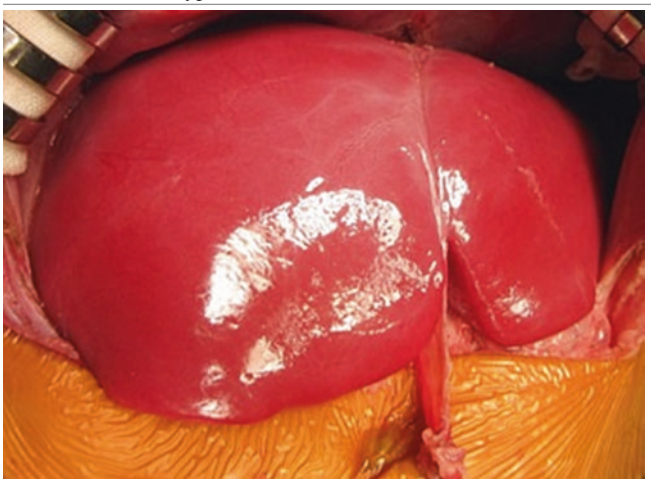
(m) Ornithine transcarbamylase deficiency: steatosis due to protein restriction



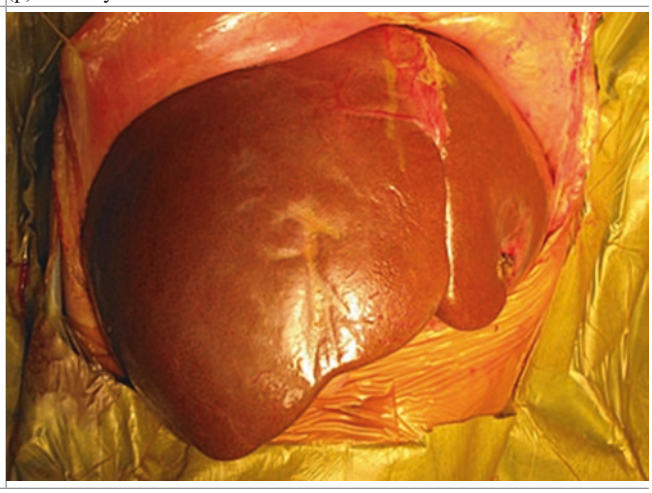
(n) Carbamoyl phosphate synthetase 1 deficiency



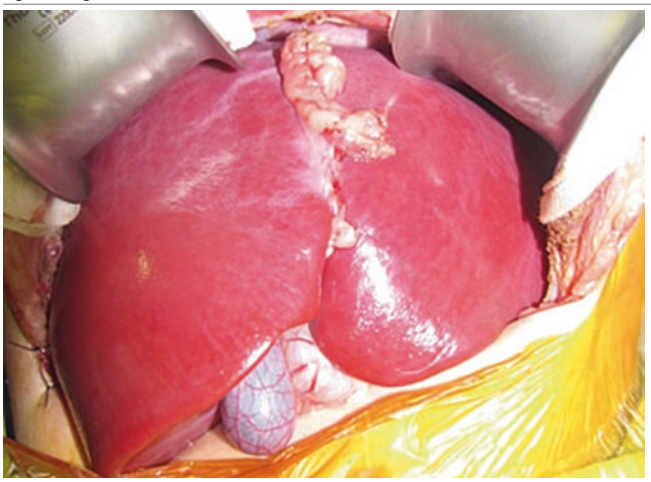
(o) Citrullinemia type I



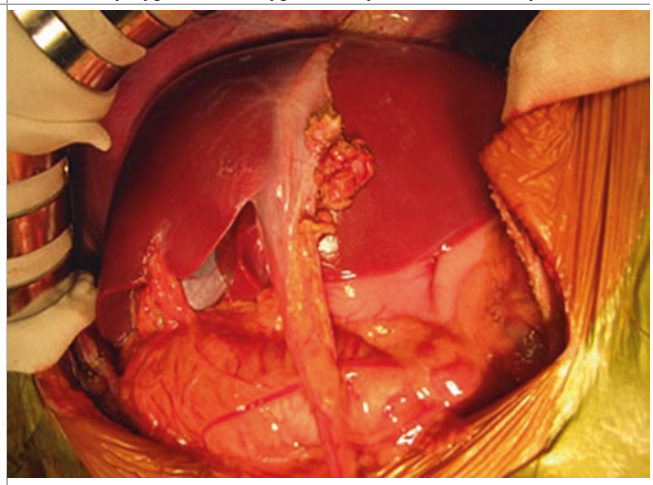
(p) Methylmalonic acidemia



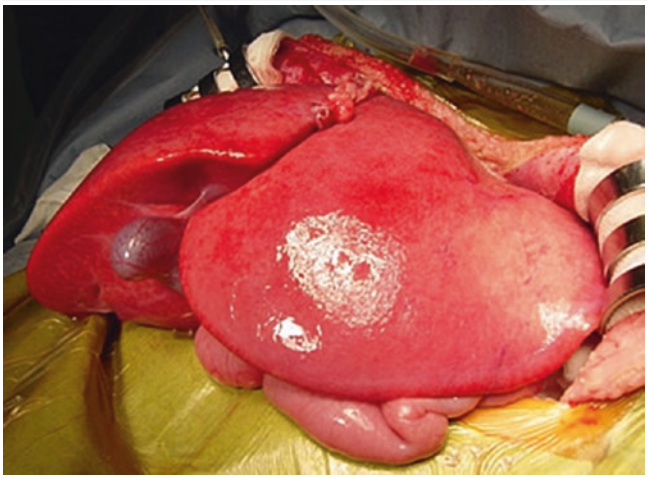
(q) Propionic acidemia



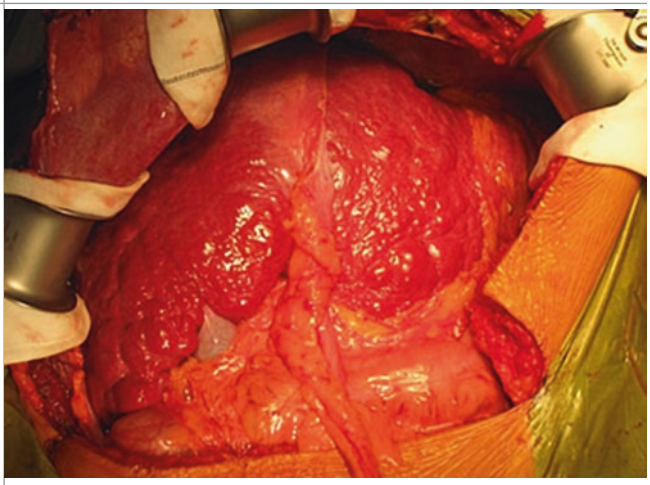
(r) Primary hyperoxaluria type I: slimy abdominal cavity



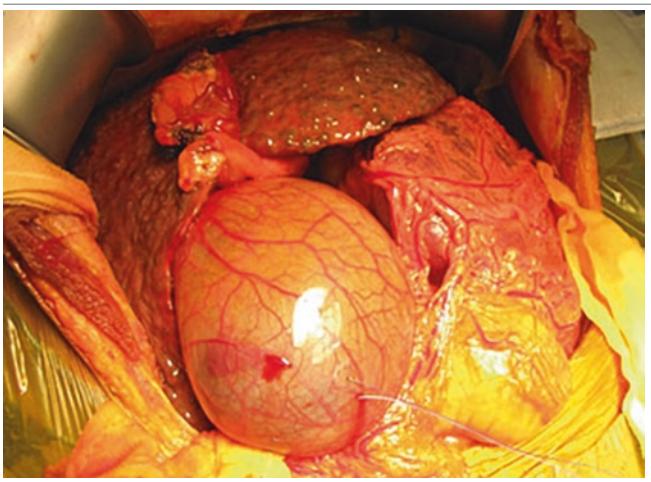
(s) Glycogen storage type Ib: hepatomegaly with steatosis



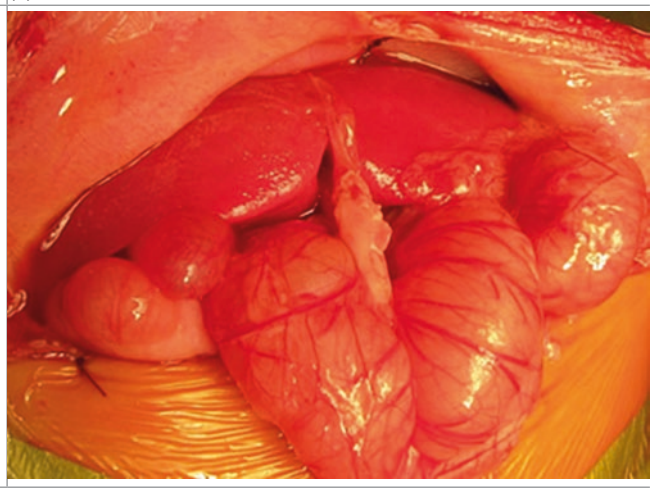
(t) Glycogen storage type IIIb



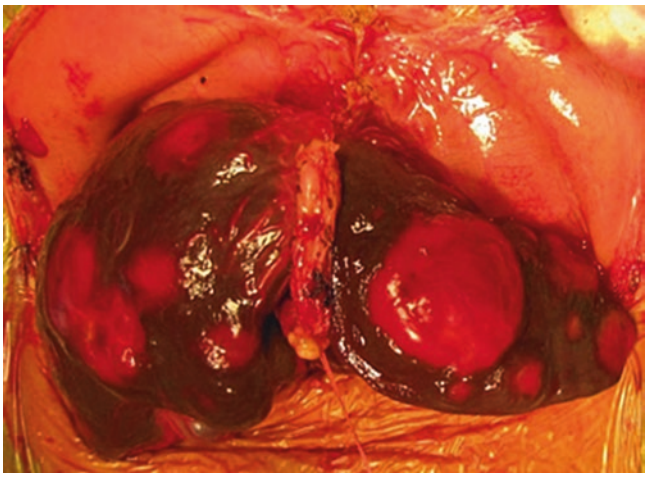
(u) Wilson's disease



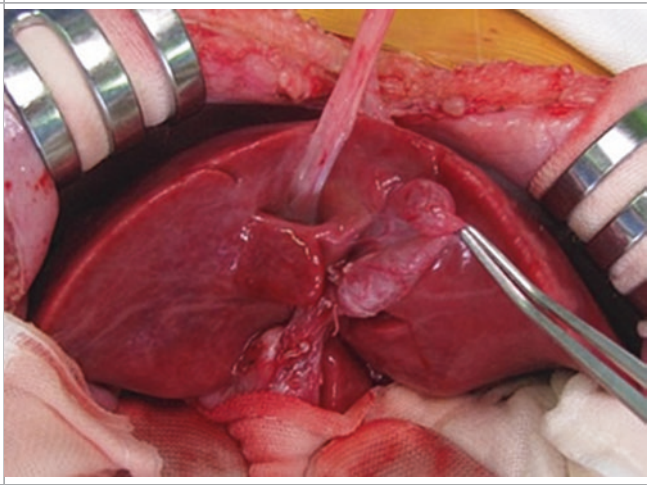
(v) Acute liver failure: fluorescent red color



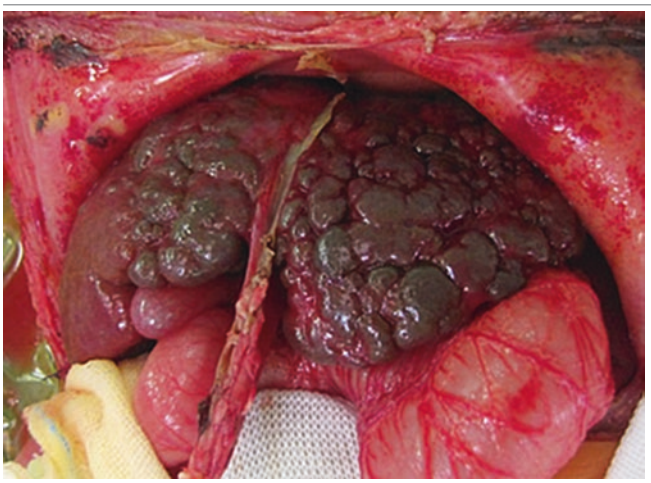
(w) Hemangioma: multiple pulsating tumor



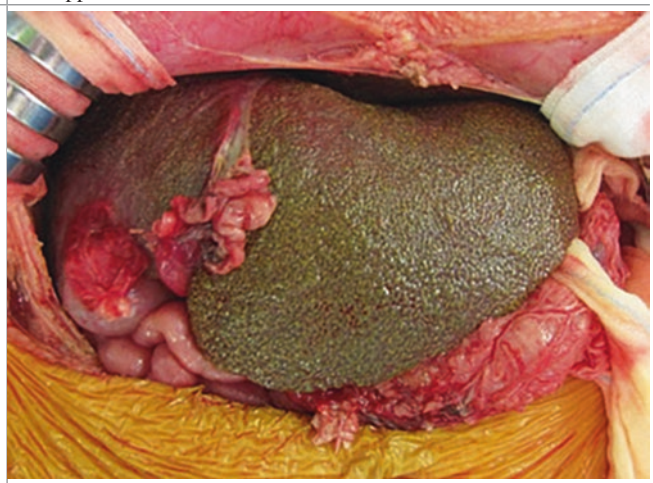
(x) Congenital absence of portal vein: symmetric liver with left-sided gall bladder



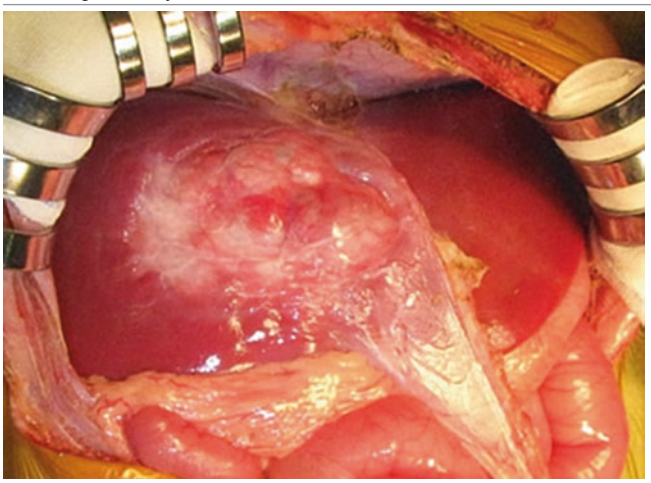
(y) Gestational alloimmune liver disease: already cirrhotic at 13 days after birth



(z) Mitochondrial depletion syndrome: small cobble stonelike appearance



(aa) Hepatoblastoma: centrally located, unresectable without total hepatectomy



The Organ Transplantation Center of National Center for Child Health and Development (NCCHD), Tokyo, Japan, has been established in 2005, and based on these 10-year experiences in pediatric LDLT and liver surgery, we have demonstrated our innovative surgical procedure, including standard technique and complicated case presentations with beautiful surgical videos, to standardize and continue to improve the quality of surgery for end-stage pediatric liver disease (Pediatric Liver Surgery and Transplantation E-learning: Surgical Technique:

- http://www.ncchd.go.jp/recruitment/movie/organ_index.html
- ID: seiiku-guest
- Password: otLEZYjC).

This LDLT chapter is useful in maintaining high-quality surgery in all pediatric patients and in avoiding unrecognized changes in surgical strategy for all involved in this field. We are also grateful for our patients from whom we have learned so much indeed.

28.2 Living Donor

28.2.1 Preoperative Evaluation and Management

In living donor liver transplantation (LDLT), the concept of "choosing voluntarily to donate an organ" is incredibly important. Once a family realizes that their child needs a liver transplant, they start thinking of who will be the donor. This is an extremely important decision, because two members of the family will undergo surgery at the same time in a LDLT.

The main examinations involve the blood type, general biochemistry, infectious diseases, tumor markers, occult blood test, urinalysis, the respiratory functions, electrocardiography (including an examination by the cardiovascular department if abnormalities are found), a chest/abdominal radiography, and contrast computed tomography (for fatty liver and lesions and to estimate the vessel paths and the size of the liver).

The donor candidate has been fully informed of the donation process and its risks and has chosen to participate; they must undergo a series of evaluations [16]. A list of the tests necessary for donor evaluation is shown in Table 28.1.

If the child receiving the transplant has any of the following diseases, additional tests are performed. When the donor candidate is a blood relative of a recipient whose transplant indication is autoimmune liver disease, such as primary biliary cirrhosis or autoimmune hepatitis, screening for autoimmune antibodies, e.g., antinuclear antibody or antimitochondrial antibody, should be conducted. When the donor candidate is a blood relative of a patient with primary sclerosing cholangitis, Caroli disease, polycystic liver disease, or congenital hepatic fibrosis, these diseases should be excluded using imaging studies [17, 18].

The advantages of obtaining a liver graft from living donors compared with deceased donors include the preoperative control of graft steatosis by diet and exercise, as well as short ischemic time during transplantation. However, thorough evaluation of potential donors is necessary to exclude serious conditions such as nonalcoholic steatohepatitis (NASH). This is possible as there is ample time for evaluation in LDLT [18, 19]. Detailed medical history and family history of donor candidates are necessary to start the evaluation for steatosis. In cases where the body mass index (BMI) is greater than 25, suggesting obesity, every effort is taken to reduce body weight to reduce the risk of perioperative complications, such as deep vein thrombosis, as well as to control graft steatosis. Ultrasound and CT are useful measures to aid the understanding of the vasculature of the graft, as well as to evaluate steatosis of the graft. Ultrasound is a noninvasive method for donor screening. However, for the quantitative evaluation, the liver/spleen ratio can also be used, i.e., the ratio of CT values of the liver divided by that of the spleen, measured using plain CT. If the ratio is greater than 1.2, the percent of macrovesicular steatosis is less than 30% in most cases based on zero-biopsy findings [19]. We do not perform liver biopsy unless there is a need to exclude NASH because liver biopsy carries a small risk of bleeding and damaging the graft. The important underlying factor in NASH is believed to be insulin tolerance. Diabetes mellitus, hypertension, hyperlipidemia, obesity, and hyperuricemia are risk factors for insulin intolerance. Family history of liver cirrhosis of unknown etiology is a warning factor as NASH can progress to cirrhosis without any other virological background. We use the homeostasis model assessment for insulin resistance [HOMA-IR; fasting blood glucose (mg/dL) × fasting insulin (μU/mL)/405] as an indicator for insulin intolerance [20]. If HOMA-IR is greater than 1.64, insulin intolerance is suspected.

The upper age limit permitted for donor candidates varies in each institute [21, 22]. In view of donor safety, as a general rule, 64 years is the maximum age permitted for living donors at our center. With regard to graft quality, despite the belief of many transplant surgeons that grafts from aged donors are somewhat worse than grafts from younger donors, no conclusive data to support this belief have been found in LDLT [21].

In liver transplantation, there are only a few reports in the literature indicating the importance of human leukocyte antigen (HLA) matching in reducing the incidence of rejection [23]. In deceased donor liver transplantation, HLA matching is of less importance for donor selection. In terms of the role of HLA

matching in rejection, it may also be the case in LDLT. However, in order to mitigate the risk of graft-versus-host disease (GVHD), HLA typing is essential in the donor evaluation process when a living donor is a person who potentially shares one haplotype with a recipient [24]. Since a parent and a child share one haplotype, one-way matching is established when the donor has homozygous HLA [25]. Liver transplant from an HLA-homozygous individual to a haplo-identical HLA-heterozygous individual in loci A, B, and DR is contraindicated because GVHD is a devastating and fatal complication.

Since it is widely known that ABO-incompatible liver transplantation has a very poor outcome, it is usually a contraindication or is performed only in exceptional situations [23, 24]. However, in Japan ABO-incompatible transplants are sometimes inevitable because a cadaveric transplant program has not yet been well established [26, 27]. It is not rare for all available living donor candidates to be ABO-incompatible. The outcome of ABO-incompatible liver transplantation is largely dependent on patient age [12, 28]. ABO-incompatible LDLT for patients aged less than 1 year and 6 months old is not necessarily contraindicated because the outcome is comparable to that of a compatible combination. We made original protocol for ABO-incompatible according to the age of the recipients. The patients younger than 1.5 years old have the standard immunosuppressive therapy consisting of tacrolimus and steroids. The patients 1.5 years old or older have additional immunosuppression using rituximab (375 mg/m^2) and mycophenolate mofetil. Plasma exchange is indicated when the recipient has the titer of blood type antibody of more than 64. ABO-incompatible LDLT is no longer considered an absolute contraindication, but an ABO-incompatible transplant should be avoided when other compatible donor candidates are available.

In order to avoid transmission of infection from donor to recipient, a thorough investigation must be performed to ensure that the donor candidate is free from infectious diseases. Human T-lymphotropic virus type I (HTLV-I) is the virus causing adult T-cell leukemia and HTLV-I-associated myelopathy. Hepatitis B virus (HBV) can often be transmitted from donor to recipient through liver transplantation if the donor has antibodies to hepatitis B core antigen [29]. When the only donor candidate is HBc positive, recipients should undergo prophylactic passive immunization with hyperimmune hepatitis B immunoglobulin (HB-IgG). Hepatitis C virus antibody-positive individuals should be excluded from the donor pool. A case of hepatic graft tuberculosis was reported, which was most likely transmitted by the graft from the living related donor [30]. This emphasizes the importance of tuberculosis screening for the donor. The tuberculin skin test (TST) was often indicated for the diagnosis of tuberculosis. However, an interferon-gamma release assay, commonly known as an IGRA or QuantiFERON-TB Gold, is a modern alternative to the tuberculin skin test (TST). Unlike the TST, QFT is a controlled laboratory test that requires only one patient visit and is unaffected by previous vaccination with bacille Calmette-Guérin (BCG) [31, 32]. Screening for syphilis is carried out using a combination of the *Treponema pallidum* hemagglutination (TPHA) test and serological tests for syphilis (STS). STS have a biological false-positive reaction.

Alagille syndrome is an autosomal dominant genetic disorder characterized by chronic cholestasis, congenital heart disease, peculiar facies, butterfly-like vertebrae, and posterior embryotoxon. Liver dysfunction is the common presentation of Alagille syndrome, and liver transplantation may be indicated. Donor selection must be carried out carefully in LDLT for patients with Alagille syndrome, because this disease can be inherited by multiple family members. One of the cases died after an operation in which a graft with unsuspected bile duct paucity was received, which resulted in persistent hyperbilirubinemia and graft dysfunction [33]. When the donor is a blood relative of the recipient, preoperative magnetic resonance cholangiopancreatography or endoscopic retrograde cholangiopancreatography should be a routine component of the pretransplant evaluation.

An inherited defect of the urea cycle enzyme often manifests soon after birth as a severe and fatal syndrome marked by hyperammonemia, coma, and devastating central nervous system impairment [34]. Ornithine transcarbamylase (OTC) deficiency is an X-linked dominant disease. Most patients who show a variety of symptoms in the neonatal period are male, and the severe cases die at a few days of life due to apnea, convulsion, and hyperammonemia-induced coma. In female patients, symptoms appear later [35]. Liver transplantation represents the best presently available therapeutic approach to cure this metabolic defect. In LDLT, many recipients with OTC deficiency may receive a liver graft from a blood relative who is a heterozygous carrier of the disease. Therefore, donors need to be assessed with regard to disease potential by urinary orotic acid excretion using the allopurinol loading test. Furthermore, it can often be confirmed by gene assays [36]. LDLT was performed in six cases of OTC deficiency: the donors were four fathers who were not considered carriers by allopurinol loading test and two mothers who were heterozygous carriers with subclinical abnormalities in the allopurinol loading test. Nonetheless, neither the donors nor the recipients who received heterozygous livers have experienced any episodes suggestive of hyperammonemia [37]. We experienced two OTCD patients who were performed LDLT from asymptomatic OTCD heterozygous donors and just after their LDLT transiently required continuous veno-venous hemodialysis [38]. They are currently doing well without intensive medical treatment. The use of asymptomatic OTCD heterozygous donors in LDLT has been accepted with careful examination. However, an OTCD heterozygous carrier donor should be avoided if there is

another donor candidate, due to the potentially fatal condition of hyperammonemia following LDLT.

Gilbert's syndrome is defined as benign, familial, mild, unconjugated hyperbilirubinemia (serum bilirubin 1–5 mg/dL) not due to hemolysis and with normal routine tests of liver function and hepatic histology. Its incidence appears to be approximately 3–7% of the population. The diagnosis of Gilbert's syndrome is based on the finding that serum bilirubin increases with fasting and nicotinic acid administration and falls on phenobarbitone administration. In liver transplantation, Gilbert's syndrome is not a donor contraindication. Recipients of transplanted grafts which had been diagnosed as Gilbert's syndrome have only a slightly elevated serum bilirubin level, and this does not affect the graft function [39, 40].

Hypertension, diabetes mellitus, hypercholesterolemia, other hyperlipidemia, and high BMI are risk factors for atherosclerosis and other cardiovascular diseases. Hypertension itself may not be a contraindication for donation if it is well controlled, but close evaluation for cardiovascular diseases is necessary, including ECG and stress testing. Arrhythmia can be a reason to preclude donor candidacy if it is ventricular and potentially associated with the risk of serious tachycardia. For an individual with bronchial asthma, complete control of attacks is the absolute requirement before becoming a living donor, and full surveillance by a respiratory specialist is needed. Usually a candidate with a significant history of asthma attack and medication is excluded from candidacy. Chronic obstructive pulmonary disease revealed by spirogram also precludes donor candidacy. The screening tests for renal disease are also very important. For example, if a candidate has immunoglobulin A nephritis, a careful assessment by a specialist is necessary even when it is asymptomatic.

Lack of organ donors is one of the most pressing problems in transplantation. Therefore, people with a history of malignancy can also be eligible to be organ donor candidates, although donation is often contraindicated in those in the active phase of malignancy. There are no apparent exclusion criteria for organ donor candidates with a history of malignancy. Of 17,639 donors, 202 (1.1%) had a history of cancer, including 61 donors with cancers classed as having an unacceptable/high risk of transmission from the transplanted and cancer registry in the United Kingdom. No cancer transmission was noted in 133 recipients of organs from these 61 donors [41]. To prevent donor transmission of malignancy, donor selection should be assessed carefully. The lung, colon, breast, and prostate also demonstrate higher rates of transmission [42]. It has been recommended that donors with a history of any of these cancers be avoided because of the transmission risks. Regarding the safe period between curative treatment and organ donation, no consensus has been obtained to date. In LDLT, more careful donor evaluations can be carried out than in deceased donor liver transplantation. Moreover if possible, other candidates who have no history of malignancy should be assessed. If there are no candidates except those with a history of malignancy, donor selection should be based on not only confirming no disease recurrence with laboratory data, radiography, endoscopy, and radioscintigraphy but also bearing in mind the biological propensity of tumor recurrence. Some types of tumor, such as the breast and lung, are known to recur in the long term after the initial diagnosis and treatment.

28.2.2 Technical Aspects of the Donor Surgery for Pediatric LDLT

28.2.2.1 Standard Left Lateral Segment Graft

The operative procedure has been previously described [43]. After 10 cm midline incision, left triangular ligament was dissected, and left lateral segment was freed from diaphragm attachment. Lesser omentum, which sometimes includes left hepatic artery from left gastric artery, was carefully opened, and sizable left gastric vein was ligated. After isolation of the donor left hepatic artery, hepatic duct, and portal branch, cholecystectomy and cholangiogram were applied. Sugita clip was placed on 3 mm left side of biliary bifurcation to make sure exact cutting line by cholangiogram. After taking liver biopsy, hepatic parenchyma of the medial segment was transected 5 mm to the right side of the falciform ligament without blood inflow occlusion or graft manipulation. Left bile duct was encircled and dissected with sharp knife. Hepatic artery, portal vein, and hepatic vein were gently clumped and dissected, and the graft was preserved in cold preservation solution. The graft liver volume, size of vessels, and bile duct were measured and were prepared for implantation on the bench surgery [44].

28.2.2.2 Reduced and Hyper-reduced Left Lateral Segment Graft (Nonanatomical Volume Reduction)

There have been technical refinements in the Japanese pediatric LDLT program, such as resolving graft size matching. The main problems associated with large-for-size grafts include the small size of the recipient's abdominal cavity, size discrepancies between vascular calibers, and insufficient blood supply to the graft, particularly in neonatal and infantile LDLT. Liver volume is one of the key determinant factors for graft liver function for recipients as well as for remnant liver function for donors. Routine use of CT volumetry is indispensable both for donor safety and for recipient survival. For the evaluation of graft volume in relation to recipient body weight, graft-to-recipient weight ratio (GRWR), which is calculated as graft weight divided by recipient body weight, is useful. The risk of vascular complications such as portal vein thrombosis and/or acute rejection is reported to be high [45]. One-year graft survival is 82% with large-for-size graft (3% GRWR <5%) and 71% with

extra-large-for-size graft (GRWR ≥5%), respectively. The lack of size-matched pediatric liver grafts has led to the development of reduced, split, and living donor liver transplantation. These techniques have expanded the potential donor pool and have decreased waiting-list mortality for children [46]. Transplantation in children who weigh less than 5 kg remains a problem because the left lateral segment (LLS) from an adult may be too large when the graft-to-recipient weight ratio is greater than 4.0% and thus may result in a large-for-size graft and its associated morbidity [45]. Further reduced LLS grafts that can be transplanted safely without compromise to patient survival have been introduced for these children to mitigate the problem of large-for-size grafts [47]. In very small children (neonates) who have no portal hypertension, hepatomegaly, or ascites, the abdominal cavity may be small, and the anteroposterior thickness of the graft remains a problem [48, 49]. The disadvantages of using large-for-size grafts include graft compression, the use of silastic mesh to close the abdomen and associated infections, splinting of the diaphragm, and delayed extubation, all of which contribute to poor outcomes [50]. These complications are amplified by the small recipient size and often associated malnutrition in a patient population that already presents a technical challenge and postoperative complexity [51]. To relieve the problem of large-for-size grafts in small babies, reduced LLS grafts have been introduced [45, 47, 48, 52]. After isolation of the left lateral segment graft, the LLSs of the donors were reduced in situ as previously reported [48, 53]. The transection line was dependent on the anatomical variation of the hepatic rather than the portal venous system. The caudal part and lateral part of LLS were resected in situ while preserving the medial branch of the left hepatic vein (Fig. 28.8). Intraoperative Doppler ultrasonography was used to avoid vessel injury. We defined "reduced LLS graft" as reduced lateral part of the LLS graft and "hyper-reduced LLS graft" as reduced both lateral and caudate part of LLS graft. The resected liver volume was weighted and was prepared for "hepatocyte transplantation program," if the informed consent is available. This procedure is useful for the small baby; however, there still remained an issue that the thickness of the graft could not be reduced.

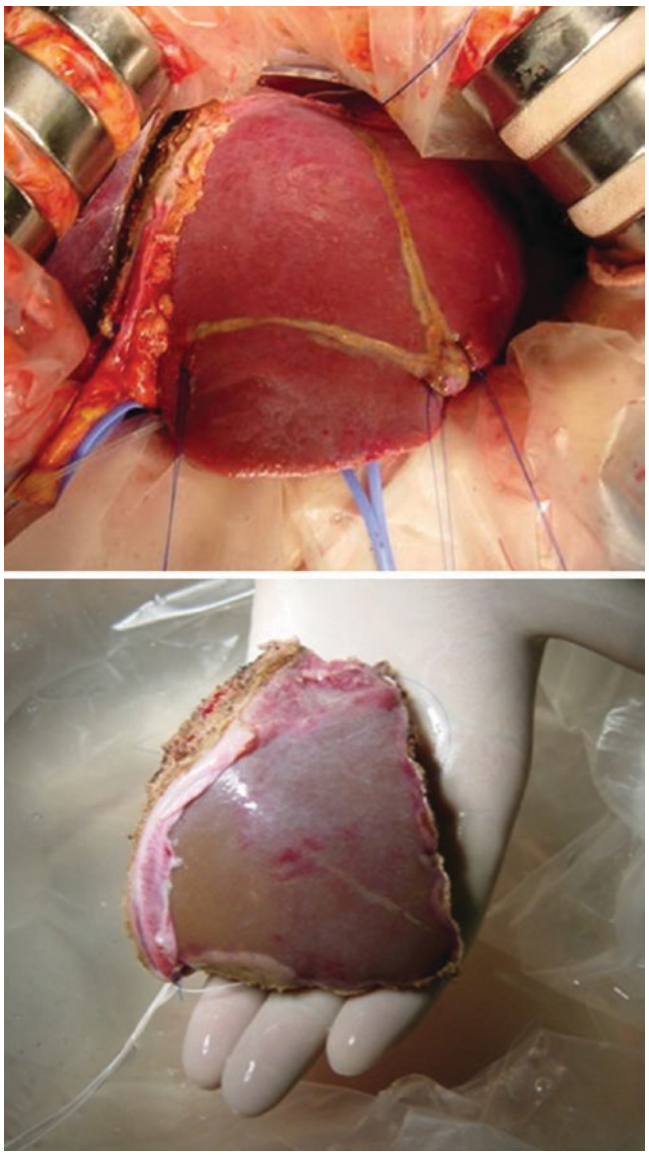


Fig. 28.8 After isolation of the left lateral segment graft, additional resection was made of reduction of caudal and lateral part of left lateral segment. It actually worked well, but there still remained an issue that the thickness of the graft could not be reduced in this procedure

28.2.2.3 Reduced-Thickness LLS Graft

Segment II Graft (Anatomical Reduction)

In addition, the size and shape of the LLS of the donor should be taken into consideration. Some LLSs are short and thick, whereas others are thin and long (Fig. 28.9). We have developed a modified LLS reduction by which the thickness of the graft is addressed and transplantation is allowed in very small infants. In the donor operation, after the isolation of the LLS graft, segment II graft can be available with meticulous technique. Following the falciform ligament toward the hepatic parenchyma and then each PV branch feeding to segment III was separately exposed (Fig. 28.10a). According to the preoperative assessment of the anatomical patterns of the PV, the relevant PV branches feeding to the reduction part of segment III were occluded to make demarcation lines on the surface between segments II and III (Fig. 28.10b). At that point, the intraoperative Doppler ultrasonography (US) could visualize the portal venous flow feeding to the graft, which planned to be preserved inside the liver. The further transection of hepatic parenchyma was horizontally performed, following those demarcation lines. If required the further reduction from the perspective of the graft volume, the removal of the lateral part of segment III was added [54, 55].

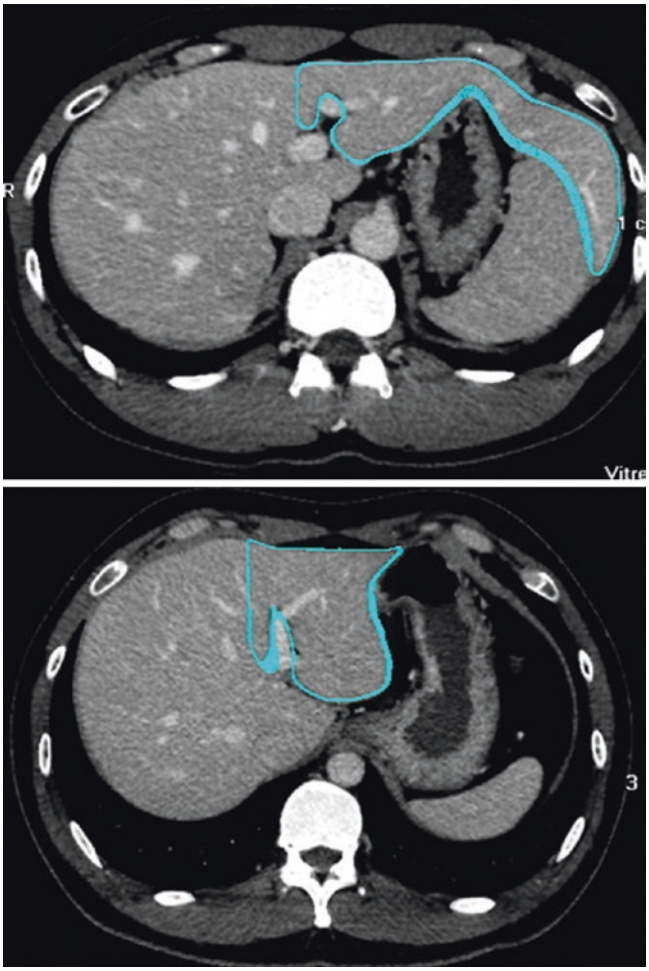


Fig. 28.9 If the LLS graft shape is flat fish-shaped type, modification as HRLLS graft is suitable. If the LLS graft shape is puffy fish-shaped type, S2 monosegment graft should be considered

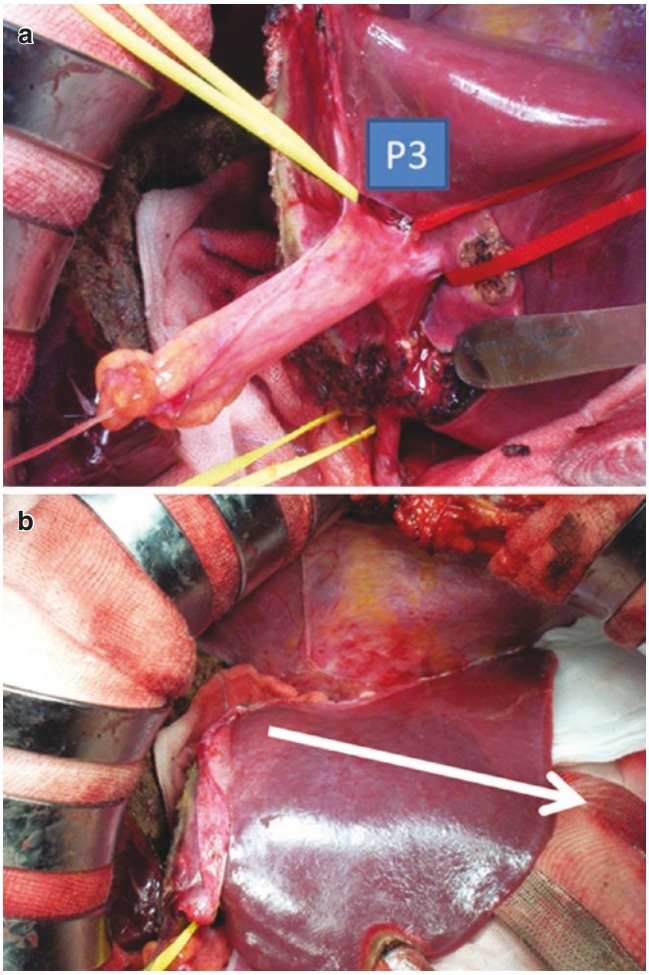


Fig. 28.10 Segment III Glissonian sheath was encircled, and parenchymal dissection has been made according to the demarcation lines between segments II and III

We have faced anatomical limitation for reducing the graft especially segment II graft. In this particular case, segments II and III hepatic arteries are raised from left hepatic artery separately; at the time of reduction, we may not know which artery should be reconstructed without proper imaging study. In this case we have sufficient imaging study and made hepatic arterial anastomosis without misunderstanding A2 and A3 (Fig. 28.11). There was another anatomical problem which had left portal vein branched to P2 and P3 inside of the left lateral segment parenchyma. This kind of anatomical variant is not suitable for taking the segment II graft (Fig. 28.12). And the crucial point of this procedure is underlying the risk of the drainage vein of the graft, because main left hepatic vein is running between P2 and P3 branch (Fig. 28.13). During that procedure, we have to paid attention to preserve the drainage veins of the graft.

Modified (P3 Preserving) Segment II Graft (Modified Anatomical Reduction)

We have developed "the modified (p-3 preserving) segment II graft" to overcome the disadvantage of segment II graft. After the left lateral segment graft is transected in the donor, segment III Glissonian sheath was encircled, and parenchymal dissection has been made according to the demarcation lines between segments II and III. During transection, we keep the cutting plain just above the main P3; the transection line for this was located horizontally on the level of the segment III branch of the PV (oblique line). Normally, main LHV is running between P2 and P3 branch. As far as one preserves P3 main branch, it never compromises outflow of the graft. This transection line could preserve the drainage vein of the graft, which drained into the inferior vena cava between the segment II and III branches of the PV (Fig. 28.10).

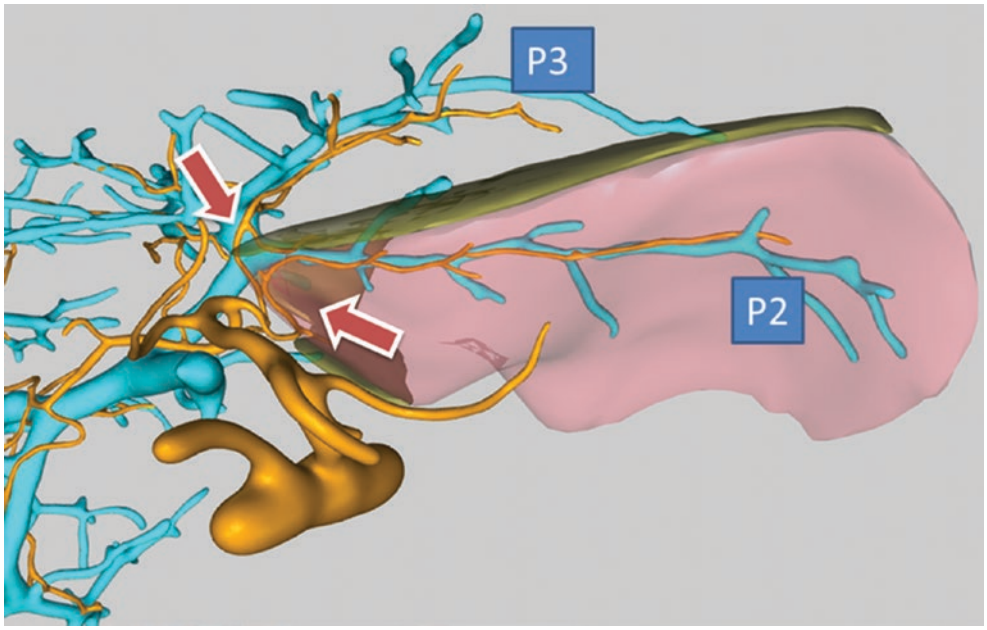


Fig. 28.11 We have anatomical limitation for reducing the graft especially segment II graft. In this particular case, segments II and III hepatic arteries arise from left hepatic artery separately; at the time of reduction, we may not know which artery should be reconstructed without proper imaging study. In this case we have sufficient imaging study and made hepatic arterial anastomosis without misunderstanding A2 and A3

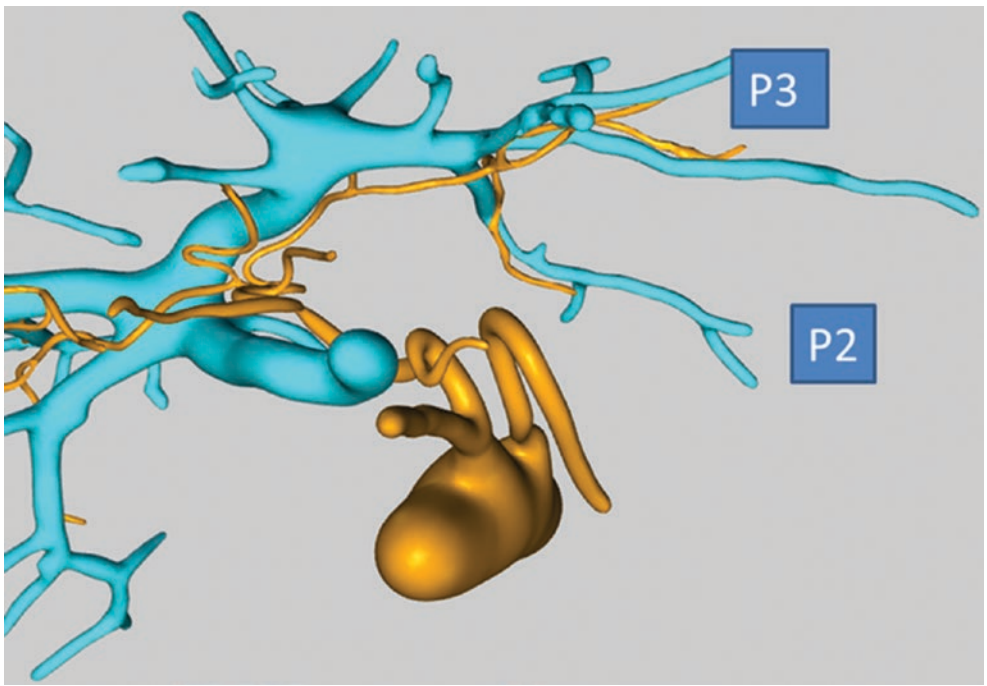


Fig. 28.12 The P2 and P3 divided inside the parenchyma; it would be tricky and better to be done by experienced surgeon with intraoperative ultrasonography

Tailoring the graft size and especially reducing the thickness of the graft might be important for small infants with end-stage liver disease. Although steps 2 and 3 of the procedure presented in this article could be done ex situ to protect the donor from the risk of bleeding and possible air embolisms, prolonged cold ischemia times and rewarming of the graft during back-table surgery have been found to be associated with increased susceptibility to ischemic/reperfusion injury in ex situ split-liver transplantation, and it might be postulated that these factors contribute to a higher incidence of graft dysfunction [56]. The procedure is associated with a much higher rate of biliary fistulas, and meticulous surgical technique and pre-/intraoperative anatomical evaluations with cholangiography/echography are recommended to prevent compromises to donor and recipient safety. By limiting adhesions in unexpected re-laparotomy during follow-up, the use of hemostatic fleeces to protect the cutting edges might be effective (Fig. 28.14).

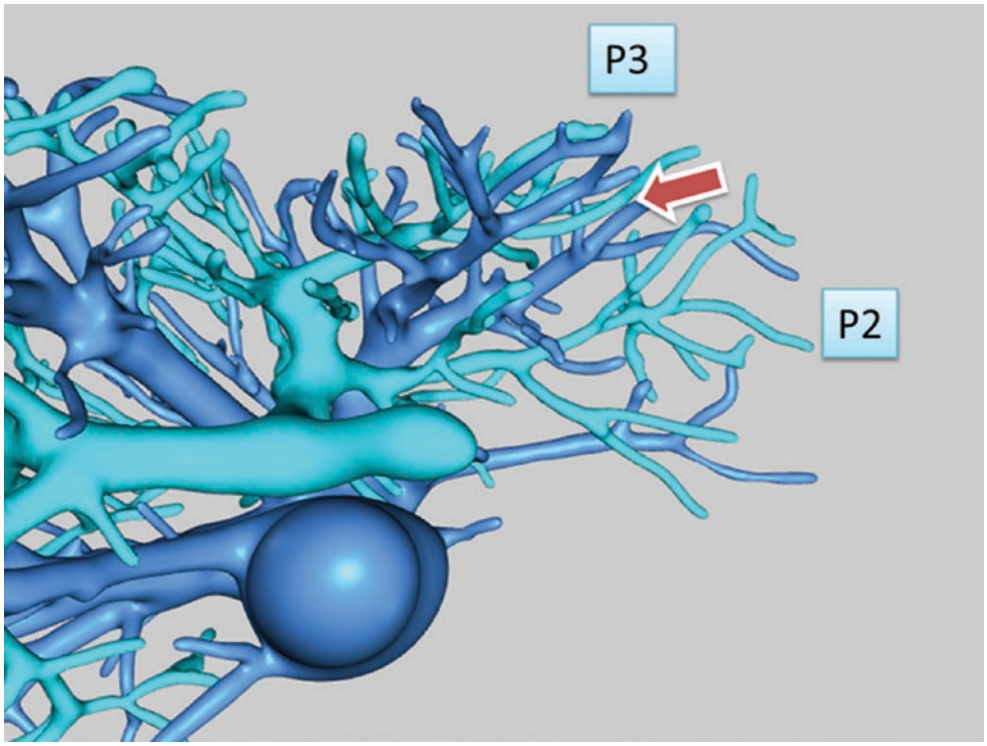


Fig. 28.13 Main LHV is always running between P2 and P3. As far as one preserves P3 branch, it never compromises the outflow of the graft

28.2.2.4 The Algorithm of Graft-Type Selection in LDLT for Smaller Children

Our series proposes the algorithm that can be used to select the graft type in LDLT for smaller children, which is simply framed in terms of the GRWR and the ratio of the thickness of the LLS to the AP diameter in the recipient's abdominal cavity. Furthermore, performing a preoperative analysis using a 3D, computer-generated model of the donor's liver can provide valuable information for the decision-making process in regard to graft-type selection.

As shown in Fig. 28.15a, b, if the maximum thickness of the donor's LLS is smaller than the AP diameter in the recipient's abdominal cavity (ratio of thickness <1.0), then segment II grafts may not be necessary for the majority of recipients. However, if a recipient is associated with a profoundly ill status before the operation, and shows severe subcutaneous edema of the abdominal wall or edematous intestines, then nonanatomically reduced LLS is unlikely to fit into the small abdominal cavity of the child. Therefore, the algorithm proposed in our experience should be refined through the further accumulation of experience, especially considering various preoperative conditions of the recipients as reference indices for graft-type selection [57].

The modified-reduced LLSs have the potential to allow these children to undergo transplantation safely without the associated complications of large-for-size grafts. Although long-term observation should be necessary to establish this technical modification, we hope that increasing experience with the technique and refinements will lead to improved outcomes in liver transplantation for small babies.

28.2.3 Postoperative Management and Outcome of the Living Donor

Between November 2005 and December 2016, 406 children underwent LDLT in the National Center for Child Health and Development (NCCHD). There were 168 male donors (41.4%) and 238 female donors (58.6%) with a median age of 35 years (range, 1–62 years) and a median body weight of 56.7 kg (range, 8.5–85.0 kg). The donors were parents in 96.3% cases, including fathers and mothers in 56.9% and 39.4% of cases, respectively, followed by domino donor (Maple syrup urinary disease) in 1.0% of cases. The blood type combination was identical in 59.6% and compatible in 22.9%, while 17.5% recipients received ABO-incompatible grafts. The graft types included modified left lateral segment in 23.6%, left lateral segment (LLS) in 64.8, left lobe in 9.9%, right lobe grafts in 1.0%, and domino whole graft in 0.7%. There are 15 donor complications (3.7%) including wound hernia in 3, wound infection in 3, duodenal ulcer in 3, paralytic ileus in 2, deep vein thrombosis in 1, biliary leakage in 1, radial nerve palsy in 1, and meningitis related to epidural tube in 1. There were no donor mortalities in our series.

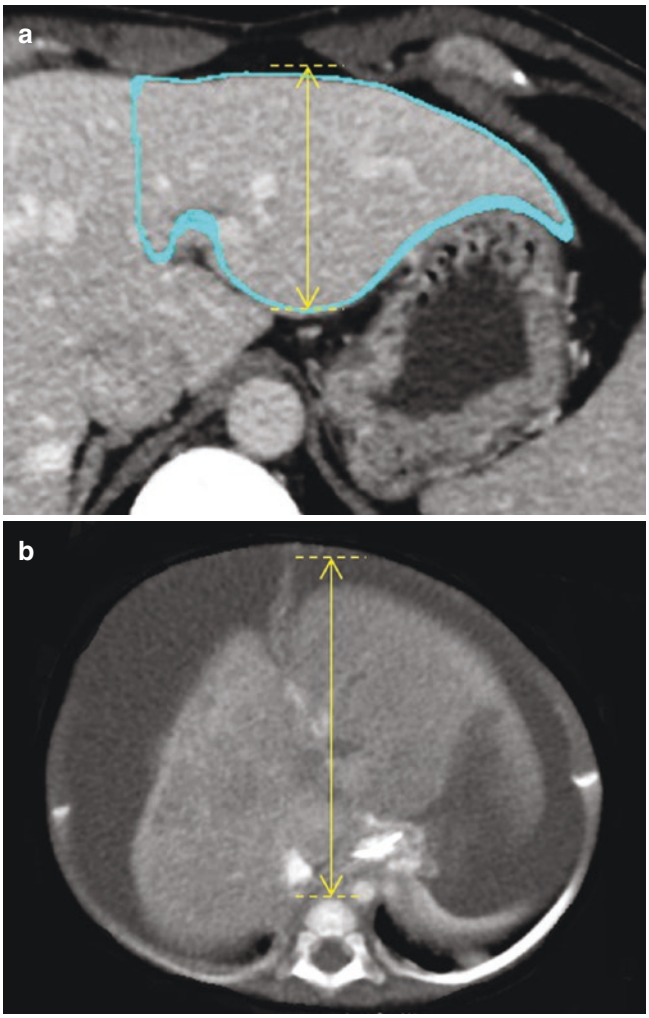


Fig. 28.14 (**a**) The maximum thickness of the donor left lateral segment graft. (**b**) The anteroposterior (A-P) diameter in the recipient abdominal cavity. From the perspective of the graft shape, if the LLS of the donor was bulky, and its maximum thickness was larger than the anteroposterior (AP) diameter in the recipient's abdominal cavity, which was identified as the length from the inside abdominal wall to the front of the vertebra on axial computed tomography images, a segment II graft was considered (when the ratio of thickness [= graft thickness/recipient A] more than 1.0)

28.3 Recipient

28.3.1 Characteristics of Recipients with Each Liver Disease Undergoing Living Donor Liver Transplantation

The indications of living donor liver transplantation (LDLT) for pediatric liver disease are mostly similar to those of deceased donor liver transplantation (DDLT). In this chapter, some of the difference in the characteristics of the recipients with each liver disease is separately described below.

28.3.1.1 Cholestatic Liver Diseases

Biliary atresia (BA) was the most common cholestatic liver diseases indicated for LDLT. Most of the patients received Kasai operation; some of them underwent redo surgeries, which might induce tight adhesions in the abdominal cavity; however, LDLT tended to be indicated earlier once the first Kasai operation was failed and anti-adhesive materials were used at the time of the operation for most of the recent cases. When the BA patients were considered to indicate LDLT, there were several important clinical features specific to BA as follows: comorbid congenital anomalies, hepatopulmonary syndrome, incidental malignancy, and portal vein hypoplasia with collateral development. Determining the surgical priority in the BA recipients with congenital heart diseases is a challenge due to the hemodynamic alterations that increase surgical risks. In order to prioritize the choice of surgery, it is essential to analyze the advantages and disadvantages of performing each procedure first. Giving priority to cardiac surgery as the first procedure would stabilize the vascular system dynamics during the subsequent LDLT, but the patient would face the risk of a coagulation disorder during cardiac surgery, as well as the risk of hepatic dysfunction after the cardiac intervention. Alternatively, if LDLT were carried out first, the patient would have good hepatic function during the cardiac intervention but would have the risk of an air embolism during the liver replacement, as well as the risk of infectious endocarditis after liver transplantation. Definitive criteria do not exist for prioritizing heart and liver operations in cases with coexistent end-stage liver disease and congenital cardiac malformations that require surgical correction. Therefore, one needs to evaluate the patient's specific situation with respect to heart disease and liver failure and carefully analyze the available data to determine the order of surgery [58].

Situs inversus (SI) occurs in association with the polysplenia syndrome with midgut malrotation, preduodenal PV, aberrant hepatic arterial supply, and absence of inferior vena cava (IVC) (Fig. 28.16). Consideration has to be given to additional vascular reconstruction at LT for BA with SI. Native liver appears asymmetric, and hepatic arteries often arise at the celiac trunk more cranially; therefore, it might be sometimes difficult to orientate hepatic arteries' anatomy, and hepatic arterial anastomosis is exposed to be with the tension. The evaluation of intrapulmonary shunting (IPS) of portal hypertensive pulmonary hypertension is important when the patients are indicated for LDLT. If those pulmonary complications have already become severe, LT should be carefully indicated. The case with IPS is often susceptible to surgical morbidities, such as biliary complications and vascular thrombosis [59]. BA cases have a risk of development of malignant tumors, such as hepatoblastoma or hepatocellular carcinoma.

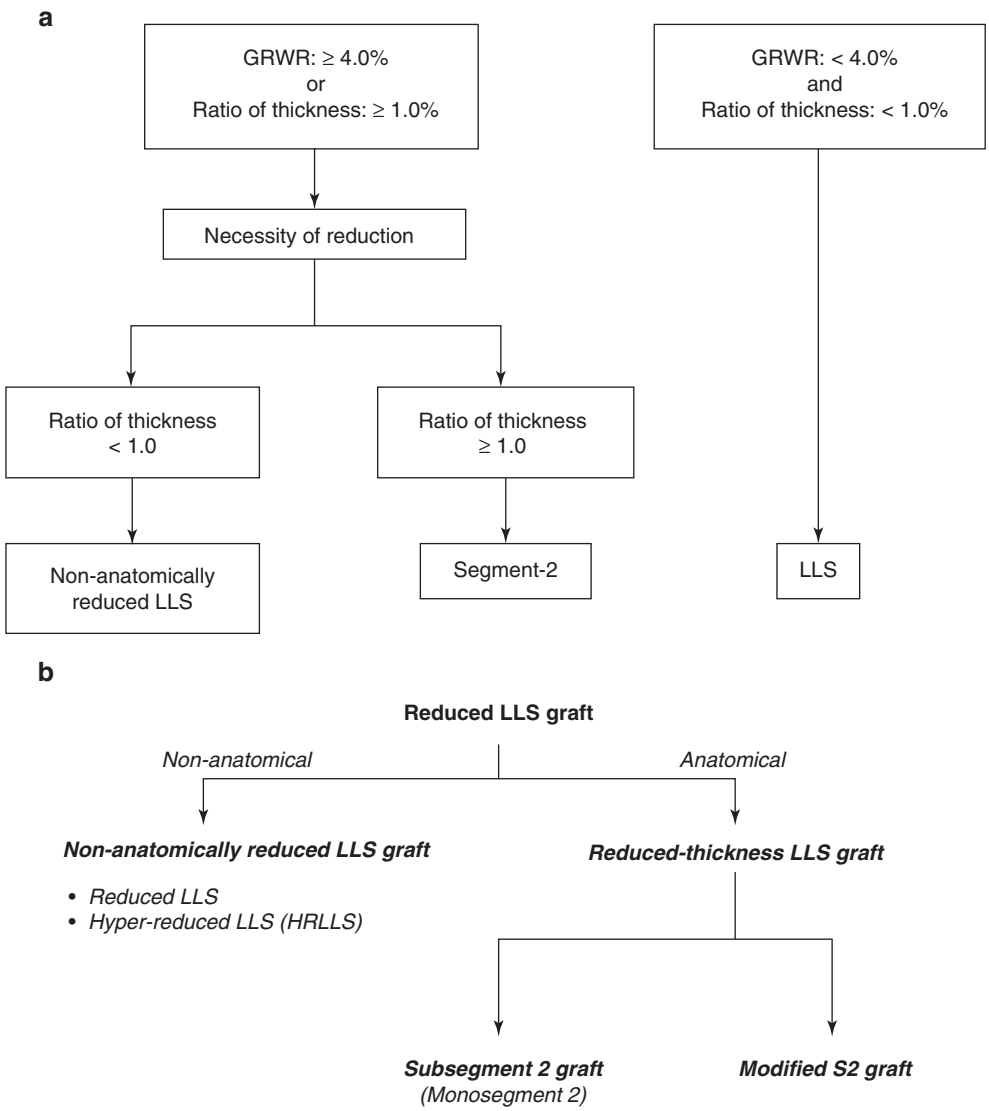


Fig. 28.15 The algorithm of graft-type selection in LDLT for smaller children: algorithm used for the preoperative assessment for graft-type selection. *GRWR* graft-to-recipient weight ratio, *LLS* left lateral segment, *ratio of thickness* the ratio of the maximum thickness of the LLS to the anteroposterior diameter in the recipient's abdominal cavity

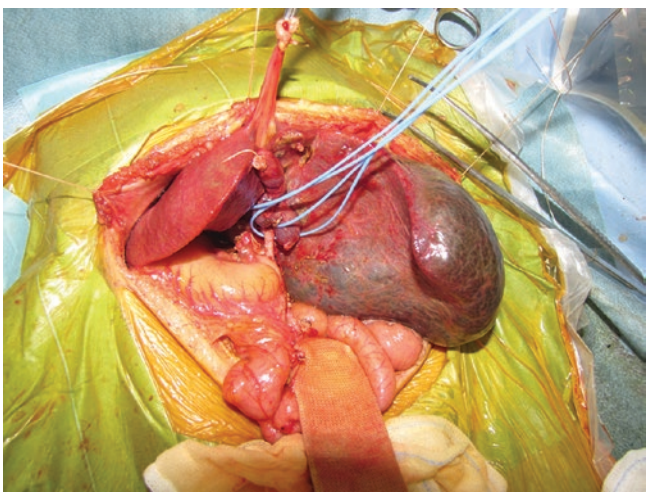


Fig. 28.16 Intraoperative findings of biliary atresia with situs inversus

Alagille syndrome (AGS) is an autosomal dominant genetic disorder, and therefore, potential LDLT donors, commonly recipients' parents, may have intrahepatic bile duct paucity or anatomical anomalies of hepatic vasculatures [60]. LDLT donors must be cautiously evaluated to rule out unsuspected bile duct paucity (Fig. 28.17). Progressive familial intrahepatic cholestasis (PFIC), including type 1 and type 2, is also indicated for LDLT. PFIC type 1, which is caused by mutations in ATP8B1 gene on hepatocytes, cholangiocytes, and enterocytes leading to cholestatic jaundice, diarrhea, and growth retardation, is often complicated by postoperative diarrhea and recurrent graft steatosis, and therefore, LT might be cautiously indicated for this type of PFIC [61].

28.3.1.2 Metabolic Liver Diseases

Urea cycle disorders (UCD), consisting of ornithine transcarbamylase deficiency (OTCD) and carbamoyl phosphate synthetase 1 deficiency (CPS1D), are the most common metabolic

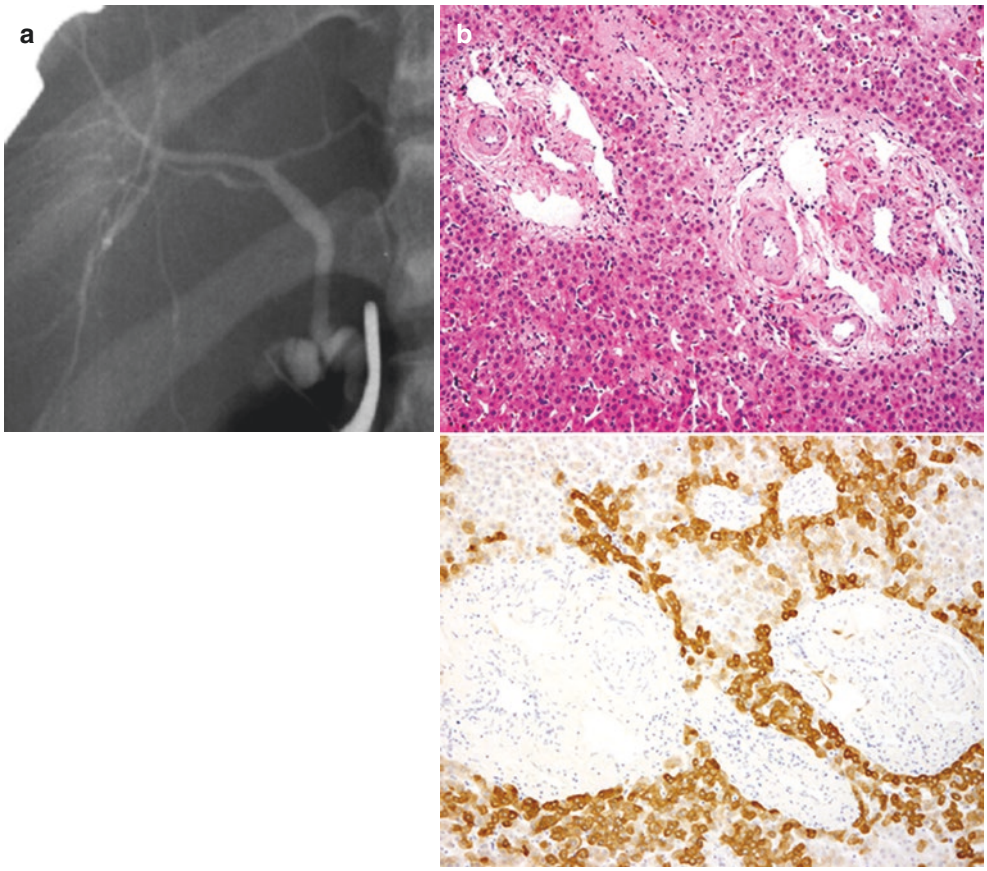


Fig. 28.17 Living donor for the recipient with Alagille syndrome. (**a**) Intraoperative cholangiogram showed scrimpy biliary trees. (**b**) Liver biopsy revealed unsuspected bile duct paucity

liver diseases indicated for LDLT [62]. If the patients with UCD are diagnosed by prenatal diagnosis, hepatocyte transplantation can be considered as a therapeutic option to bridge LDLT once their body weight reached 6.0 kg. The source of hepatocytes is derived from remnant liver tissue, which is voluntarily donated from unrelated living donors receiving in situ reduction procedure at the time of left lateral segmentectomy for their recipients [63]. Although OTCD is an X-linked inheritance, the use of asymptomatic heterozygous donors has been accepted with careful examinations in LDLT. However, few cases with OTCD, receiving grafts from their mothers, may experience severe hyperammonemia following LDLT, and therefore, an OTCD heterozygous carrier donor should be avoided if there is another donor candidate [38].

Organic acidemias, consisting of methylmalonic academia and propionic academia, are also indicated for LDLT. Although implanted liver grafts produce deficient enzymes, LDLT only partially corrects the biochemical defects. However, the benefits of an improved quality of life associated with the elimination of episodes of decompensation and improved protein tolerance must be weighed against the potential for renal and neurological injury [64].

Glycogen storage disease (GSD) 1b shows the added features of neutropenia and neutrophil dysfunction, which require the regular administration of recombinant human granulocyte colony stimulating factor (G-CSF). GSD1b recipients are susceptible to infection, especially catheter-related blood stream infection, and therefore, unnecessary catheter placement has to be avoided. Neutropenia may not be able to be cured by LDLT, and it thus remains an open question whether LT improves neutropenia in patients with GSD1b [65].

In the patients with primary hyperoxaluria type 1 (PH1), overproduction and urinary excretion of oxalate lead to urolithiasis, and nephrocalcinosis may consequently result in renal failure. Transplantation strategies for PH1 have been proposed based on concomitant renal insufficiency. If renal insufficiency becomes chronic kidney disease (CKD) stage 5 under dialysis at the time of LDLT, concomitant or sequential liver-kidney transplantation have to be considered. Preemptive LDLT for PH1 patient with mild renal insufficiency, below CKD stage 3, may be a reasonable therapeutic option to avoid further renal replacement therapy, including kidney transplantation [66].

28.3.1.3 Acute Liver Failure

All of the patients suspected of ALF are admitted to the pediatric intensive care unit, and multidisciplinary management is commenced. Consultation with a pediatrician who specialized in neurology, electroencephalogram, and brain

computed tomography imaging findings is considered to evaluate the neurological impairment. Artificial liver support therapy in combination with continuous veno-venous hemodiafiltration (CVVHDF) and plasma exchange (PE) is initially performed for all patients under mechanical ventilation, while the precipitating cause of ALF is searched as much as possible; once the cause of ALF is determined, specific therapy is initiated [67]. If the liver function does not sufficiently recover despite conservative treatment, while preparing for LT, then the indications for LT are discussed based on the clinical course and liver pathology. LT is mainly considered when there is at least one of the following symptoms: exacerbation of hepatic encephalopathy by analysis of electroencephalogram and/or progression of liver atrophy on ultrasound (US) and/or prolonged international normalized ratio of prothrombin time (PT-INR) [68]. While the patients are put on the waiting list for DDLT, the living donor candidates are also evaluated in parallel. The rejection rate appears to be higher than the other liver diseases, and moreover the majority of them suffer from repeated episodes of rejection. The pathological findings of liver biopsies at the time of severe liver dysfunction commonly reveal centrilobular injuries, consisting of central venulitis, hemorrhage, and necrosis, which are considered as pathological features refractory to steroid bolus therapy [69]. Anti-thymocyte globulin can be effective to rejection presenting centrilobular injuries.

28.3.1.4 Congenital Hepatic Fibrosis/Caroli Disease

Congenital hepatic fibrosis (CHF) and Caroli disease are often associated with autosomal recessive polycystic kidney disease (ARPKD). The concomitant renal insufficiency may lead to a poor prognosis for the patients undergoing LDLT. Recent remarkable advances in LDLT have yielded survival for pediatric recipients. Therefore, LDLT should be performed before renal insufficiency becomes far advanced to avoid missing the proper timing [70]. Even though sequential KT has to be considered when there is progression of renal insufficiency after LDLT, the recovery of liver function provides advantages for the successful outcome of this procedure.

28.3.1.5 Liver Tumors

Hepatoblastoma (HBL) is the most common pediatric liver tumor indicated for LDLT. Therapeutic strategy for advanced HBL, classified into pretreatment extent of disease (PRETEXT) III and IV, consists of neoadjuvant chemotherapy and surgical interventions. Neoadjuvant chemotherapy (NAC) includes the Société Internationale d'Oncologie Pédiatrique-Epithelial Liver Tumor Study Group (SIOPEL), the Children's Oncology Group (COG), or the Japanese Study Group for Pediatric Liver Tumor (JPLT) guidelines. After 2–4 cycles of NAC, the possibility of surgical interventions including LDLT is assessed [71]. If lung metastases still exist, however, the number of metastases becomes countable after NAC, lung resection is performed, and then surgical intervention to primary liver tumors is scheduled 2 weeks later. LDLT is considered to be a better option than DDLT, because LDLT can be timely scheduled LT. A final judgment of surgical resectability is made during the operation by macroscopic findings and intraoperative US, and therefore, LDLT donors have been already prepared for a backup option of LDLT at the same time. Adjuvant chemotherapy depends on the patients' general conditions, especially liver and renal functions; however, there are no promising guidelines for adjuvant chemotherapy after LT. In contrast to the total hepatectomy for the other liver diseases, the procedures including limited mobilization of the native liver and inflow occlusion at the hepatic hilum are always introduced to prevent tumor spread during the operation. Furthermore, if portal vein thrombosis is not suspected, temporary portocaval shunt is made in the beginning of the operation to reduce intraoperative blood loss and maintain hemodynamic stability (Fig. 28.18) [72]. LDLT provides a valuable alternative treatment, given the appropriate timing for scheduled LT, with excellent results in children with HBL [73].

28.3.1.6 Retransplants

Retransplants using grafts from living donors (Re-LDLT) are challenging. At the time of re-LDLT, surgical procedures are always complicated, especially vascular reconstructions. The length of vasculatures, such as portal vein and hepatic artery, at the recipient side often becomes short, and therefore, interpositional vein graft is needed. DDLT may cope with the complexity of vascular reconstructions in re-LT because of the necessity of vascular grafts.

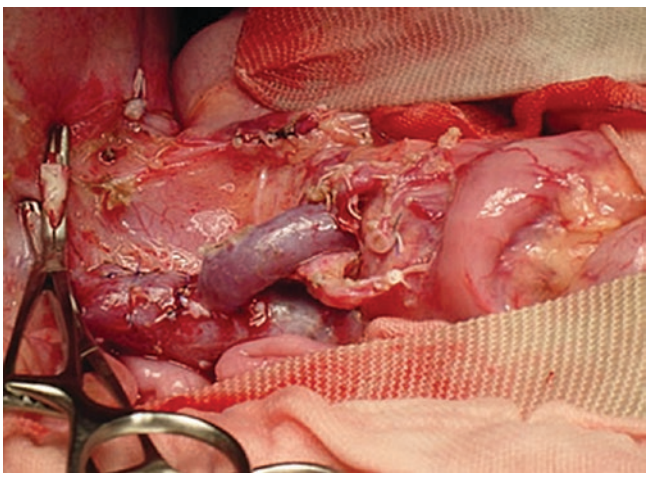


Fig. 28.18 Temporary portocaval shunt during total hepatectomy of hepatoblastoma

28.3.1.7 ABO-Incompatible Donors

Previous reports related to ABO-incompatible liver transplantation (ABO-I LT), including Kyoto University experience [74], showed that ABO-I LT was safely performed for pediatric cases, especially under 1 year. However, elderly patients might have considerable risk of antibody-mediated rejection (AMR) similarly as adult patients. Various preconditioning regimens for B-cell desensitization, including rituximab, have been applied for pediatric ABO-I living donor LT (LDLT), although the regimens appropriate to pediatric candidates still remain controversial. Preconditioning regimens for B-cell desensitization have been changed reflecting emerging trends. Until rituximab was indicated for ABO-I LDLT in the early 2000s, several sessions of plasmapheresis were performed to decrease anti-donor AB antibodies immediately before LDLT, and local infusion therapy through portal vein or hepatic artery, including steroids, was indicated for the elder children [75]. Recent standard preconditioning regimens for B-cell desensitization consist of rituximab administration 1 month before a scheduled LDLT, and mycophenolate mofetil is added to the conventional immunosuppressive regimens with calcineurin inhibitor and low-dose steroids. Additional splenectomy is controversial in the setting of pediatric ABO-I LDLT, and it is contraindicated for the recipients younger than 2 years.

28.3.2 Surgical Challenges in Recipient Operation in Living Donor Liver Transplantation

28.3.2.1 Standard Recipient Operation

The standard recipient operation for post-Kasai BA patient is demonstrated. After reverse T incision, left and right triangular ligament is dissected. Then the liver is mobilized from the right side until it reaches to the left lesser omental cavity. Roux-en-Y (RY) limb for Kasai operation is identified just above the duodenum. Hepatic arteries (HA) and portal veins (PV) are dissected as distally as possible. If preoperative US shows retrograde PV flow, one can cut PV completely because the patient has collaterals. And if the PV diameter is less than 4 mm and looks attenuated, it is better to use interpositional vein graft for reconstruction [76]. Otherwise, left PV is preserved to prevent intestinal congestion. Potential collaterals are devascularlized to get sufficient PV front flow. After a total hepatectomy, the top vena cava is freed from its diaphragmatic attachments, by dividing the phrenic veins, and is skeletonized to allow adequate spacing for the hepatic vein anastomosis. During anhepatic period, a portosystemic shunt is made between the right portal branch and the inferior vena cava (IVC) to prevent portal hypertension in the patients without collaterals. The orifice of the left, middle, and right hepatic veins are enlarged with a transverse incision, making a natural triangular orifice to obtain sufficient outflow. Anastomosis of the hepatic veins (HV) is accomplished in an end-to-end fashion with interrupted sutures for anterior wall and a continuous suture for posterior wall (*5-0 Prolene*). Portal vein reconstruction is made with interrupted sutures for anterior wall and a continuous suture for posterior wall (*6-0 PDS*) using native PV branch patch technique. Arterial reconstruction is carried out using *9-0 Prolene* with surgical microscope. Biliary reconstruction is carried out with RY hepaticojejunostomy with *four Fr* biliary stent tubes.

28.3.2.2 HA Reconstruction with Surgical Microscope

HA anastomosis might be one of the key factors for successful pediatric liver transplantation, and the use of operative microscope has dramatically reduced the incidence of HA thrombosis in pediatric segmental LT. Peripheral branch of native HA is used for HA reconstruction with *9-0 Prolene* interrupted suture. Because of the short stump of graft left HA and size discrepancy between native HA and graft left HA, nonanatomical HA reconstruction could be applied in some cases using gastroduodenal artery, right gastroepiploic artery, sigmoid artery interposition, mesentery artery of Roux-en-Y limb, and donor/recipient radial artery (Fig. 28.19). If gastroduodenal artery is dissected, elongation of PV would be easier.

Although several hepatic arteries may supply the segmental graft in LDLT, it is not necessary to reconstruct all of them as far as backflow of remnant looks sufficient.

28.3.2.3 How to Get Sufficient Portal Front Flow? Cruise Technique

It has been reported that the vascular complication rate in pediatric LDLT is higher than that of adult LDLT, because of the size discrepancy between the graft and native vasculature. Obtaining sufficient PV front flow may contribute to prevent PV complications in children. The collateral vessels, including left gastric vein, splenorenal shunts, and retroperitoneal shunts, must be carefully devascularized. Splenorenal shunt ligation from anterior approach would be effective to get sufficient front flow (Fig. 28.20) [77]. The measurement of PV pressure might be a feasible index of PV front flow; if PV pressure after the devascularization of collateral vessels shows more than 30 mmH_2O, PV front flow may be sufficient enough.

28.3.2.4 Interpositional Vein Graft for PV Reconstruction

If the native PV is sclerotic with insufficient front flow, especially small caliber of the native PV (less than 4 mm), PV anastomosis by using interpositional vein graft is

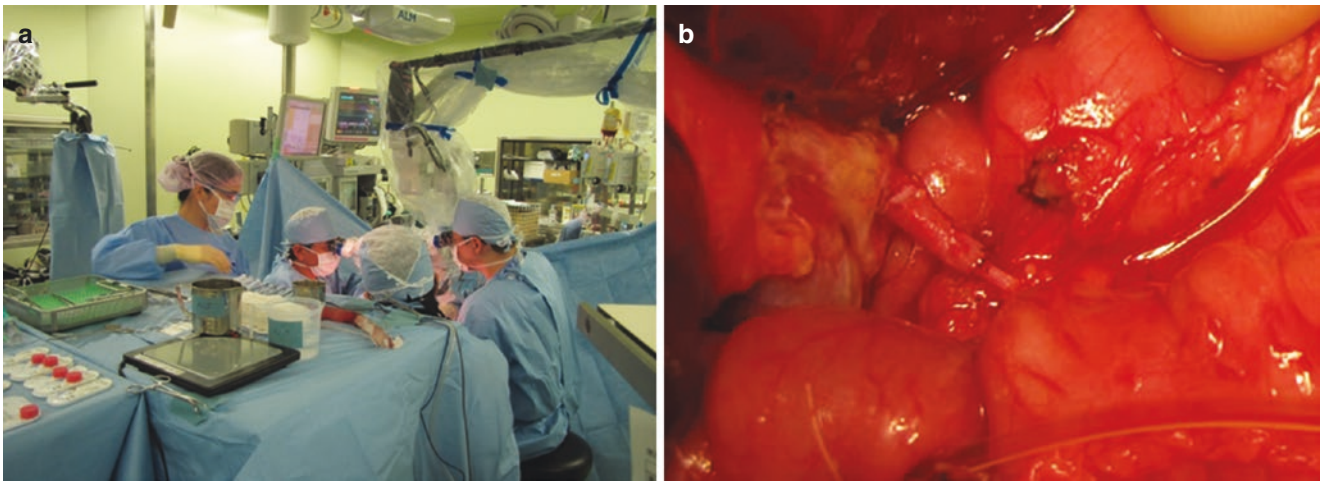


Fig. 28.19 Hepatic artery reconstruction. (**a**) Operative microscope. (**b**) Nonanatomical reconstruction with native right gastroepiploic artery and graft left hepatic artery

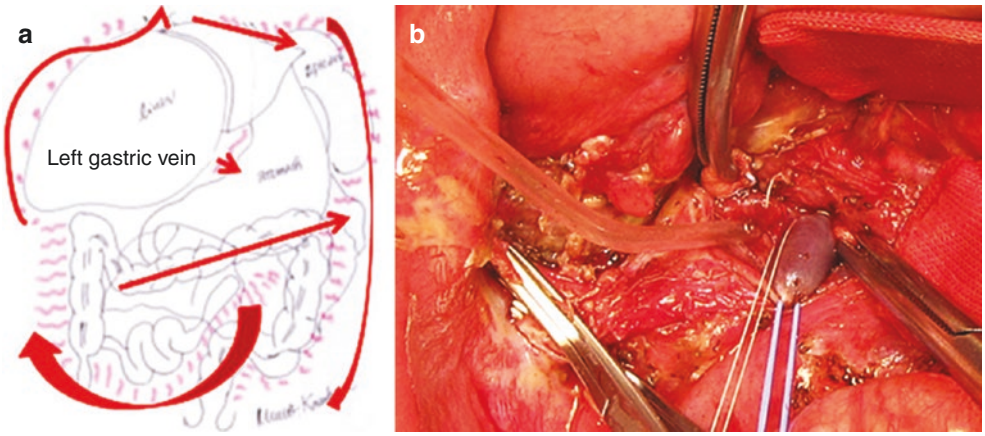


Fig. 28.20 The devascularization of collateral vessels. (**a**) Cruise technique. (**b**) Splenorenal shunt ligation with anterior approach. Left renal vein (blue sling) and splenorenal shunt (white sling)

indicated [76]. Donor ovarian vein or inferior mesenteric vein is usually used for interpositional vein graft. An interposition vein graft is first anastomosed to the confluence of the superior mesenteric vein and the splenic vein after cutting the narrowing and sclerotic native PV trunk (Fig. 28.21). Branch patch between the stump of left gastric vein and main PV trunk can be used for anastomosis. Perioperative anticoagulant therapy is not routinely performed. The use of the interposition vein graft appears to be a feasible option, with better graft survival and fewer PV complications than conventional methods.

28.3.2.5 Pediatric Living Donor Domino Transplantation from Maple Syrup Urinary Disease

Due to the organ shortage in liver transplantation, domino liver transplantation has been increasingly applied using the explanted liver from maple syrup urinary disease (MSUD) without compromising *second* recipient long-term survival [78]. Because the recipients of liver grafts from MSUD donors are not likely to develop protein intolerance, 60% of branched-chain ketoacid dehydrogenase activity occurs in the muscle. In the setting of living donor domino liver transplantation, livers obtained from patients with MSUD, who had undergone LDLT, inherently lack the retro-hepatic IVC and have multiple vessel and bile duct orifices. It is important to evaluate the transection site of the vessels based on the findings of *3D*-CT of the first donor and recipient before the operations. The first recipient's intraoperative findings are sent to second recipient operators to make sure cutting line of each vessel. Vascular plasty of the HVs is needed to be conducted on the back table (Fig. 28.22). The right HV, middle HV, left HV, and left superficial vein are sutured together to create one orifice. The unified graft HVs are anastomosed with the orifice of the united recipient HVs. PV, HA, and biliary reconstructions are performed in the standard manner as described above.

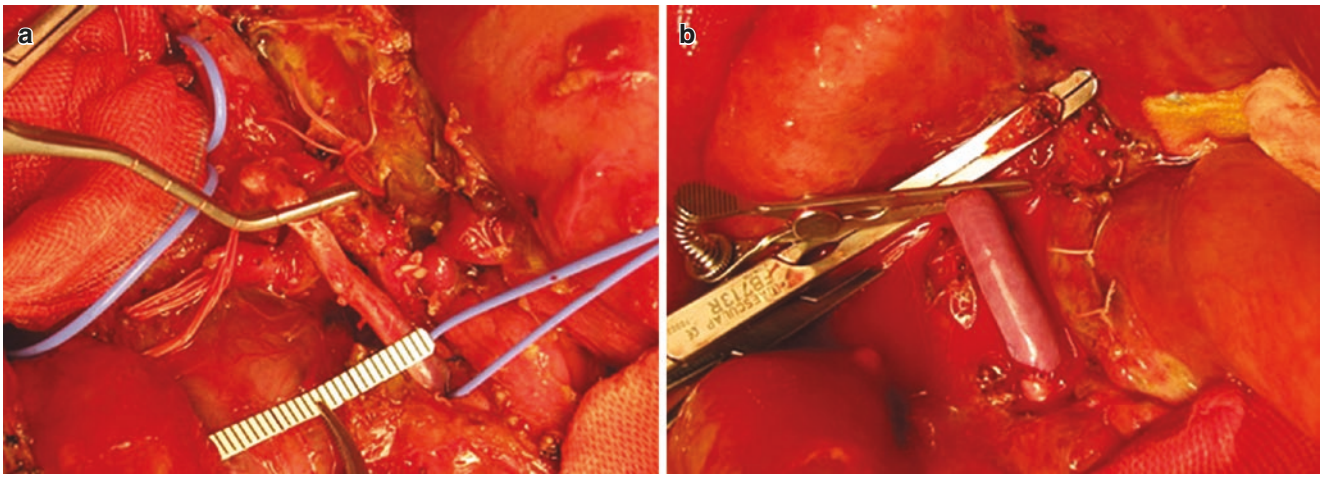


Fig. 28.21 Interpositional vein graft for portal vein reconstruction. (**a**) The native portal vein appears narrowing, and its diameter is smaller than 4 mm. (**b**) Vein graft with ovarian vein graft is obtained from the maternal donor

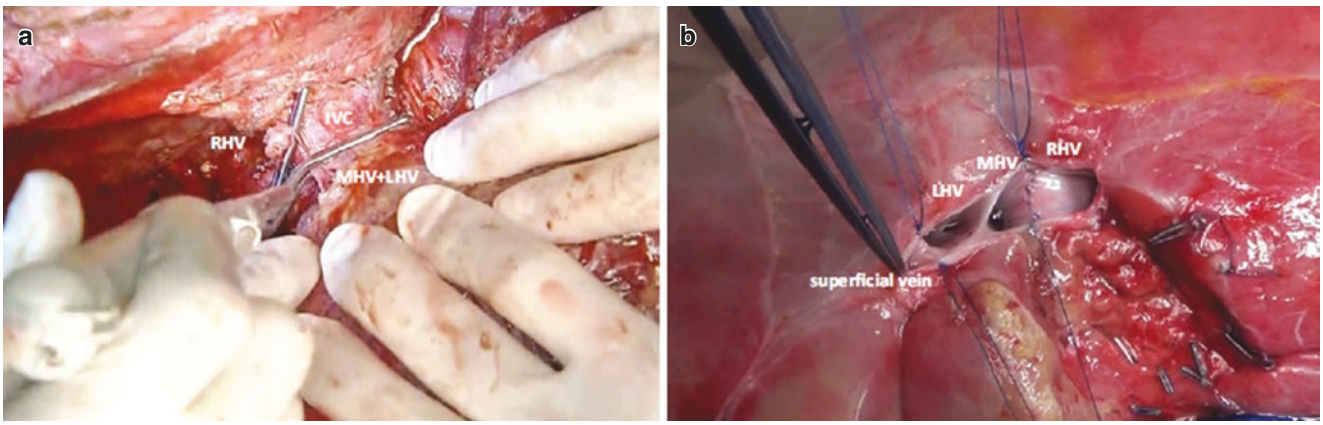


Fig. 28.22 Pediatric living donor domino transplantation. (**a**) The HVs were exteriorized as far as possible in the native liver parenchyma. (**b**) The RHV, MHV, LHV, and superficial vein were sutured together by venoplasty at the back table

28.3.3 The Outcomes of Living Donor Liver Transplantation

In a multicenter Organ Procurement and Transplant Network (OPTN) analysis, LDLT has been associated with improved outcomes particularly in the youngest recipients under the age of 2 years [79]. Unmatched overall living donor outcomes at 5 and 10 years are incrementally better as compared with deceased donor outcomes in the Scientific Registry of Transplant Recipient database between 1991 and 2013 [80]. A recent study from the Registry of the Japanese Liver Transplantation Society analyzed the results of the largest world cohort of 2224 LDLT pediatric recipients; the 1-year, 5-year, and 10-year patient survival rates were 88.3%, 85.4%, and 82.8%, respectively [81]. In that study, etiology of liver disease, recipient age, ABO incompatibility, and the transplant era were found to be significant predictors of overall survival. Patients with cholestatic liver disease showed a significantly better patient survival rate than those with metabolic disease, neoplastic disease, or acute liver failure (Fig. 28.23). Retransplantation with living donors, accounted for 3.3% of cases, showed a significant worse patient survival rate compared with the patients receiving single grafts (48.1% and 84.0% at 10 years, respectively). Liver graft size matching is one of the major factors determining a successful outcome in pediatric LDLT. Relative to the older pediatric recipients, infants had worse overall patient survival rates. The disadvantage of using large-for-size grafts in infants is that insufficient tissue oxygenation and graft compression are observed in association with a relatively high incidence of vascular complications that result in poor outcomes. Reduction procedures for adult left lateral segments (LLSs) have been developed to eliminate size mismatch in living donor LT for small children [82, 83]. Reduced LLS grafts have been changed reflecting emerging trends, from nonanatomically reduced LLS grafts to reduced-thickness LLS grafts. In our recent series accumulating 96 infants receiving

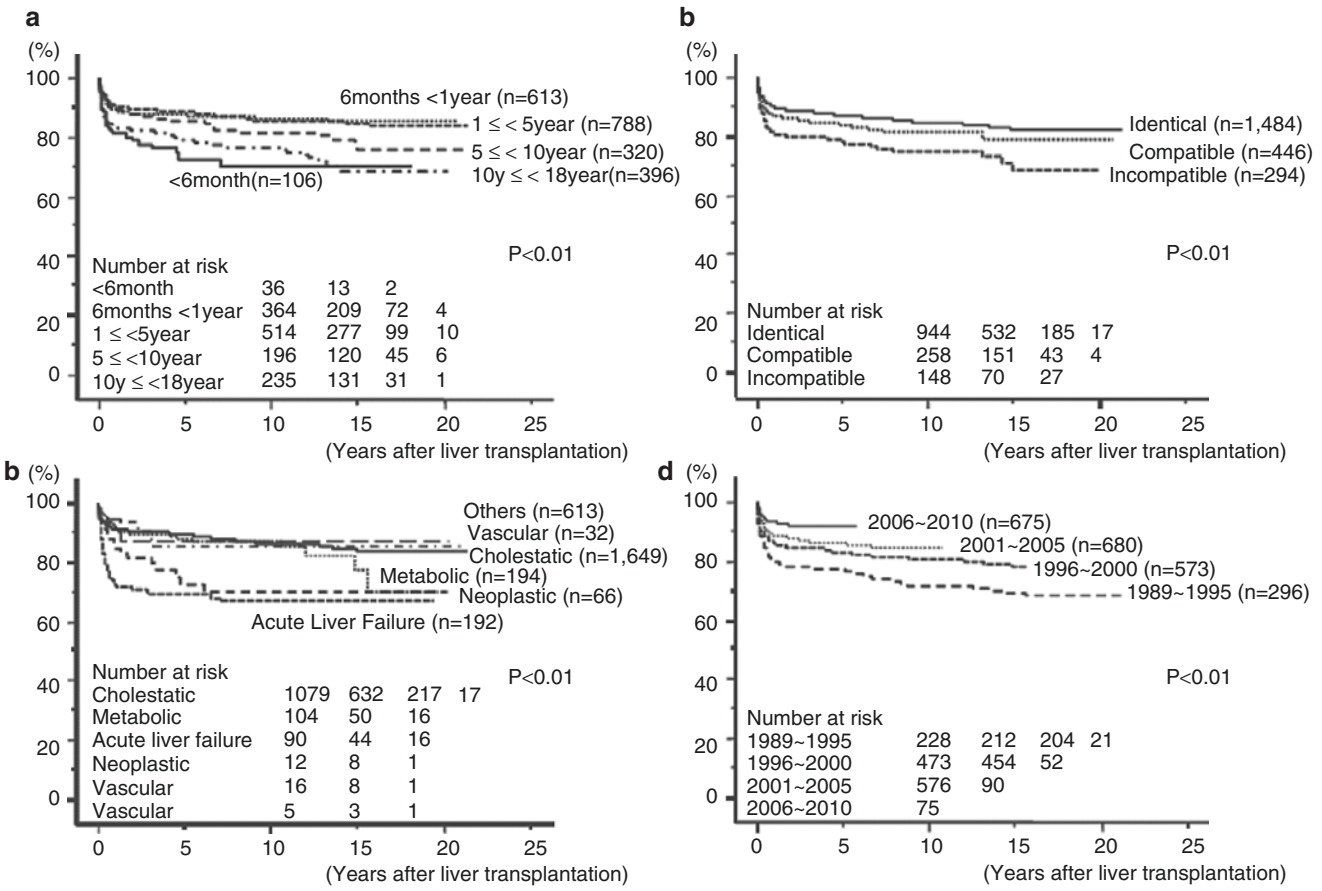


Fig. 28.23 Recipient survival in pediatric living donor liver transplantation from the Registry of the Japanese Liver Transplantation Society [81]. (**a**) Recipient age, (**b**) ABO compatibility, (**c**) original liver disease, (**d**) transplant era

Table 28.1 Surgical complications in living donor liver transplantation at National Center for Child Health and Development

Surgical complications		Number	Incidence
Portal vein	Thrombosis	4	0.9%
	Stricture	19	4.3%
Hepatic vein	Stricture	5	1.1%
Hepatic artery	Thrombosis	0	0.0%
Bile duct	Leakage	7	1.6%
	Stricture	25	5.7%
	Accidental ligation of B2	5	1.1%

reduced LLS grafts, reduced-thickness LLS grafts showed a significantly better patient survival rate compared with the patients receiving nonanatomically reduced LLS grafts (94.8% and 80.8% at 3 years, respectively, unpublished data). LDLT for smaller children is technically more challenging due to the smaller vascular structures and size discrepancies with the grafts. Various surgical innovations have overcome the technical issues in LDLT for smaller children, as described in the "surgical procedures" above. According to recent published studies, the incidence of hepatic artery, portal vein, and hepatic venous outflow complications were decreasing, below 3% [84], 10% [85], and 5% [86], respectively. Portal vein complications are reported as the most frequent vascular complications in pediatric LDLT. Biliary atresia, the most common disease indicated for pediatric LDLT, is often associated with PV hypoplasia, which is caused by rapidly progressing sclerosis and fibrosis, previous Kasai procedure, and repeated attacks of cholangitis that could lead to PV inflammation [85]. Although various techniques to enlarge the diameter of hypoplastic PV, including the use of interpositional vein graft, have been applied to PV reconstruction, obtaining sufficient PV front flow, which can be provided by careful devascularization of collateral vessels, may contribute to prevent PV complications.

In terms of vascular and biliary complications in our series of 440 LDLT cases until the end of 2016, there were PV complications in 23 cases (5.2%); 3 cases required stent placement for PV stricture, and 4 cases underwent reanastomosis of PV and HV complications in five cases (1.1%); 2 cases required stent placement for HV stricture, and 1 case underwent reanastomosis of HV and biliary complications in 32 cases (7.3%), including biliary leakage in 7 cases and biliary stricture in 25 cases. Fortunately, we have not yet encountered any HA thrombosis. All of the patients with biliary stricture were successfully treated by percutaneous biliary

balloon dilatation; however, two cases of them finally received biliary reanastomosis after repeated episodes of restricture. Biliary duct of segment 2 (B2) was accidentally ligated during the donor operation, and biliary reconstruction of B2 had to be performed in five cases (Table 28.1).

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