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REVIEW

Feasibility of using marginal liver grafts in living donor liver transplantation

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Abstract

Liver transplantation (LT) is one of the most effective treatments for end-stage liver disease caused by related risk factors when liver resection is contraindicated. Additionally, despite the decrease in the prevalence of hepatitis B virus (HBV) over the past two decades, the absolute number of HBsAg-positive people has increased, leading to an increase in HBV-related liver cirrhosis and hepatocellular carcinoma. Consequently, a large demand exists for LT. While the wait time for patients on the donor list is, to some degree, shorter due to the development of living donor liver transplantation (LDLT), there is still a shortage of liver grafts. Furthermore, recipients often suffer from emergent conditions, such as liver dysfunction or even hepatic encephalopathy, which can lead to a limited choice in grafts. To expand the pool of available liver grafts, one option is the use of organs that were previously considered "unusable" by many, which are often labeled "marginal" organs. Many previous studies have reported on the possibilities of using marginal grafts in orthotopic LT; however, there is still a lack of discussion on this topic, especially regarding the feasibility of using marginal grafts in LDLT. Therefore, the present review aimed to summarize the feasibility of using marginal liver grafts for LDLT and discuss the possibility of expanding the application of these grafts.

Key words: Marginal liver grafts; Living donor liver transplantation; Liver transplant waiting lists; Small-for-size grafts; Older donors; ABO-incompatible; Steatosis; Chronic hepatitis

Core tip: There are few reviews concerning the feasibility of using marginal liver grafts in living donor liver transplantation (LDLT). We reviewed more than 300 articles, summarized new findings, and confirmed that marginal grafts are a feasible option for expanding options for patients on liver transplant waiting lists in emergency situations in LDLT (*e.g.*, liver failure or hepatic encephalopathy). However, such grafts place the recipients at greater risk for adverse events. Although some indispensable treatments are needed to address the deficiencies of these grafts, recipients can receive a favorable prognosis, similar to that of patients who receive standard liver grafts, under these treatments.

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INTRODUCTION

The high mortality of patients on waiting lists due to the shortage of cadaveric donors is a major challenge in liver transplantation (LT)[1]. This challenge has led to the emergence of living donor liver transplantation (LDLT) after the first successful procedure in 1989[2,3]. However, following a sharp increase in recipients who suffer from emergency situations, the wide gap between the demands of patients and suitable living donors is gradually increasing[4,5]. Therefore, the transplantation community has focused on the search for strategies to increase the pool of available liver grafts, including the use of organs that were previously considered "unusable" by many and often labeled "marginal" organs[6].

An accepted definition of marginal donors remains unclear in LDLT. These expanded-criteria grafts have the potential to increase the risk of poor graft function or primary nonfunction and are referred to as "marginal" organs[7]. In this review, we define marginal liver grafts for LDLT as small-for-size grafts, older donors, moderate or severe steatosis of liver grafts, chronic hepatitis, and grafts with tumors. The survival of recipients with marginal organs can be the same as that of patients with high-quality liver grafts under proper treatment[8].

Many previous studies have reported on the possibilities of using marginal grafts in orthotopic liver transplantation (OLT), but there is still a lack of discussion on this topic, especially regarding the feasibility of using marginal grafts in LDLT. Therefore, the present review aimed to summarize and discuss the possibility of expanding the application of marginal grafts in LDLT.

SMALL-FOR-SIZE GRAFTS IN LDLT

Choosing to use a liver graft can be a remarkably complex decision. There is an increasing trend of patients dying while on waiting lists due to the everyday risk of death or serious complications while waiting; this risk must be balanced against the use of a marginal graft, which may not be feasible. Size mismatching between the graft and the recipient is a critical predictor of the so-called "marginal liver grafts" in LDLT recipients. A small-for-size graft has become the main reason for unsuitability for liver donation in some transplantation centers[9]. The most common index with which to evaluate graft size matching is the graft-to-recipient weight ratio (GRWR) or graft volume (GV)/standard liver volume (SLV). The GRWR was first reported to require a safety range of above 1%; otherwise, the rate of graft survival could decrease[10]. With the increased demand for LDLT and the improvement of surgical techniques, however, many expanded-criteria grafts are used. Accordingly, the accepted arbitrary requirement for GRWR was reduced to 0.8%, and the GV/SLV value was 40%[11,12]. As many transplantation centers accumulated experience on small-for-size grafts for LDLT, grafts with a GRWR < 0.8% were used and reported to be as safe as those with a GRWR ≥ 0.8%[13-17]. After challenging the boundary of GRWR = 0.8%, the acceptable minimum GRWR has been continuously lowered. Lee SD *et al*[18] reported that a GRWR as low as 0.7% is safe and that there is no need to modulate portal pressure in adult-to-adult LDLT using the right-lobe in favorable conditions, such as a low Model for End-Stage Liver Disease (MELD) score. Furthermore, Alim A *et al*[19] even suggested that a GRWR as low as 0.6% may be safe if the MELD score is < 20, donor age is < 45, and there is no evidence of liver steatosis in the donor graft during portal inflow modulation performed according to the portal flow. To date, the reported lowest GRWR of grafts that have been successfully used is between 0.40% and 0.46% (Table 1)[20].

Small-for-size syndrome (SFSS), including small-for-size dysfunction (SFSD) and small-for-size nonfunction (SFSNF), is a concerning and life-threatening complication in patients receiving grafts with a GRWR < 0.8%[21,22]. The incidence of SFSS varies from 4.7% to 27.5% in different LT centers[23-30]. Specifically, the syndrome rate can be as high as 50%-75% in left-lobe LDLT or small-for-size grafts group and as low as 8.4% in right-lobe LDLT[31,32]. Graft size is the only independent predictor of SFSS[31]. However, other studies have described that SFSS can occur even in the presence of a normal GRWR[16]. Regardless of the definition used for SFSS, it seems clear that other key factors should be considered in addition to a mismatched graft size. The

Table 1 Recommended minimum graft-to-recipient weight ratio in different studies

Ref.	Recommended minimum GRWR	*n* (small *vs* large)	One-year survival (small *vs* large)	Five-year survival (small *vs* large)	Study type
Kiuchi *et al*[10] (1999)	1%	276 (49 *vs* 215)	61.2% *vs* 92.6%	NS	RS
Lee *et al*[11] (2003)	0.8%	141 (10 *vs* 131)	Univariate and multiple analysis	NS	RS
Moon *et al*[13] (2010)	Less than 0.8%	427 (35 *vs* 392)	87.8% *vs* 90.7%	74.1% *vs* 79.4%	RS
Lan *et al*[14] (2009)	Less than 0.8%	89 (15 *vs* 74)	73.3% *vs* 71.6%	NS	RS
Selzner *et al*[15] (2009)	Less than 0.8%	271 (22 *vs* 249)	91.0% *vs* 89.0%	83.0% *vs* 87%	RS
Chen *et al*[16] (2014)	Less than 0.8%	196 (45 *vs* 151)	82.2% *vs* 81.4%	71.1% *vs* 75.5%	RS
She *et al*[17] (2017)	Left lobe graft *vs* right lobe graft	218 (19 *vs* 199)	89.5% *vs* 95.9%	89.5% *vs* 86.8%	RS
Lee *et al*[18] (2014)	Less than 0.7%	317 (23 *vs* 294)	100% *vs* 93.2%	NS	RS
Alim *et al*[19] (2016)	0.6%	649	Seven patients had GRWR of 0.6%. If MELD score was below 20, donor age below 45, and no signs for any hepatosteatosis, GRWR of 0.6% was safe		RS
Lee *et al*[20] (2015)	0.40%	NS	Lowest GRWR of 0.40% had been successfully used		RS

PS: Prospective study; RS: Retrospective study; Ref.: Reference; GRWR: Graft-to-recipient weight ratio.

Table 2 Incidence of small-for-size syndrome when using small-for-size grafts *n* (%)

Ref.	*n*	SFSS (Incidence)	Factors to SFSS	Study type
Goldaracena *et al*[21] (2017)	NS	NS	A graft GRWR < 0.8% of predisposes the graft to SFSS	RE
Graham *et al*[22] (2014)	NS	NS	GRWR of 0.8 to 1.0 was established as a lower limit to prevent SFSS	RE
Botha *et al*[23] (2010)	21	1 (4.7)	Hemi-portocaval shunt can decrease SFSS incidence	RS
Goralczyk *et al*[24] (2011)	22	5 (22.7)	Posterior cavoplasty can decrease SFSS incidence	RS
Soejima *et al*[25] (2003)	36	8 (22.2)	Cirrhosis predisposes the graft to SFSS	RS
Ben-Haim *et al*[26] (2001)	40	5 (8)	Child's class B or C with received grafts of GRWR < 0.85% predisposes the graft to SFSS	RS
Sudhindran *et al*[27] (2012)	NS	10%-20%	Left lobe grafts predisposes the graft to SFSS	RE
Yi *et al*[28] (2008)	29	8 (27.5)	Left lobe grafts predisposes the graft to SFSS	RS
Soejima *et al*[29] (2012)	312	43 (15.3)	Left lobe grafts predisposes the graft to SFSS	RS
Gruttadauria *et al*[30] (2015)	83	13 (15.7)	Non-surgical modulation of the portal inflow can decrease SFSS incidence	RS
Shoreem *et al*[31] (2017)	174	20 (11.5)	Left lobe grafts predisposes the graft to SFSS	RS
Lauro *et al*[32] (2007)	8	4 (50)	Surgical modulation of the portal inflow can decrease SFSS incidence	RS

RE: Review; RS: Retrospective study; SFSS: Small-for-size syndrome; GRWR: Graft-to-recipient weight ratio.

incidence of SFSS is listed in Table 2.

Middle hepatic vein (MHV) or outflow reconstruction of the liver graft is associated with size mismatch. A small-for-size graft without MHV reconstruction can lead to various degrees of congestion of the anterior segment and a greater loss of hepatocellular function[33]. In our early observational studies with small sample sizes, we recommended a GRWR > 1.0%[34] or even 1.2%[35] as a security threshold for patients without MHV reconstruction. Asakuma M *et al*[36] established an algorithm known as the estimated congestion ratio (ECR, ECR = regional volume of v5 + v8 / right-lobe volume) to estimate whether MHV should be reconstructed for low-GRWR grafts. A liver with an ECR > 0.4 is an MHV-dominant liver, and higher GRWR grafts should be used. However, it is still unknown how far we can lower the GRWR following the improvement of postoperative management and surgical technique if there is no reconstruction of outflow. In addition to outflow reconstruction, the inflow of grafts, including portal hypertension following reperfusion and the hyperdynamic splanchnic state, is reported as a major factor that can trigger SFSS[37-39]; however, these views are controversial[40]. Enhanced cholestasis, hepatocyte ballooning, disruption of the sinusoidal line, and transformation of activated Ito cells into fibroblasts are observed under the conditions of portal hypertension, or overperfusion[41,42]. Recipients with a final portal vein pressure (PVP) ≤ 15 mmHg or a pressure gradient of PVP-central vein pressure (CVP) ≤ 5 mmHg have a better prognosis[43]. In another study, liver-graft-to-spleen-volume ratio was used to predict early graft function in children and young adults undergoing LDLT, in which < 0.88 predicted portal hyperperfusion[44]. Moreover, a MELD score > 20[45], a decline in the platelet (PLT) count at post operation day (POD) 3 > 56%[46] and donor age > 45 years are also risk factors for a poor prognosis in recipients of small-for-size grafts[19].

To increase the safety of the expanded use of small-for-size grafts, some treatments are recommended. Graft inflow or PVP modulation is at the forefront of these treatments. Portosystemic shunting techniques

Table 3 Remedies when using small-for-size graft

Ref.	*n*	Remedy for using small-for-size graft	Study type
Botha *et al*[23] (2010)	21	Hemi-portocaval shunt can decrease SFSS incidence	RS
Goralczyk *et al*[24] (2011)	22	Posterior cavoplasty can decrease SFSS incidence	RS
Kim *et al*[47] (2017)	160	Preserving collateral veins on small-for-size grafts	RS + PSM
Hessheimer *et al*[48] (2011)	NS	Portocaval shunt	AE
Xiao *et al*[49] (2012)	1	Transjugular intrahepatic portosystemic shunt	CR
Sato *et al*[50] (2008)	4	Portocaval shunt using ligamentum teres	CR
Nutu *et al*[51] (2018)	2	Complete splenic embolization	CR
Badawy *et al*[52] (2017)	164	Splenectomy	RS
Troisi *et al*[53] (2016)	NS	Splenic artery ligation, splenectomy, meso-caval shunt, spleno-renal shunt, portocaval shunt, and splenic artery embolization	SR
Xu *et al*[54] (2015)	NS	Dual grafts	RE
Gao *et al*[55] (2017)	NS	Adipose-derived mesenchymal stem cells tranplantation	AE
Kobayashi *et al*[56] (2009)	5	Auxiliary partial liver transplantation	CR

PSM: Propensity score matching; AE: Animal experiments; CR: Case report; SR: Systematic review; RE: Review; SFSS: Small-for-size syndrome.

or preservation of collateral veins[19,47-50], as well as splenectomy or splenic artery ligation/embolization[51-53], are effective ways to address post-transplantation portal hyperperfusion. In cases where the GRWR of grafts is very low, dual grafts can be considered[54]. Moreover, autologous stem cell implantation[55] and auxiliary partial LDLT (a second transplant) are also reported to treat SSFS[56]. Remedies when using small-for-size grafts are listed in Table 3.

Generally, a GRWR < 0.8% is no longer a critical predictor for recipients and can even be lowered to 0.5%-0.6% if there are accompanying factors of PVP ≤ 15 mmHg, MHV reconstruction, or young donor age.

OLDER DONORS IN LDLT

Because LDLT allows more choices in the use of a suitable liver graft compared with OLT, elderly donors were rarely considered in the early years of transplantation. However, following the increasing demands for LDLT and the urgent need to save the lives of patients suffering from hepatic encephalopathy, the use of elderly liver grafts has been reported more frequently in recent years as a means to increase the donor pool and address high waiting list mortality[57]. In Japan, the percentages of donors older than 50 and 60 years were 18.1% and 4%, respectively[58]. It is expected that the number of older donors will increase in the future because of the continuing donor shortage[59].

The definition of older donors is quite different in different transplantation centers. In the present review, we define older donors as donors older than 50 years. Controversy exists regarding the use of livers from older donors. The liver regeneration rate is impaired in older donors (donor age ≥ 50 years) compared with young donors (donor age < 30 years), according to computed tomography (CT) volumetric data after LDLT at POD 7[60], and donor age (≥50 years) was independently correlated with impaired remnant liver regeneration at 3[61] and 6 mo in right-lobe LDLT[58]. Kawano Y *et al*[62] analyzed telomeres in the hepatocytes of 12 paired donor-recipients and found that donor age was a crucial factor affecting the sustainability of telomere length in hepatocytes after pediatric LDLT. Based on the conclusion that older donors were significantly associated with impaired liver regeneration, some researchers found that the recipients of grafts from donors older than 45-50 years old, along with a GW/SLV ratio < 35%-40%, had worse outcomes[63,64]. Yoshizumi T *et al*[65] established the following formula, called a predictive score, to evaluate the impact of donor age, graft size, and MELD score on prognosis: predictive score = 0.011 × graft weight (%) - 0.016 × donor age - 0.008 × MELD score - 0.15 × shunt (if present) - 1.757. Patients with a predictive score ≥ 1.3 had a lower incidence of postoperative complications and a better prognosis.

Additionally, more studies have shown that LDLT using older donors could induce more serious postoperative complications and higher mortality rates than transplants using younger donors[66-70]; similarly, having a donor older than the recipient by > 20 years is problematic[68]. Moreover, it has been reported that fibrosis progression in patients with recurrent hepatitis C tended to be faster after LDLT with grafts from older donors[71]. Donor age is an independent, strong prognostic factor in LDLT. However, other researchers found that grafts from older donors can be used safely, even though the regenerative capacity of older grafts is impaired when the donor age is ≥ 50 years[72-75] or even ≥ 55 years[76]. The impact of older donors on the 1- and 5-year survival of recipients is shown in Table 4.

While donor age is a controversial topic, the impaired regenerative capacity of older grafts has been confirmed in some studies. According to these previous studies, older liver grafts can be prudent candidates but cannot be used in the presence of other marginal conditions (*e.g.,* small-for-size grafts or moderate and severe steatosis). More high-quality and prospective studies are needed on this topic.

Table 4 Older donors for living donor liver transplantation

Ref.	Definition of older donors	*n* (older *vs* young)	One-year survival (older *vs* young)	Five-year survival (older *vs* young)	Study type
Tanemura *et al*[58] (2012)	50 yr old	101 (24 *vs* 77)	Older donor livers might have impaired regenerative ability		RS
Ono *et al*[60] (2011)	50 yr old	15 (6 *vs* 9)	Liver regeneration is impaired with age after donor hepatectomy		RS
Akamatsu *et al*[61] (2007)	50 yr old	299 (62 *vs* 237)	85.0% *vs* 93.0%	72.0% *vs* 87.0%	RS
Kawano *et al*[62] (2014)	NS	12	Donor age is a crucial factor affecting telomere length sustainability in hepatocytes after pediatric LDLT		PS
Imamura *et al*[63] (2017)	NS	198	A worse outcome might be associated with aging of the donor		RS
Dayangac *et al*[64] (2011)	50 yr old	150 (28 *vs* 122)	78.6% *vs* 83.4%	NS	RS
Yoshizumi *et al*[65] (2008)	NS	28	Graft size, donor age, and patient status are the indicators of early graft function		RS
Han *et al*[66] (2014)	55 yr old	604 (26 *vs* 578)	Median OS (M): 31.2 ± 31.3 *vs* 50.6 ± 40.6		RS
Kamo *et al*[67] (2015)	60 yr old	1597 (69 *vs* 1528)	69.5% *vs* 81.2%	62.0% *vs* 79.3%	RS
Shin *et al*[68] (2013)	Donor-recipient age gradient > 20	821	Worse graft survival was observed if the donor is older than the recipient by > 20		RS
Kubota *et al*[69] (2017)	50 yr old	315 (126*vs* 189)	73.0% *vs* 80.9%	39.7% *vs* 47.1%	RS
Katsuragawa *et al*[70]	NS	24	G/SLV and donor age were independent factors that affected graft survival rates		RS
Wang *et al*[72] (2015)	50 yr old	159 (10 *vs* 149)	100% *vs* 93.0%	90.0% *vs* 87.0%	RS
Ikegami *et al*[73] (2008)	50 yr old	232 (32 *vs* 200)	80.0% *vs* 81.7%	73.8% *vs* 76.7%	RS
Li *et al*[74] (2012)	50 yr old	129 (21 *vs* 108)	90.0% *vs* 86.0%	66.0% *vs* 75%	RS
Goldaracena *et al*[75] (2016)	50 yr old	469 (91 *vs* 378)	92.0% *vs* 96.0%	83.0% *vs* 79.0%	RS
Kim *et al*[76] (2017)	55 yr old	540 (42 *vs* 498)	95.2% *vs* 94.6%	NS	RS

LDLT: Living donor liver transplantation; CR: Case report; RS: Retrospective study.

ABO-INCOMPATIBLE LDLT

Although more high-quality liver grafts are available for patients in LDLT than in OLT, donors are restricted to family members or domestic relationships in many transplantation centers because of ethical norms. ABO-incompatible LTs are performed only in emergencies, when ABO-compatible grafts are unavailable. Therefore, breaking ABO blood group barriers becomes inevitable. ABO-incompatible LT was first performed and reported by Starzl *et al*[77], and no acute rejections were observed after transplantation. Subsequently, ABO-incompatible LT gradually began to be performed in some LT centers, and hyperacute rejection was commonly reported[78,79].

In addition to antibody-mediated rejection, ABO-incompatible LDLT can involve other complications. Thrombotic microangiopathy (TMA) is a rare complication following LT, but it is reported to have a slightly higher incidence in ABO-incompatible LDLT[80-82]. ABO incompatibility, cyclophosphamide and recipient blood group (type O) are closely correlated with the occurrence of TMA[80,82]. The incidence of TMA is 37.9% following ABO-incompatible LDLT and 0.0%-2.8% following ABO-compatible LDLT (OR = 44.7)[80]. The elevation of fibrinolytic function markers, such as plasminogen activator inhibitor type 1, can be considered a predictor of TMA following LDLT. The incidence of biliary tract complications is more common than that of TMA. Biliary strictures are one of the most important complications associated with ABO incompatibility, with reported incidence rates between 15.8% and 20.7%[83,84]. An isoagglutinin attack on the graft vascular endothelium can result in ischemic cholangiopathy, and isoagglutinin can even directly attack the endothelium of the graft bile duct[85,86]. CT scans can provide a clear indication of biliary strictures in ABO-incompatible LDLT[87]. Yamada Y *et al*[88] reported a case of idiopathic hypereosinophilic syndrome following ABO-incompatible LDLT. The patient suffered from portal vein thrombosis on postoperative day 10, and the histopathological findings of the thrombus revealed dense eosinophilic deposition. Studies on the impact of ABO incompatibility on LDLT are listed in Table 5.

Despite serious complications, ABO-incompatible LDLT can be a feasible option for patients if certain essential treatments are included[89,90]. Rituximab, an anti-CD20 immunoglobulin (IgG)1 terminating B-lymphocytes with an affinity for IgG Fc receptor (FcγR), is a critical strategy in the regimens for desensitization for ABO-incompatible LDLT and yields outcomes for ABO-incompatible LDLT that are similar to those for ABO-compatible LDLT[91,92]. Rituximab is given for 3 d[93], 3 wk, or even as soon as a suitable donor that is ABO-compatible is selected[94] at a dosage of 375 mg/m^2. In the early stage of transplantation, rituximab was usually given along with one or more other protocols, such as a splenectomy[95,96], plasma exchanges[97-102], intravenous IgG[100,103], and intrahepatic arterial infusion of prostaglandin E1[92,104,105]. In some recent studies, pre-transplant rituximab and/or basiliximab monotherapy, without additional treatments, also yielded outcomes that are comparable to those of procedures with additional treatments[106]. The affinity between IgG Fcγ Receptor (FcγR) and rituximab, however, is influenced by the single-nucleotide polymorphisms (SNPs) of FcγR. SNPs of FCGR2A (131H/R) and FCGR3A (158F/V) are the alleles that encode FcγR. FCGR2A (131H/H) had a higher affinity for IgG1 than FCGR2A (131H/R

Table 5 Impact of ABO-incompatible on living donor liver transplantation

Ref.	*n*	Complications	Incidence of related complication (%)	Risk factors	Study type
Miyata *et al*[80] (2007)	57	Thrombotic microangiopathy	7.0	ABO-incompatibility, CPA, and recipient blood group (type O)	RS
Oya *et al*[81] (2008)	1	Thrombotic microangiopathy	NS	ABO-incompatible LDLT (type B to O)	CR
Kishida *et al*[82] (2016)	129	Thrombotic microangiopathy	10.1	ABO-incompatible, tacrolimus	RS
Song *et al*[83] (2014)	1102	Biliary stricture	15.8	ABO-incompatible, acute cellular rejection	RS
Ikegami *et al*[84] (2016)	408	Biliary stricture	20.4	ABO-incompatible	RS
Yamada *et al*[88] (2010)	1	Idiopathic hypereosinophilic	NS	ABO-incompatible	CR

LDLT: Living donor liver transplantation; CR: Case report; RS: Retrospective study.

or R/R). Accordingly, patients with FCGR2A (131H/H) have a better reaction to the effects of rituximab on B cells[91]. The treatment results of ABO-compatible LDLT are summarized in Table 6.

These findings reveal that rituximab monotherapy in ABO-compatible LDLT is feasible, but it is better to test the SNPs of FcγR; otherwise, multiple treatments, such as plasma exchanges and intravenous IgG, must be performed in addition to rituximab if there is a lower affinity between IgG FcγR and rituximab. There is still a lack of more persuasive evidence to confirm the feasibility of splenectomy in conjunction with ABO-compatible LDLT treatments.

LIVER GRAFT STEATOSIS

Steatosis is a common feature used to identify marginal liver function, and reports on the utility of steatotic liver grafts in clinical practice have yielded controversial results. The use of steatotic liver grafts has been confirmed to have a significant relationship with increased complications and poorer outcomes[107,108]. Traditionally, steatotic livers with > 60% fat must be discarded. Livers with < 30% fat are feasible and anticipated to have good function. Livers with 30%-60% fat have poor results, with decreased graft survival and decreased patient survival[109]. Moreover, hepatic steatosis is reported to be a leading cause of donor rejection in LDLT[110]. In some transplantation centers, approximately 40% of donor grafts are discarded because of severe liver steatosis[9]. Because of the release of inflammatory cytokines and inhibition of the capacity to differentiate steatosis hepatocytes, the early regenerative capacity of the remnant liver is injured, and, as a result of impaired hepatocyte replication, compensatory expansion of hepatic progenitor cells occurs during steatotic liver regeneration after LDLT[111]. Furthermore, Cho *et al*[112] confirmed that hepatic steatosis is associated with intrahepatic cholestasis and transient hyperbilirubinemia during regeneration after LDLT. In this study, 67 LDLT recipients examined on POD 10 were scored based on the numbers of portal tracts per area of liver tissue and intrahepatic cholestasis, and the preoperative degree of macrovesicular steatosis was found to be independently associated with cholestasis after LDLT. However, these researchers also found that the long-term capacity of hepatocyte regeneration was not impaired after LDLT with mild macrovesicular steatosis grafts[113]. Based on this finding, some recent studies have found that moderately steatotic liver grafts and donors with a BMI ≥ 30 kg/m^2 are not contraindications for LDLT, and complications and survival are not significantly different compared with those associated with non-steatosis grafts[114,115]. Moreover, the risk of steatosis was determined by the presence of microsteatosis and macrosteatosis, rather than the total quantitative degree of steatosis. The grafts with high microsteatosis (30%) mixed with macrosteatosis showed no significant difference in postoperative biochemical liver function, 2-wk graft regeneration, postoperative complications, and 5-year survival[116]. The studies on the impact of graft steatosis on LDLT outcomes are listed in Table 7.

To decrease the risk associated with fatty liver grafts, especially with severe steatosis, some treatments are suggested (Table 8). According to Oshita *et al*[117], donors who are diagnosed with hepatic steatosis pre-transplantation should undergo a diet treatment consisting of an 800-1400 kcal/d diet and a 100-400 kcal/d exercise regimen without drug treatment with a target body mass index of 22 kg/m^2. After these strategies, the average BMI was reduced from 23.3 ± 0.6 to 21.9 ± 0.4 kg/m^2. The liver biopsy results of most of these donors showed stage 0/1 fibrosis and minimal/mild steatosis after the diet therapy. In addition, surgical outcomes and overall survival did not significantly differ between the recipients of grafts from non-steatosis and diet-treated donors (with steatosis). In another study, bezafibrate (400 mg/d) was used along with a protein-rich (1000 kcal/d) diet and exercise (600 kcal/d) for 2-8

Table 6 Remedies when using ABO- incompatible on living donor liver transplantation

Ref.	*n*	Immunosuppression strategy	Remedies	Conclusion	Study type
Kawagishi *et al*[89] (2009)	105	TAC + MP + AZ	Rituximab	ABO-incompatible LDLT can be feasible used if humoral rejection are overcome	RS
Yoon *et al*[90] (2018)	918	TAC + MP + steroids	Rituximab and PE	ABO-incompatible LDLT is a feasible option under remedies	RS
Sakai *et al*[91] (2017)	20	TAC+ MP	Rituximab and PE	FCGR SNPs influence the effect of rituximab on B-cells	PS
Egawa *et al*[92] (2017)	33	TAC	Rituximab, PE, local infusion, splenectomy and immunoglobulins	Only rituximab dose is a significantly favorable factor for AMR	RS
Ikegami *et al*[93] (2007)	1	TAC + MP + steroids	Rituximab and PE	Rituximab and plasma exchanges seemed ineffective	CR
Ikegami *et al*[94] (2009)	7	TAC + MP + steroids	Rituximab, IVIG, and PE	Rituximab, IVIG, and PE seems to be a safe treatment	RS
Usui *et al*[95] (2007)	73	TAC + MP + steroids	Rituximab, PE and splenectomy	Bone suppression is a big challenge when using rituximab	RS
Chen *et al*[96] (2017)	2	TAC + MP + steroids	Basiliximab combine with splenectomy	ABO-i LDLT with splenectomy is undoubtedly life-saving	CR
Uchiyama *et al*[97] (2011)	15	TAC + MP + steroids	Rituximab and PE	Isoagglutinin mediated-rejection should be more concerned	RS
Soin *et al*[98] (2014)	3	TAC + MP + steroids	Rituximab and PE	ABO-incompatible LDLT is a feasible option under remedies	CR
Rummler *et al*[99] (2017)	10	TAC + MP + steroids	PE	Immunosuppression only combining with PE is feasible	RS
Kim *et al*[100] (2016)	182	TAC + MP + steroids	Rituximab, IVIG, and PE	ABO-incompatible LDLT can be safely performed under remedies	RS
Kim *et al*[101] (2013)	22	TAC + MP + steroids	Rituximab and PE	ABO-incompatible LDLT can be safely performed under remedies	RS
Kawagishi *et al*[102] (2005)	3	TAC + MP + steroids	Rituximab and PE	ABO-incompatible LDLT can be safely performed under remedies	CR
Kim *et al*[103] (2017)	43	TAC + MP + steroids	Rituximab and IVIG	A simplified protocol using rituximab and IVIG for ABO-I LDLT is safe	RS
Yoshizawa *et al*[104] (2005)	8	TAC + MP + cyclophosphamide	Rituximab and PGE1 infusion	Rituximab prophylaxis and HA infusion therapy is feasible	RS
Egawa *et al*[105] (2008)	118	TAC + steroids	Methylprednisolone and PGE1 infusion	Recipients with preexisting high effector CD8 T- cells are unfavorable candidates for ABO-I LDLT	RS
Yamamoto *et al*[106] (2018)	40	TAC + MP + steroids	Rituximab monotherapy	Rituximab monotherapy is feasible	RS

LDLT: Living donor liver transplantation; CR: Case report; RS: Retrospective study; SNPs: Single-nucleotide polymorphisms.

wk[118]. Even severely steatotic livers could be used for LDLT grafting subsequent to this short-term treatment regimen. Furthermore, a 1200 kcal/d diet and a minimum of 60 min/d of moderate cardio training are also recommended to rapidly reverse liver steatosis in donors[119]. In addition to lifestyle and dietary changes, dual-graft LDLT was reported when one donor had severe liver steatosis and another had a low GRWR[120].

In conclusion, steatosis in the donor must be thoroughly evaluated before LDLT, either by biopsy or imaging diagnosis. The proportion of macrosteatosis is now considered a crucial predictor of the prognosis of recipients. If there are no further options, donors with hepatic steatosis can reach donation criteria through lifestyle and dietary changes in a short time.

CHRONIC HEPATITIS OF GRAFTS

The use of liver grafts that test positive for chronic hepatitis or other blood disseminated diseases found in epidemic areas is usually inevitable in cases of organ shortages associated with OLT. However, because LDLT recipients, to some degree, have more choices regarding his/her donors, there are a few studies reporting on HBsAg or HBcAb(+) liver grafts, while no studies refer to HCV-positive living liver grafts.

HBsAg(-) LDLT patients who have received HBsAg or HBcAb(+) grafts have a high risk of *de novo* HBV

Table 7 Impact of graft steatosis on living donor liver transplantation

Ref.	n	Conclusion	Study type
Dirican et al[9] (2015)	161	Approximately 40% of donor grafts are discarded because of severe liver steatosis	RS
Perkins et al[109] (2006)	NS	Typically steatotic livers with > 60% fat are not transplanted; with < 30% fat are usable and anticipated to have good function; with 30%-60% fat give poor results	Comments
Kotecha et al[110] (2013)	340	Hepatic steatosis is a leading cause of donor rejection in LDLT	PS
Cho et a[111]l (2010)	54	Hepatocyte replication is impaired during steatotic liver regeneration after LDLT	PS
Cho et al[112] (2006)	67	Hepatic steatosis is associated with intrahepatic cholestasis and transient hyperbilirubinemia during regeneration	PS
Cho et al[113] (2005)	55	Mildly steatotic graft did not increase the risk of graft dysfunction or morbidity in LDLT	PS
Gao et al[114] (2009)	24	Moderately steatotic (30%-60%) liver grafts provide adequate function in the first phase after transplantation and can be used for transplantation	RS
Knaak et al[115] (2017)	105	Donors with BMI > 30, in the absence of graft steatosis, are not contraindicated for LDLT	RS
Han et al[116] (2015)	211	The risk of steatosis may be determined by the relative composition of MiS and MaS, rather than the total quantitative degree	RS

LDLT: Living donor liver transplantation; RS: Retrospective study; PS: Prospective study.

Table 8 Treatments for fat donors

Ref.	n	Treatments	Study type
Oshita et al[117] (2012)	128	Diet treatment consisting of an 800 to 1400 kcal/d diet and a 100 to 400 kcal/d exercise regimen without drug treatment, targeting body mass index of 22 kg/m²	RS
Nakamuta et al[118] (2013)	11	Bezafibrate (400 mg/d) was used along with a protein-rich (1000 kcal/d) diet and exercise (600 kcal/d) for 2-8 wk	RS
Choudhary et al[119] (2015)	16	1200 kcal/d and a minimum of 60 min/d of moderate cardio training are also recommended to rapidly reverse liver steatosis in donors	PS
Moon et al[120] (2006)	2	Dual-graft living donor liver transplantation for severe graft steatosis	CR

RS: Retrospective study; PS: Prospective study; CR: Case report.

infection after transplantation (Table 9). However, these grafts are still considered to be safe and feasible with antiviral prophylaxis in both adult and pediatric LDLT[121-126]. Patients were given HBV vaccinations to achieve anti-HBs > 1000 IU/L pre-transplantation and > 100 IU/L post-transplantation, with a standard post-transplantation treatment regimen of high-dose hepatitis B IgG, lamivudine and/or adefovir (in cases of lamivudine resistance)[126]. Specifically, some studies have proposed a new strategy; specifically, patients with a pre-transplantation anti-HB titer > 1000 IU/L do not need post-transplantation prophylaxis; patients with a low pre-transplantation titer, < 1000 IU/L, should be given lamivudine post-transplantation (at a dose of 100 mg/d or 3 mg/kg/d for at least 2 years after transplantation) or adefovir prophylaxis (with lamivudine at a dose of 10 mg/d if a mutant strain for lamivudine is identified) and, hopefully, will respond appropriately to post-transplantation vaccinations by maintaining anti-HB titers > 100 IU/L; and low titer non-responders (anti-HB titer < 100 IU/L despite vaccination) should be given continuous lamivudine or adefovir indefinitely[121]. In some transplantation centers, nucleotide analogs (lamivudine) are routinely used first if HBsAg(-) LDLT patients receive HBsAg or HBcAb(+) grafts, regardless of the anti-HB titer, for at least 2 years. Moreover, patients who had a YMDD mutation were given adefovir combined with lamivudine[123]. Hara Y *et al*[127] reported one patient who experienced spontaneous eradication of *de novo* HBV after LDLT with an HBcAb(+) graft without any treatment. This 8-year-old female patient (HBsAg-negative) underwent LDLT, received an HBcAb(+) left-lobe graft, and was subsequently infected with HBV. Sixteen years after LDLT, her serological HBV status was as follows: HbsAg(-), HBsAb(+), HBeAb(-), HBeAb(+), HbcAb(+), and HBV DNA(-). In another study, recipients with HCV genotype 2 infections who had received an HBcAb(+) graft were given sofosbuvir and ribavirin, along with hepatitis B IgG to prevent recurrence of HCV and HBV[128].

In HbsAg(+) LDLT patients who receive HBsAg or HBcAb(+) grafts, the antiviral protocol must be performed as for HBsAg(-) LDLT patients to maintain the HBV DNA at a low or negative level, despite the persistence of the HBV marker (HBsAg). High-dose HBV IgG, lamivudine, famciclovir, and interferon were recommended (Table 10)[129-131].

Populations with HBsAg-negative/HBcAb-positive and undetectable serum HBV DNA have been gradually increasing over the past several decades. Most patients are now considered to have a covert HBV infection and have a high risk of HBV reactivation when treated with

Table 9 Impact of HBsAg or HBcAb(+) grafts on HBsAg(-) living donor liver transplantation patients

Ref.	Donor	Incidence of *de novo* HBV infection (%)	Prevention of *de novo* HBV infection	Study type
Wang[121] (2017)	HBcAb(+)	4.2	HBV vaccinations with the aim of achieving anti-HBs > 1000 IU/L pre-transplant and > 100 IU/L post-transplant	RS
Xi *et al*[122] (2013)	HBcAb(+)	23.9	No prophylaxis, adefovir, and lamivudine are given to *de novo* patients	RS
Dong *et al*[123] (2017)	HBcAb(+)	7.9	HBIG 100 IU/kg during the operation and lamivudine 3 mg/kg per day after the surgery for at least 1 year until HBV vaccine reaction	RS
Loggi *et al*[124] (2016)	HBsAg(+)	NS	HBIG and lamivudine, adefovir or tenofovir	SR
Lei *et al*[125] (2013)	HBcAb(+)	15.0	No specific prophylaxis	RS
Lin *et al*[126] (2007)	HBcAb(+)	3.3	Lamivudine monoprophylaxis, HBV vaccinations	RS
Hara *et al*[127] (2016)	HBcAb(+)	NS	Lamivudine first and adefovir dipivoxil were combined with lamivudine 2 yr later	CR

HBV: Hepatitis B virus; RS: Retrospective study; SR: Systematic review; CR: Case report.

Table 10 Impact of HBsAg or HBcAb(+) grafts on HBsAg(+) living donor liver transplantation patients

Ref.	Donor	Incidence of *de novo* HBV infection	Prevention of De Novo HBV infection	Study type
Hwang *et al*[129] (2006)	HBsAg(+)	NS	High-dose HBIG and lamivudine, famciclovir and interferon; a final regimen of lamivudine and adefovir	CR
Soejima *et al*[130] (2007)	HBsAg(+)	NS	lamivudine and adefovir dipivoxil	CR
Jeng *et al*[131] (2015)	HBsAg(+)	NS	Entecavir 0.5 mg once daily	RS

HBV: Hepatitis B virus; CR: Case report; RS: Retrospective study.

Table 11 Graft with hepatic benign tumor

Ref.	*n*	Type of tumors in grafts	Prognosis	Study type
Li *et al*[133] (2017)	15	Cavernous hemangioma, perivascular epithelioid cell tumor, inflammatory pseudotumor, and focal nodular hyperplasia	One patient died from pulmonary embolism	OS
Fuchino *et al*[134] (2017)	1	HBsAg(+) and inflammatory pseudotumor	Tumor vanished after 3 yr	CR

OS: Observational study; CR: Case report.

a robust immunosuppressive agent[132]. Therefore, the use of HBsAg-negative/HBcAb-positive liver grafts has a high risk of *de novo* HBV for HBsAg(-) recipients. However, with active immunization and an antiviral protocol, the HBsAg-negative/HBcAb-positive liver grafts can be transplanted safely.

GRAFTS WITH A BENIGN HEPATIC TUMOR

Usually, there are rare recipients of LDLT or doctors who are willing to make an active choice to use a graft with an undetermined tumor. This is not only an ethical issue but also indicates a high risk for recipients to face rapid dysfunction of their liver grafts. However, if recipients are in an emergency situation and have no other proper donors, grafts with benign tumors may be a last choice. Li G *et al*[133] recently reported on 15 consecutive recipients using an otherwise discarded, partial liver resection graft with a benign hepatic tumor. These benign tumors are as follows: Cavernous hemangioma, perivascular epithelioid cell tumor, inflammatory pseudotumor, and focal nodular hyperplasia. One patient died from a pulmonary embolism, and the other 14 patients had a good prognosis. Additionally, a vanishing tumor in a liver graft from an HBV(+) donor was observed. Contrast-enhanced magnetic resonance imaging (MRI) showed hypervascularity in the arterial phase and in the hepatobiliary phase, the tumor showed a low intensity, findings similar to those in HCC. Regardless, the graft with suspected HCC was accepted by the recipient, and the tumor disappeared completely within several months after LDLT[134].

For LDLT patients using grafts with a benign hepatic tumor, only two observational studies with a small sample size are present in the literature (Table 11). It seems that grafts with benign tumors are feasible in some conditions, but more studies with long-term follow-ups are needed to evaluate the safety of these

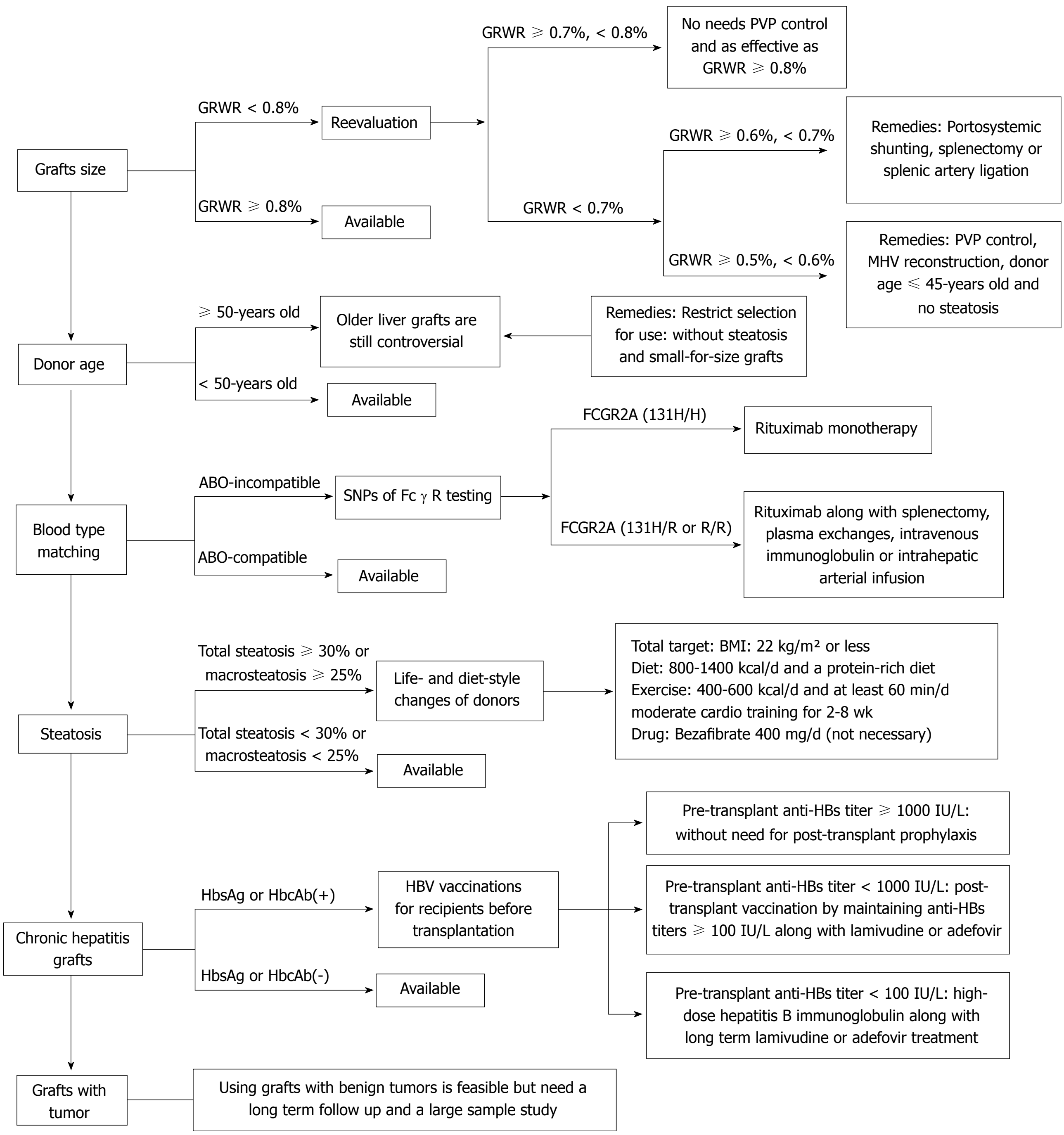

Figure 1 Selective strategies and remedies of using marginal donors in living donor liver transplantation.

marginal grafts.

CONCLUSION

To our knowledge, this is the first review on marginal donors specifically for LDLT. This review, which includes cohort studies, case-control studies, and case reports on marginal liver grafts in LDLT, demonstrated that marginal grafts are a feasible way to expand the options for patients on LT waiting lists in emergency situations (*e.g.*, liver failure or hepatic encephalopathy); however, these grafts place the recipients at a greater risk of liver dysfunction. Some indispensable treatments are needed to address the deficiencies of these grafts.

There are some new findings in this review: (1) It is permissible for the GRWR to be as low as 0.5%-0.6% (not 0.8%, as currently specified) if PVP is controlled under 15 mmHg; otherwise, outflow reconstruction is needed. (2) There is controversy surrounding older liver grafts. These grafts can be used prudently, but other marginal conditions must be absent (*e.g.,* small-for-size grafts or moderate and severe steatosis). (3) Splenectomy is no longer necessary when an ABO-incompatible LDLT is performed. Rituximab monotherapy is even confirmed to be an effective treatment if there is a high affinity between IgG FcγR and rituximab. (4) Total steatosis of liver grafts is not a proper predictor of prognosis. Instead, the presence of microsteatosis and macrosteatosis is a crucial factor. Donors with steatosis of the liver can meet the donation criteria through lifestyle and dietary changes before surgery. (5) HbsAg or HbcAb(+) grafts increase the risk of *de novo* HBV infection after transplantation in HBsAg(-) LDLT patients but can also be used safely with active immunotherapy. And (6) Grafts with benign tumors that have been discarded from other patients are feasible, but the long-term prognosis cannot be determined.

According to the new findings of this review listed above, we summarized a selection of strategies for different types of marginal liver grafts in LDLT and their related treatments (Figure 1). With this review, based on more than 100 references, we expect that the transplantation pool can be effectively and safely expanded in the situation of organ shortage.

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