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ORIGINAL ARTICLE

Outcome of the use of paediatric donor livers in adult recipients: A single Chinese centre experience

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KEYWORDS
Paediatric donor;
Adult recipients;

Summary
Background: Paediatric liver allografts sometimes are allocated to adult recipients when there are no suitable paediatric recipients on the waiting list. However, debate exits regarding the reported outcomes of liver transplants using such small grafts.

Abbreviations: PD, paediatric donor; AD, adult donor; TB, total bilirubin; ERLW, estimated recipient liver weight; RBC, red blood cell; DBD, donation after brain death; DCD, donation after cardiac death; DBCD, donation after brain death followed by circulatory death; MELD, model for end-stage liver disease; ICU, intensive care unit; GW, graft weight; RW, recipient weight; IVC, inferior vena cava; WIT, warm ischaemia time; CIT, cold ischaemia time; PNF, primary graft non-function; EAD, early allograft dysfunction; SFSS, small-for-size liver syndrome; HAT, hepatic artery thrombosis; UNOS, united network for organ sharing; ALT, alanine aminotransferase; AST, aspartate aminotransferase; INR, international normalised ratio.

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Liver transplantation;
Clinical outcome

Methods: Records from adult patients undergoing liver transplantation between February 2010 and January 2016 who received whole grafts from paediatric ($\leq$ 13 years) donors or ideal deceased adult (18—35 years) donors were reviewed. Patient and graft survival, post-transplant liver function, and complications between the two groups were compared.
Results: The baseline characteristics were comparable, except that the paediatric donor allografts had smaller size. The 3-month, 1-year, and 3-year rates of patient survival were 91.3%, 85.2%, and 85.2% in the paediatric donor group and 93.4%, 88.9%, and 85.0% in the adult donor group ($P = 0.947$), respectively. One patient receiving a paediatric allograft developed small-for-size liver syndrome post-transplantation. There was no difference in primary non-function, early allograft dysfunction, biliary complications, vascular complications, or infection between the two groups.
Conclusion: Our study indicates that using paediatric donor livers in well-selected adult recipients is a safe procedure, considering there was no suitable paediatric recipient. However, the risk of portal hyperperfusion should be considered in clinical cases such as size-mismatched transplants.

Introduction

Marginal donor organs, such as steatotic livers, serologically positive hepatitis C/B virus (HCV/HBV) livers, and elderly donor livers, have been included in the donor organ pools due to extreme organ shortages. Consequently, any organs procured from viable donors are considered for transplantation to minimise organ discards. Because the Chinese government has set up an organ donation program from deceased citizens [1], paediatric donor (PD) organs have become available for the first time in China. PD livers are allocated preferentially to paediatric recipients. However, when there is no available paediatric recipient for the paediatric donors, PD organs may be allocated to a suitable adult recipient.

Due to organ shortages, small grafts are widely accepted for liver transplantation. Previous studies have shown favourable outcomes in living donor liver transplantation (LDLT) [2,3] and split LT [4]. Moon JI et al. reviewed 392 cases of LDLT with graft-to-recipient weight ratio (GRWR) of 0.8 or greater, and observed a 1-year rate of survival of over 90% [5]. In deceased donation LT, it is known that the use of PD livers in adult patients is associated with decreased patient/graft survival and increased vascular complications [6,7]. In contrast, Ghabril M et al. reported that in selected patients, the paediatric-to-adult combination can yield an outcome comparable to an adult-to-adult combination [8]. A recent report from Germany shows a beneficial long-term outcome of nine adult recipients using paediatric livers from donors less than 6 year of age [9]. Therefore, the outcome of this combination is still under debate.

In China, there were a total of 2766 organ donations in 2015, according to the China organ transplant response system (COTRS) report [1]. The percentage of each donation type is described as follows: 39.37%, donation after circulatory death (DCD, China Category II); 15.95%, brain death followed by circulatory death (DBCD, China Category III); 44.68%, donation after brain death (DBD, China Category I). DCD donor organs have been shown to be associated with diminished outcomes compared with DBD donor organs [10]. Furthermore, most adult patients on the liver transplant waiting list in China had HBV-related end-stage liver disease. Therefore, considering the discrepancy in both donors and recipients, it is still unknown whether the use of paediatric liver allografts in adult recipients would lead to increased risks of graft loss and complications in the Chinese population.

The present study is the first to explore the largest series of liver transplant in adults using PD allografts in the Chinese population.

Patients and methods

Characteristics of the patients

In total, 304 cases of adult liver transplantation from deceased donors were performed in our centre between February 2010 and January 2016. Recipients were grouped according to donor age of 13 years or younger (PD group, $n = 23$) and 18-to-35 year olds (adult donor, AD group, $n = 77$). Patient characteristics were recorded based on the following parameters: age, gender, height, weight, estimated recipient liver weight (ERLW), calculated model of end-stage liver disease (MELD) Score, and Child-Pugh Score at transplant. Donor characteristics were also recorded, including age, height, weight, graft weight (GW), warm ischaemia time (WIT), and cold ischaemia time (CIT). We reviewed intraoperative factors, such as operation time, blood loss, red blood cell transfusion and use of a partial portacaval shunt. In this study, we used both graft-to-recipient weight ratio (GRWR) and ratio of graft weight to estimated recipient liver weight (GW/ERLW) to define whether the donor graft matched or mismatched the corresponding recipient. GW was measured at the conclusion of the back-table allograft preparation,

and ERLW was calculated by the reported formula: ERLW (cm^3) = 6 × weight (lb) + 4 × age (y) + 350.

This clinical study was performed strictly according to the declaration of Helsinki, and no data in this clinical study were related to organs from executed prisoners. The study was approved by the ethics committee of the First Affiliated Hospital of Sun Yat-sen University.

Surgical procedures

The procedure of organ donation and procurement was performed strictly according to Chinese guidelines of organ donation [11]. For DBD, organ procurement was performed with the donor on mechanical ventilation. For DCD and DBCD, withdrawal of life support in donors started in the intensive care unit (ICU) or operating room after full informed consents were obtained from the donors' families. Following the declaration of death, a further 2 or 5 minutes of mandatory observation was performed, which was similar to previous studies and the American Society of Transplant Surgeons guidelines [12,13]. Procurement of organs followed standard surgical techniques.

All liver allograft transplants in the PD group and the AD group used either a modified ''piggyback'' or classic orthotopic procedure. A partial portal-systemic bypass was performed in three patients of the PD group because significant congestion of the reperfused livers was identified by the surgeons through visual and physical inspection. After anastomosis of the portal vein and inferior vena cava (IVC) were done, portal-IVC bypass was performed using the iliac vein from the same donor, in which end-to-side anastomosis were constructed between the bypass vessel and the recipients' portal vein, and between the bypass vessel and the recipients' IVC (Fig. 1A). Then, the hepatic artery and bile duct were reconstructed. The hepatic artery was anastomosed between the donor and recipient's common hepatic artery using an end-to-end technique. The recipient common bile duct was anastomosed to the donor common bile duct using an end-to-end technique.

Immunosuppressive regimen

All recipients received anti-IL-2 receptor antibody and methylprednisolone as induction therapy. Tacrolimus-based maintenance immunosuppressive regimen was employed. Tacrolimus started on day 4 post-transplantation. The initial dose of tacrolimus was 0.04 mg/kg/d, and the target trough tacrolimus level was 8 to 12 ng/mL within the first 3 months, and 5 to 8 ng/mL thereafter. A dose of 500 or 750 mg mycophenolate mofetil (MMF) was used twice a day during the first year post-transplantation.

Post-operative management

The serum chemistries, liver function tests, coagulation function, and Doppler flow ultrasonography were monitored following transplantation. In the PD group, empirical anticoagulation treatment was used according to prothrombin time and platelet counts. When the patient's coagulation function recovered, which refers to prothrombin time less than 16 s and platelet counts higher than 50×10^9/L, prostaglandin E1 (20 μg, twice a day) and low-molecular-weight heparin (20 mg/0.2 mL, once a day) were used to prevent thrombosis. Complications were closely monitored, including but not limited to primary graft non-function (PNF), early allograft dysfunction (EAD), small-for-size liver syndrome (SFSS), and hepatic artery thrombosis (HAT). PNF was defined as an irreversible graft failure requiring emergency liver replacement within the first 10 days of liver transplantation according to United network for organ sharing (UNOS) criteria [14]. EAD was determined by the presence of one or more of the following variables:

- bilirubin171 mg/dL or greater on post-operative day 7;
- INR1.6 or greater on post-operative day 7;
- alanine aminotransferase (ALT) or aspartate aminotransferase (AST) greater than 2000 IU/mL within the first 7 post-operative days.

SFSS was defined as dysfunction of a ''small'' liver graft during the first post-operative week after the exclusion of other cause, in the presence of two of the following on 3 consecutive days: bilirubin greater than100 μmol/L, INR greater than 2, and encephalopathy grade 3 or 4 [15].

Statistical analysis

Survival analysis was performed using the Kaplan—Meier method, and survival of the two groups was compared with the log-rank test. Continuous variables were compared using the student *t*-test. Categorical data were compared using the Chi^2 test. Two-tailed *P*-values were calculated, and when they were less than 0.05, factors were considered to have statistical significance. All statistical analysis was performed using SPSS 20.0 (SPSS Inc., Chicago, IL) and GraphPad Prism 6 (GraphPad Software Inc., La Jolla, CA).

Results

Baseline characteristics

The baseline characteristics of the PD and AD groups are shown in Table 1. The gender distribution of the recipients had a higher proportion of women, and recipients' height and weight were similar in the PD group. The MELD Score was lower in the PD group, whereas no difference of the Child-Pugh Score was observed.

Due to the PD group having significantly lower levels of age, height, weight, and GW, recipients in the PD group had a significantly lower mean GRWR (mean: 1.41 ± 0.37%; range: 0.75%—2.38%), and two had a ratio of less than 0.8%. The GW/ERLW in the PD group was 0.62 ± 0.15 (0.31—1.22), and three had a ratio of lower than 0.5. The blood transfusion volume tended to be larger in the PD than in the AD group, although the difference was not significant.

Survival and complications

The 3-month, 1-year, and 3-year patient survival rates were 91.3%, 85.2%, and 85.2% in the PD group, and 93.4%, 88.9%,

Table 1 Clinical characteristics of adult liver transplants using paediatric and adult grafts.

	PD group	AD group	*P*-value
Recipient characteristics			
Age (y)	50.8 + 12.7 (16—69)	50.5 + 9.6 (27—72)	0.667
Gender (male)	16/23	73/77	0.003
Height (cm)	165.3 + 5.8 (155.0—175.0)	169.5 + 6.3 (153.0—185.0)	0.027
Weight (kg)	58.8 + 10.1 (40.0—78.0)	66.5 + 10.1 (43.0—90.0)	0.002
ERLW	1331.2 + 147.6 (1219.0—1527.6)	1404.9 + 143.2 (1222.7—1669.1)	0.004
Child-Pugh Score	8.7 + 2.2 (5.0—13.0)	8.8 + 2.1 (5.0—14.0)	0.974
MELD Score	14.6 + 8.9 (0.7—36.0)	20.5 + 12.6 (7.0—49.0)	0.029
ICU stay (h)	37.1 + 45.1 (0.0—245.5)	48.4 + 54.9 (7.5—347.0)	0.437
Hospital stay (d)	33.6 + 20.2 (5.0—86.4)	27.5 + 17.5 (1.0—85.0)	0.182
Follow up (d)	697.8 + 615.8 (4.0—2468.0)	478.0 + 438.9 (1.0—1735.0)	0.062
Donor characteristics			
China Category I/II/III	7/11/5	39/29/9	0.191
Causes of death		0.362	
Craniocerebral trauma	12	56	
Cerebrovascular diseases	3	13	
Others	8	8	
Age (y)	8.2 + 2.9 (3—13)	25.8 + 5.3 (18—35)	< 0.001
Height (cm)	126.5 + 22.0 (123.0—158.0)	169.1 + 8.5 (153.0—178.0)	< 0.001
Weight (kg)	28.1 + 9.5 (9.5—50.0)	64.0 + 20.4 (43.0—90.0)	< 0.001
GW (g)	814.8 + 177.2 (390.0—1147.2)	1466.3 + 152.6 (1112.0—2026.0)	< 0.001
GRWR (%)	1.41 + 0.37 (0.75—2.38)	2.26 + 0.42 (1.44—3.49)	< 0.001
GW/ERLW	0.62 + 0.15 (0.31—1.22)	1.04 + 0.15 (0.73—1.39)	< 0.001
Warm ischaemia time (min)	10.5 + 2.9 (6.0—18.0)	10.7 + 3.2 (7.0—26.0)	0.781
Cold ischaemia time (h)	8.6 + 3.5 (3.0—16.0)	7.5 + 2.2 (3.0—16.3)	0.068
Operation data			
Operation time (h)	8.3 + 2.7 (5.0—15.2)	8.0 + 1.9 (4.7—16.3)	0.476
Blood loss (mL)	2330.4 + 3087.8 (200.0—15000.0)	1614.9 + 1340.3 (300.0—8000.0)	0.123
RBC transfusion (mL)	1195.7 + 1336.0 (0—5600.0)	742.7 + 970.1 (0—6000.0)	0.082
Portal-IVC bypass	3/23	0	0.016

PD: paediatric donor; AD: adult donor; ERLW: estimated recipient liver weight; MELD: model for end-stage liver disease; ICU: intensive care unit; GW: graft weight; RW: recipient weight; RBC: red blood cells; IVC: inferior vena cava.

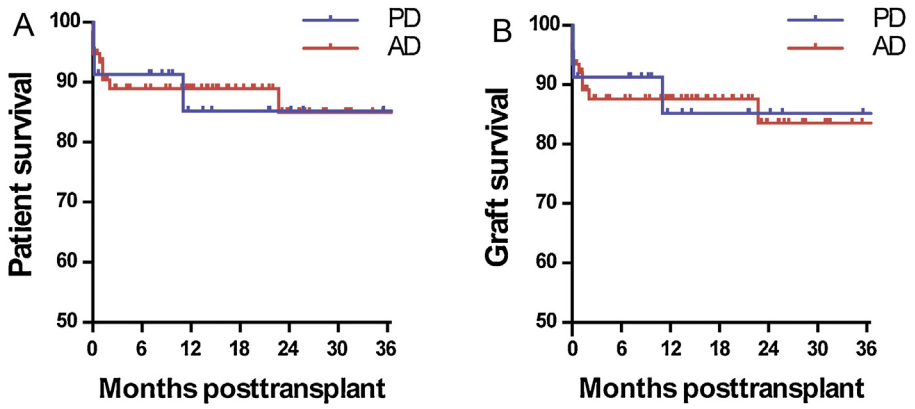

Figure 1 Dynamic monitoring of the portal-IVC bypass after transplantation. (A) The figure shows the bypass construction after implanting the liver graft. Portal vein (the black arrow), inferior vena cava (IVC, the white arrow), portal-IVC bypass (the blue arrow). (B) A representative ultrasound image depicting blood flow in the bypass at the early post-transplantation period. (C) The graph shows the dynamic changes in the velocity of blood flow through the bypass in one case detected by Doppler ultrasonography. In this case, the blood flow through the bypass vessel could not be detected on 90 days post-transplantation.

and 85.0% in the AD group ($P = 0.947$) (Fig. 2A). Meanwhile, the 3-month, 1-year, and 3-year graft survival rates were 91.3%, 85.2%, and 85.2% in PD group and 92.1%, 87.6%, and 83.6% in the AD group ($P = 0.923$) (Fig. 2B). One patient with a MELD score of 36 in the PD group died of portal vein thrombosis and subsequent liver graft failure. The other patient in

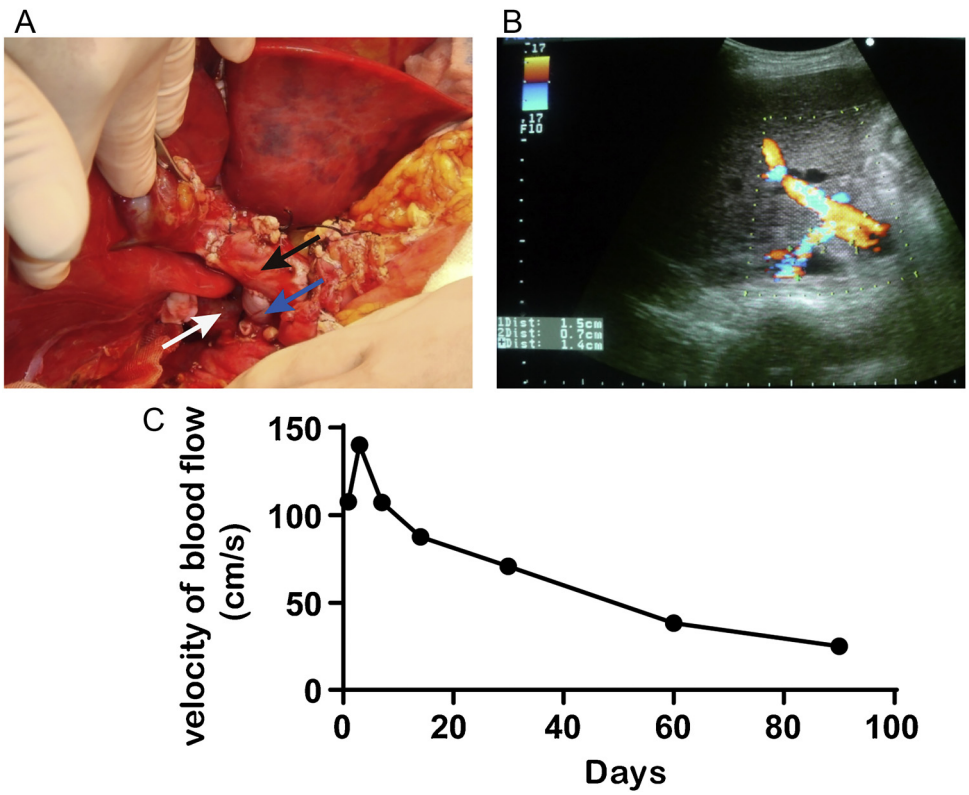

Figure 2 The Kaplan—Meier survival curves showing patient survival and graft survival in PD and AD groups post-transplant with comparison using the logrank test.

the PD group died on day 7 post-operation due to allograft PNF. Eight donors survived 6 or fewer years of age in the PD group, and all the recipients survived with a favourable liver function.

The incidence of PNF, EAD, biliary complications, rejection, portal vein thrombosis (PVT), HAT, and infection were not different between the two groups (Table 2). One patient developed gastrointestinal bleeding in the PD group, although the incidence was not significantly different. A higher incidence of prolonged cholestasis (total bilirubin level > 85.5 mg/dL on post-transplant day 7) was observed in the AD group, but was not statistically different, which may due to the use of a steatotic graft. Although the GRWR reached 1.13%, one patient in the PD group presented hyperbilirubinaemia, large amount ascites, and coagulopathy within the first week and was empirically diagnosed with SFSS. After supportive treatment, this patient recovered and was discharged. The three patients who underwent portal-IVC bypass did not show symptoms of SFSS. We observed no difference in terms of HBV recurrence and cancer recurrence between the two groups.

Liver function recovery pattern

Total bilirubin level on day 7 post-transplant was significantly lower in the PD group compared with the AD group (51.6 + 29.5 vs. 120.3 + 120.2, $P = 0.024$), which became comparable on day 30 post-transplant (22.7 + 14.1 vs. 42.4 + 60.1, $P = 0.205$). The ALT levels on day 7 tended to be lower in the PD group, although the difference was not significant (81.5 + 66.8 vs. 160.4 + 175.2, $P = 0.077$). The international normalised ratio (INR) on day 7, and the peak ALT and AST levels, were similar between the PD and AD groups.

Blood flow of the portal-IVC bypass

Blood flow of the portal-IVC bypass was monitored by Doppler ultrasonography and computed tomography (CT) scan in the patients who received the current procedure. The blood flow and the velocity of flow were observed and measured on days 7, 14, 30, 60, 90 post-operatively (Fig. 1B). Some of these flow rates were as high as 60 cm/s to greater than 100 cm/s. Interestingly, the blood flow diminished gradually when the portal vein pressure decreased as the liver graft function recovered (Fig. 1C). CT scans showed the portal-IVC bypass vascular stenosis, which eventually become invisible, suggesting the possibility of spontaneous occlusion.

Discussion

The safety and risk factors of using PD livers in adult recipients should be carefully considered. Table 3 summarises a few studies that have reported the outcomes of adult liver transplant using paediatric grafts. Two studies in early 21st century reported lower 1-year graft survival rates in the PD group compared with the adult donor group [6,16], whereas a research study conducted by Ghabril et al. showed no

Table 2 Post-transplant complications of liver transplants using paediatric and adult donor grafts.

	PD group ($n=23$)	AD group ($n=77$)	*P*-value
Primary graft non-function	1 (4.4%)	2 (2.6%)	0.548
Early allograft dysfunction	3 (13.0%)	23 (29.9%)	0.749
Small-for-size syndrome	1 (4.4%)	0 (0%)	0.230
Prolonged cholestasis	2 (8.7%)	23 (29.9%)	0.155
Biliary complication	2 (8.7%)	3 (3.9%)	0.324
Rejection	0 (0%)	1 (1.3%)	1.0
Portal vein thrombosis	2 (8.7%)	3 (3.9%)	0.324
Hepatic artery thrombosis	1 (4.4%)	1 (2.4%)	0.409
Gastrointestinal bleeding	1 (4.4%)	0 (0%)	0.230
Infection	7 (30.4%)	16 (20.8%)	0.399

PD: paediatric donor; AD: adult donor.

Table 3 Summary of reports of paediatric donor liver for adult patient transplantation.

	Nation	Publication year	Donor age (Year)	CIT (hour)	WIT (min)	1-year patients survival (%)	Maximum follow-up (year)
Adam et al.[7]	France	1993	< 12	9	NA	68	4.2
Emre et al.[6]	US	2001	< 13	10.9	NA	83	5
Yasutomi M et al.[16]	US	2001	< 12	NA	NA	64	1
Ghabril et al.[8]	US	2009	≤ 13	7.9	35	87	3
Schukfeh N et al. [9]	Germany	2015	≤ 6	8.9	31	89	6.6
Croome KP et al.[18]	US	2016	< 12	7.3	NA	88	NA
Own series	China	2017	≤ 13	8.6	10.5	85.2	6.8

WIT: warm ischaemia time; CIT: cold ischaemia ti.

significant difference in 1-year graft survival rate between the two groups [8]. In the current study, the 3-year survival rate of patient and graft was comparable between the two groups, with a rate as high as 60.0% for circulatory dead donors who were considered as marginal donors harbouring the higher graft loss rate. In a recent report published by Schukfeh N et al, allocation of liver grafts from donors 6 years of age or younger to adult recipients yielded a good long-term survival. As was similar to this study, the recipients receiving grafts from donors 6 years of age or younger all observed favourable outcomes.

SFSS is a lethal problem when using such a small-for-size graft. Multiple factors are considered to participate in the development of SFSS, including liver size, vascular inflow, and recipient-related factors [15]. Significant progress has been made to clarify the optimal graft volume for the recipients in the past decade, and it has been widely accepted that grafts that weigh greater than 0.8% of the recipient body weight are safer for small-for-size liver transplants [17]. The recent study from Croome KP et al. reviewed the large US national database and found that recipients with GRWR of 0.8 had a better short-term graft survival than those with GRWR less than 0.8. In our study, the GRWRs were higher than 0.8%, except in two combinations. Females with lower height and lower weight r are the combination of factors better able to accept a paediatric graft, which is believed to be one of the major reasons for the good outcomes in this study.

In addition to graft size, portal hyperperfusion is also a critical factor in the development of SFSS. Sinusoidal congestion and haemorrhage, mitochondrial swelling, as well as vacuolar changes in hepatocytes were observed in small-for-size transplants in an animal model due to excessive portal perfusion [18,19]. Indeed, despite no statistical difference, there was a higher incidence of upper gastrointestinal bleeding in the current series, indicating higher risks of portal hyperperfusion post-transplant. It has been reported that avoidance of portal overflow is crucial to SFSS prevention in living donor liver transplantation. Reducing portal inflow can be achieved by splenic artery ligation, splenectomy, and construction of portosystemic shunts [20].

In the current study, a portal-IVC bypass procedure was constructed to modulate portal inflow in three patients who had lower GR/WR ratio (including the two patients with GRWR of less than 0.8%) and significant hepatic congestion after reperfusion. All these recipients survived and no SFSS occurred. However, one of the patients who did not receive portal-IVC bypass developed SFSS, although the GRWR reached 1.13%. Notably, according to Ghabril's study [8], 73% of recipients received a partial portacaval shunt procedure and the GRWR of some cases were greater than 0.8% or even greater than 1%. These results indicated that a portal-IVC bypass procedure should be considered even in liver transplants with GRWR greater than 0.8% if patients are exposed to a high risk of SFSS or higher portal vein pressure. Collectively, we believe modulation of portal inflow

by portal-IVC bypass can be used as an alternative method to prevent SFSS in adult liver transplants using PD livers. But, the portal-IVC bypass procedure also can result in the prolonged cold ischaemia time and larger volume of blood transfusion, although there is no statistical difference. Therefore, it remains unclear concerning the selection of a group of patients to receive a portacaval shunt procedure and the size of the shunt. Intraoperative measurement of portal vein pressure and flow may help in the decision making.

In addition to graft loss, a higher rate of complications has been reported in adult liver transplant using PD livers, including vascular complications and prolonged cholestasis [7]. Studies have shown a significantly higher incidence of HAT in this combination [21]. A GW/ERLW ratio of less than 0.4 and prolonged ischaemic time are believed to be risk factors for HAT. However, Ghabril et al. reported a 0% HAT in 15 adult liver transplants using PD allografts [8]. They considered the beneficial outcome to be attributable to the limited ischaemia times using the piggyback procedure. One patient had HAT in the current series. It is essential to limit the ischaemia time and prophylactic use of heparin and prostaglandin E1 based on our own experience. Moreover, high portal venous inflow may also contribute to HAT because it leads to a reactive vasoconstriction in the hepatic arterioles, increasing resistance and further diminishing arterial flow [16]. Therefore, modulation of portal inflow might not only prevent the occurrence of SFSS, but also contribute to HAT prevention.

In summary, we demonstrated, for the first time in the current settings of organ donation practice in China, that the outcomes of the use of PD allografts in selected adult recipients is comparable to those that used ideal adult donor livers. Of note, our results suggest that appropriate selection of donors, including low recipient's MELD Score, and GRWR of 0.8 or greater, are warranted to improve the prognosis. Portal inflow modulation, such as the portacaval shunt procedure, may also contribute to the good outcomes.

Disclosure of interest

The authors declare that they have no competing interest.

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