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ABO-incompatible liver transplantation for severe hepatitis B patients

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Summary

Effect of ABO-incompatible liver transplantation on patients with severe hepatitis B (SHB) remains unclear. Herein, we summarized 22 cases with SHB in whom were performed emergency liver transplantation from ABO-incompatible donors. The immunosuppressive protocol consisted basiliximab, tacrolimus, steroids and mycophenolate mofetil. The mean MELD score was 35.2 ± 7.1. Major complications included rejection, infections, biliary complications, hepatic artery thrombosis or stenosis and portal vein thrombosis. Patient survival rates were 40.9%, 78.9% and 82.3% in 1 year, 29.2%, 66.8% and 72.9% in 3 years, and 21.9%, 60.1% and 62.5% in 5 years for ABO-incompatible, ABO-compatible and ABO-identical groups. Graft survival rates were 39%, 78.9% and 82.3% in 1 year, 27.8%, 66.4% and 71.1% in 3 years, and 20.9%, 57.9% and 61.0% in 5 years for incompatible, compatible and identical ABO graft-recipient match. The 1-, 3-, 5-year graft and patient survival rates of ABO-incompatible were distinctly lower than that of ABO-compatible group ($P < 0.05$). Our results suggested that ABO-incompatible liver transplantation might be a life-saving procedure for patients with SHB as a promising alternative operation when ABO-compatible donors are not available and at least bridges the second opportunity for liver retransplantation.

Introduction

Currently, the organ shortage is increasingly serious, resulting in the number of patients in waiting list always being multiple times of the number of liver donors. Many critical patients died of donor deficiency without the same blood type. The urgency of liver transplantation and the increase of waiting list have prompted us to expand the donor pool through exploring higher risk or more unconventional techniques.

ABO-incompatible (ABO-In) liver transplantation has always been a controversial issue. The focus of the debate included severe cell-mediated rejection, antibody-mediated rejection, vascular thrombosis, acute liver necrosis, ischaemic bile duct complications and sepsis [1–6]. The two most common indications for ABO-In liver transplantation are as follows: emergency transplants for acute liver failure, and donor transplants are urgent need in life-threatening situation when no ABO-compatible (ABO-C) donor is available [3]. Recent results showed that 5-year survival rate of graft had improved up to 60.0% [7–9], which is higher than that of early pioneer stage with 20.0% 5-year survival rate of graft. Thisgreat progress was presumably due to the improvement of perioperative management of liver

transplantation, optimizational protocols of immunosuppression from triple to quadruple drug, and frequent addition of splenectomy, plasmapheresis, prostaglandin E1 or intravascular infusion of methylprednisolone [10,11]. However, effect of ABO-In liver transplantation on those specific patients with severe hepatitis B (SHB), experiencing persistent infection of hepatitis B virus (HBV) and progressive deterioration of preoperative clinical condition, still remains unpredictable. This study especially discussed the effect of ABO-In emergency liver transplantation on adult patients who experienced fulminant liver failure owing to SHB.

Patients and methods

Patient selection

A total of 103 adult transplanted patients for emergency acute liver failure secondary to SHB from January 2006 to December 2010 (The First Affiliated Hospital, Sun Yat-Sen University, Guangzhou, China) were included in the study. The medical records of all patients were retrospectively analysed, including blood group information of recipients, model for end-stage liver disease (MELD) score, intraoperative and postoperative clinical data. All transplants were divided into three groups of ABO-In, ABO-C and ABO-identical (ABO-Id) according to ABO-compatibility. The 22 patients in the ABO-In group did not have suitable ABO-C donors and had to conduct ABO-In liver transplantation. These 22 patients were urgently transplanted due to fulminant liver failure mainly caused by severe acute HBV infection and acute-on chronic course. This study has been approved by the local ethical committee before liver transplantation, and the signed informed consents have been obtained.

Immunosuppressive protocol

All ABO-In recipients were treated with a quadruple drug immunosuppression regimen, including Basiliximab as induction, calcineurin inhibitor, steroids and mycophenolate mofetil (MMF). All transplant recipients were given 1000 mg intravenous methylprednisolone (MPD) during the anhepatic phase and 500 mg of intravenous MPD at postoperative day 1, followed by a daily spiral diminishing dosage of 240, 200, 160, 120, 80 and 40 mg in the next 6 days, and then switched to oral 48 mg of prednisolone per day for 1 week, followed by a decreased dose 8 mg weekly until 4 mg per day, and prednisolone was discontinued at 3 months after transplantation. Tacrolimus treatment was initiated on the first postoperative day, the optimal blood drug concentration level was maintained at 10–12 ng/ml, reduced to 8–10 ng/ml 1 month after surgery, and then reduced to 6–10 ng/ml 3 months after surgery. 750 mg MMF was used twice per day since the first postoperative day. Steroid-resistant patients with acute cell rejection were treated with rabbit anti-human thymocyte globulin (ATG).

ABO-C and ABO-Id recipients were considered as the control groups and were treated according to the standard protocol, including calcineurin inhibitor and Basiliximab and steroids. All transplant recipients of these two groups were only given 500 mg intravenous MPD during the anhepatic phase and 500 mg intravenous MPD at the first postoperative day. Tacrolimus treatment was initiated on postoperative day 4, the optimal blood drug concentration level was maintained at 8–10 ng/ml, reduced to 6–8 ng/ml at 3 months postoperatively, and then reduced to 5–8 ng/ml at 6 months postoperatively. Several patients in these two groups received postoperatively short-term MMF or sirolimus.

Infection prophylaxis and treatment of hepatitis B virus recurrence

Postoperative infection prophylaxis consisted 4.5 g intravenous piperacillin/tazobactam three times a day for at least 7 days, fluconazole 400 mg per day for 7 days and ganciclovir 250 mg twice a day for 14 days. In addition, adefovir dipivoxil combined with intravenous hepatitis B immunoglobulin (HBIG) was used to prevent HBV recurrence postoperative.

Follow-up, complications definition and statistical analysis

Graft and patient survival rates were analysed over a mean follow-up of 34.2 $\pm$ 20.3 months (range: 2–67). Complications, including abnormal hepatic function, acute rejection, infection, vascular complications, biliary complications, were only assessed for the first post-transplant year. Data were retrospectively collected. Of which, acute rejection was diagnosed depending on clinical manifestation, the monitoring of hepatic function and liver biopsies. Infections were diagnosed by clinical manifestation, laboratory and aetiological examination. Vascular complications were diagnosed by colour Doppler ultrasound and hepatic artery angiography. The diagnosis of biliary complications was diagnosed by the Doppler ultrasound, CT scan, the magnetic resonance cholangiopancreatography (MRCP), percutaneous transhepatic cholangiography (PTC) and endoscopic retrograde cholangiopancreatography (ERCP). The treatments of biliary complications included percutaneous transhepatic cholangial drainage (PTCD), stent implantation through ERCP, improving the microcirculation and anti-inflammatory cholagogue.

All enumeration data were expressed by mean $\pm$ standard deviation. Survivals were analysed by the Kaplan–Meier

method, and differences between the groups were further tested by long-rank test. Analysis was also performed by one-way ANOVA or chi-squared test when applicable. Fisher's exact test was used when the two cells (50%) have expected count <5. Statistical analysis was conducted by SPSS 13.0 (Armonk, NY, USA), and a value of $P < 0.05$ was considered statistically significant.

Results

Clinical characteristics

From January 2006 to December 2010, 103 patients were urgently performed liver transplantation secondary to SHB. 22 cases of them were performed ABO-In liver transplantation, 19 cases for ABO-C and 62 cases for ABO-Id transplants. During the same period, a total of 455 liver transplantations were performed in our centre.

Recipients' characteristics were similar among the three ABO combinations. There were 19 males and three females in the ABO-In group, 16/3 (m/f) in the ABO-C group and 57/5 (m/f) in the ABO-Id group. The mean ages were 43.5 ± 9.1 (range: 28–60), 45.5 ± 10.3 (range: 29–63) and 46.6 ± 8.4 (range: 29–64) years old in the ABO-In group, ABO-C group and ABO-Id group, respectively. The donor's characteristics were summarized in Table S1, and the percentage of ABO-incompatible, ABO-compatible, ABO-identical donors was equally distributed among the two types of donors. All of these recipients were Chinese.

Blood-group-incompatible mismatches included 8 A donors to O recipients (36.3%), 3 AB to O (13.6%), 6 B to O (27.2%), 2 A to B (9%) and 3 AB to A (13.6%). In total, 17 of the 22 ABO-In recipients were of blood group O (Table 1).

The indication for transplant was an emergency acute liver failure for SHB. The 103 emergent transplants were performed using a whole liver graft. Twenty-two ABO-In grafts were used in the 103 urgent liver transplantations. Mean MELD scores were 35.2 ± 7.1 (range: 20–44), 33.0 ± 7.7 (range: 18–41), 32.0 ± 7.0 (range: 18–43), in the ABO-In, ABO-C and ABO-Id groups (ABO-In vs. ABO-C, $P > 0.05$; ABO-In vs. ABO-Id, $P > 0.05$).

The median cold ischaemia time was similar among the three groups [378 min (190–725), 385 min (200–680) and 368 (180–710) in the ABO-In, ABO-C and ABO-Id ($P > 0.05$)].

Immunosuppression in ABO-In recipients

All ABO-In patients received quadruple immunosuppression. All cases received similar maintenance therapy,

Table 1. Clinical data of blood type, induction and maintenance immunosuppression combinations in the ABO-incompatible recipients.

Case	D	R	BAS	TAC	MMF	SRL	PLA	SPL	STER	Rejection
1	A	O	+	+	+				+	
2	A	O	+	+	+				+	
3	B	O	+	+	+		+		+	ACR-S
4	A	O	+	+	+			+	+	
5	AB	O	+	+	+				+	ACR-S
6	A	O	+	+	+		+		+	
7	A	O	+	+	+	+			+	ACR-S
8	A	B	+	+	+			+	+	ACR-S
9	AB	O	+	+	+				+	ACR-R
10	B	O	+	+	+		+		+	
11	AB	A	+	+	+			+	+	
12	A	B	+	+	+		+		+	
13	A	O	+	+	+				+	ACR-R
14	AB	O	+	+	+	+			+	
15	B	O	+	+	+				+	ACR-S
16	A	O	+	+	+				+	ACR-S
17	B	O	+	+	+				+	
18	AB	A	+	+	+	+			+	
19	A	O	+	+	+				+	ACR-R
20	AB	A	+	+	+				+	
21	B	O	+	+	+				+	
22	B	O	+	+	+				+	

This table includes induction and maintenance immunosuppression only; please refer to the text for acute rejection therapy. A, blood group A; B, blood group B; AB, blood group AB; D, donor blood group; R, recipient blood group; BAS, basiliximab; MMF, mycophenolate mofetil; SRL, sirolimus; PLA, plasmapheresis; STER, steroids; TAC, tacrolimus; SPL, splenectomy; ACR-S, acute cell rejection, steroid sensitive; ACR-R, acute rejection, steroid resistant.

including Basiliximab, calcineurin inhibitor, steroids and MMF. Plasmapheresis was preoperatively used in only four patients with hyperbilirubinemia. Splenectomy was neither a routine procedure for ABO-C liver transplant recipients nor a particular feature of some ABO-In liver transplants in our centre. Splenectomy, using in only three cases with too big size of spleen as well as the liver graft with large volume in ABO-In group, aimed to facilitate to conduct suturing the abdominal cavity (Table 1).

Graft and patient survival rates and rejection

Survival rates in patients who underwent emergency liver transplantation and graft survival rates were 72.8%, 67.0% in 1 year, and 61.2%, 61.2% in 3 years, and 52.4%, 50.5% in 5 years, respectively.

Patient survival rates were 40.9%, 78.9% and 82.3% in 1 year, 29.2%, 66.8% and 72.9% in 3 years, and 21.9%, 60.1% and 62.5% in 5 years for ABO-In, ABO-C and ABO-Id groups, respectively (Fig. 1a). Graft survival rates were 39.0%, 78.9% and 82.3% in 1 year, 27.8%, 66.4% and 71.1% in 3 years, and 20.9%, 57.9% and 61.0% in 5 years for incompatible, compatible and identical ABO graft-recipient match, respectively (Fig. 1b). There were no significant differences on 1-, 3-, 5-year survival rates of graft and patients between ABO-C and ABO-Id groups. The 1-, 3-, 5-year survivals rates of graft and patients in ABO-In group were distinctly lower than that of ABO-C group ($P < 0.05$, Fig. 1).

Acute cell rejection was similarly distributed among the three groups (Table 2), except for acute cell rejection steroid-resistant episodes, which were more frequent in ABO-In group than that in ABO-Id group ($P2 < 0.05$). Six ABO-In patients experienced acute cell rejections sensitive to steroids and another 3 acute cell rejections were steroid-resistant. The latter failed to recover and finally died. The incidences of acute rejection were 9.7%, 10.5% and 40.9% in the ABO-Id, ABO-C and ABO-In groups, respectively (Table 2).

Complications

As shown in Table 2, the most frequent infectious complications were varieties of pneumonia, bacteremia, urinary tract infection and intra-abdominal infection. The infection incidences were 20.9%, 26.3% and 54.5% in the ABO-Id, ABO-C and ABO-In groups, respectively. The incidences of vascular complications, including hepatic artery thrombosis, hepatic artery stenosis and portal vein thrombosis, were 4.8%, 5.2% and 18.1% in the ABO-Id, ABO-C and ABO-In groups, respectively. The incidences of biliary complications, including biliary stricture and biliary ischaemia necrosis, were 8.0%, 10.5% and 31.8% in the ABO-Id, ABO-C and ABO-In groups, respectively. Significant differences existed between ABO-Id and ABO-In group on biliary and bacterial infectious complications ($P2 < 0.01$, Table 2). No significant differences existed on vascular complication between ABO-Id and ABO-In groups ($P2 > 0.05$, Table 2). However, there were no significant differences on biliary, vascular, bacterial infectious complications between the ABO-C and ABO-Id groups ($P1 > 0.05$, Table 2).

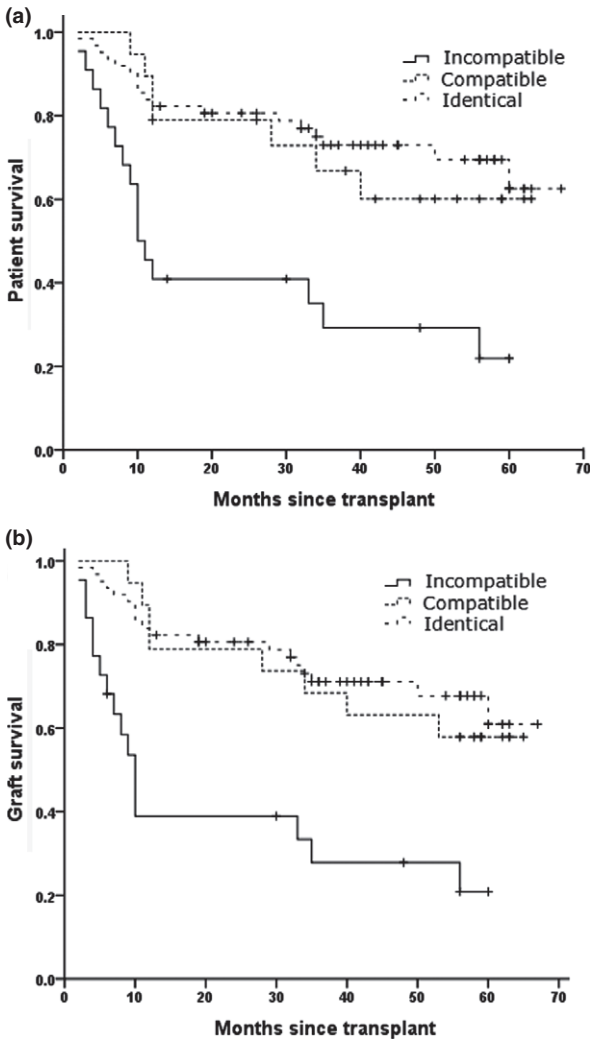

Figure 1 Patient (a) and graft (b) survivals were significantly lower in ABO-In group compared with ABO-Id group ($P < 0.05$).

In the 22 cases of ABO-In group, four cases died of sepsis, three cases died of steroid-resistant acute rejection, two cases died due to hepatic artery thrombosis, three cases died due to biliary ischaemia necrosis and one case died due to multiple organ dysfunction syndrome (Table 3). Hepatic artery thrombosis and biliary ischaemia necrosis were considered as associating with immune factors.

Table 2. Complications in ABO-incompatible, ABO-compatible and ABO-identical group after liver transplantation.

ABO status	Incompatible	Compatible	Identical	*P*1	*P*2
ACR	27.2% (6/22)	10.5% (2/19)	9.7% (6/62)	1.000	0.071
ACR-steroid resistant	13.6% (3/22)	0 (0/19)	0 (0/62)		0.016
Biliary complications	31.8% (7/22)	10.5% (2/19)	8.1% (5/62)	0.664	0.000
Vascular complications					
Hepatic artery thrombosis	9.1% (2/22)	5.3% (1/19)	1.6% (1/62)	1.000	0.073
Hepatic artery stenosis	4.5% (1/22)	0 (0/19)	1.6% (1/62)		
Portal vein thrombosis	4.5% (1/22)	0 (0/19)	1.6% (1/62)		
Bacterial infections					
Pneumonia	18.2% (4/22)	15.6% (3/19)	17.7% (11/62)	0.753	0.006
Bacteremia	9.1% (2/22)	5.3% (1/19)	1.6% (1/62)		
Urinary tract infection	4.5% (1/22)	5.3% (1/19)	0 (0/62)		
Intra-abdominal infections	13.6% (3/22)	0 (0/19)	0 (0/62)		
Other bacterial infections	9.1% (2/22)	0 (0/19)	1.6% (1/62)		

ACR, acute cell rejection. *P*1, compatible versus identical; *P*2, incompatible versus identical. Fisher's exact test was used when the 2 cells (50%) have expected count <5.

Table 3. Causes of death in ABO-incompatible, ABO-compatible and ABO-identical group after liver transplantation.

ABO status	Incompatible	Compatible	Identical	*P*1	*P*2
Sepsis	18.2% (4/22)	15.8% (3/19)	16.1% (10/62)	1.0000	1.000
MODS					
Severe infection	4.5% (1/22)	10.5% (2/19)	11.3% (7/62)	1.000	0.168
Acute renal failure	0 (0/22)	5.3% (1/19)	8.1% (5/62)		
ACR-steroid resistant	13.6% (3/22)	0 (0/19)	0 (0/62)		0.016
Biliary ischemia necrosis	13.6% (3/22)	5.3% (1/19)	8.1% (5/62)	1.000	0.426
Hepatic artery thrombosis	9.1% (2/22)	5.3% (1/19)	0 (0/62)	0.235	0.066
Other	0 (0/22)	5.3% (1/19)	4.8% (3/62)	1.000	0.563

MODS, multiple organ dysfunction syndrome; ACR, acute cell rejection. *P*1, compatible versus identical; *P*2, incompatible versus identical. Fisher's exact test was used when the two cells (50%) have expected count <5.

Discussion

SHB is a disease with significant morbidity and mortality. The People's Republic of China has one of the world's highest incidences of HBV infection despite the availability of an effective vaccine [12]. It is estimated that 93 million individuals in China are infected with HBV. SHB is a major cause of acute liver failure in China. SHB-induced liver failure patients who require liver transplantation represented a particular challenge because most SHB recipients died during the first month after liver transplantation [13]. However, it is very different from Western countries as pregnancy and drugs are the common causes of acute liver failure. Currently, it was reported that patient age, serum total bilirubin concentration, hepatic encephalopathy and international normalized ratio for prothrombin time were independent factors affecting the post-transplantation mortality of patients with SHB [14].

We reported 22 adult ABO-In liver transplantations due to SHB, with 22.0% patient survival rate and 20.2% graft survival rate in 5 years, respectively, despite their severe clinical illnesses. It is well known that emergent liver transplantation itself has higher risk of complications and lower long-term survival compared with liver transplantation in nonurgent candidates. Published data on emergency transplant showed graft survival closed to 63.0% in 3 years in the ABO-Id or ABO-C group compared with 30.0% in the ABO-In group [15]. With the application of quadruple drug immunosuppression and improvement of perioperative management, this study showed a positive result compared with earlier published studies, focusing on the investigation of ABO-In adult emergency liver transplants of patients with SHB who bore fulminant liver failure.

ABO-In liver transplantation is regarded as a relative contraindication because of the high incidences of rejection, biliary duct, vascular complications and sepsis. To lessen humoral rejection, a variety of strategies have been investigated, including plasmapheresis, hepatic perfusion, various immunosuppressive agents, steroids, rituximab and splenectomy [8,16]. In this retrospective study, the

immunosuppression protocols used are based on quadruple drug therapy, with Basiliximab as an inducer in all ABO-In cases. This protocol is a modest increase in the level of immunosuppression compared with the standard protocols of triple therapy used in the ABO-C patients. We believe that this choice may be responsible for a high incidence of infectious complications compared with those in the identical and compatible groups.

Currently, there is no consensus on the effect of splenectomy. Although splenectomy has some benefits for desensitization protocols in ABO-In liver transplantation [8], other researchers also suggested that splenectomy should be routinely performed in ABO-In living donor liver transplantation in view of the fact that this procedure could eradicate remnant antibody-producing plasma cells that cannot be eliminated by plasma exchange and rituximab and significantly reduce excessive portal vein flow [17]. But regrettably, in our present study, 2 of 3 splenectomy cases in the ABO-In group died of severe infection postoperatively. This result seems to confirm that splenectomy avoidance could decrease the risk of long-term lethal infections [18,19]. Additionally, it was also reported that splenectomy does not appear to offer any immunological benefit in ABO-In liver transplantation [20]. Taken together, we believe that routine splenectomy in ABO-In liver transplantation may be an even greater challenge and should be cautiously considered. On the other hand, the effects of plasmapheresis and prostaglandin E1 on ABO-In liver transplantation are more clear. The plasmapheresis could eliminate antidonor antibody in the blood of recipient. The prostaglandin E1 could improve hepatic blood flow and microcirculation by its vasodilating effects and inhibiting platelet/leucocyte adhesion.

Biliary and hepatic artery complications were considered as major causes of poor prognosis for ABO-In liver transplantation recipients. The biliary complications observed in the ABO-In group may be related to direct immunological mechanisms, because bile ducts epithelium could also express ABO antigens, being a target for antibody-mediated injury [21–23]. In fact, biliary complication was one of major causes of death in this study and resulted in three deaths.

Recipient age also might be a key factor in the outcomes of ABO-In liver transplantation. Published data showed that adult ABO-In liver transplantation presented a worse outcome than children [10]. Moreover, some researchers showed that recipient age was obviously related to antibody-mediated rejection and that paediatric ABO-In liver transplantation did not present worse graft survivals compared with age-matched liver transplantation [6,24,25]. Egawa *et al.* suggested that the patient survival rate after ABO-In liver transplantation gradually declined with the rise of recipients' age. The 5-year survival rate of patient was 85.0% in infants and only 52.0% in adults [6]. Although the patient and graft survival rates were lower than that of published data, this study focused on emergent ABO-In liver transplantation in adult with SHB, this procedure is really for these high selective patients for life-saving.

HBV recurrence is a common complication, occurring in up to 12% of patients after liver transplantation [26]. In this study, HBIG plus adefovir dipivoxil was used to prevent HBV recurrence. Interestingly, after a mean follow-up of 34.2 $\pm$ 20.3 months, HBV recurrence did not observe, it indicated that protocol of HBIG plus adefovir dipivoxil was reliable.

Of course, there are some limitations in this study. On the one hand, these patients in ABO-In group, with a mean MELD score of 35, would probably have a very high mortality rate without liver transplantation; what is more, our result also showed that the survival rates of these patients after transplant were low. But ABO-In liver transplantation is a life-saving measure for these patients with SHB, at least bridges the second opportunity of retransplantation. Anyway, we should be more prudent to choose the recipients in order to make the use of donor resources more optimized. On the other hand, the limitation of the nontesting of isoagglutinin IgM and IgG levels pre- and postoperatively, and the nonroutine use of plasmapheresis existed in the present study. It would be encouraged to perform these examinations and treatments in the further study and clinical practice.

In conclusion, we analysed patient and graft survivals in all ABO-compatibility settings in a series of 103 adult emergency liver transplants due to SHB. These outcomes showed the overall improvement in the management of ABO-In transplants, including perioperative management and immunosuppressive strategies. We believe that ABO-incompatibility should not be considered an absolute contraindication to the patients with SHB, especially in urgent need of life-saving. Therefore, under the condition of achieving informed consent of patient and family members, ABO-In liver grafts might be viewed as a practicable treatment option in high critically ill adult patients with SHB in need of an emergency liver transplantation.

Authorship

ZJ, JW, WD and HX: research design. ZJ, JW, WD, JX and ZHU: data collection. ZJ, YX and JW: data analysis. ZJ, JX, ZX and HX: writing.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1 Donor characteristic.

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