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ORIGINAL ARTICLE

Safety of donor right hepatectomy for adult-to-adult living donor liver transplantation

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Summary

The purpose of this study was to ascertain the usefulness of preoperative evaluations of donors by computed tomography (CT) volumetry and CT cholangiography for prevention of unexpected liver failure and biliary complications after donor right hepatectomy for adult-to-adult living donor liver transplantation. Fifty-two donors who underwent right hepatectomy without the middle hepatic vein were enrolled in this study. The values of graft weight (GW) were significantly correlated with those of estimated graft volume (GV; $P < 0.0001$). GW was predicted by the following formula: $GW = 155.25 + 0.658 \times GV$; $r^2 = 0.489$. CT cholangiography revealed anatomical variants of biliary structure in one-third of the donors and also clearly showed one or two small biliary branches from the caudate lobe to the right hepatic ducts or the confluence in 58% of the donors. Biliary leakage, which was treated by conservative therapy, occurred in only one donor (1.9%). No donors received homologous blood transfusion. Hyperbilirubinemia (serum total bilirubin >5 mg/dl) occurred in 5.8% of the donors during their early postoperative periods. Precise evaluations of liver remnant volume by CT volumetry and biliary variation by CT cholangiography are essential for performing safe donor hepatectomy, preventing hepatic insufficiency and minimizing the risk of biliary tract complications.

Introduction

As the first successful living donor liver transplantation (LDLT) from an adult donor to an adult recipient [1], LDLT is rapidly emerging worldwide as an effective treatment for selected adult patients with end-stage liver disease [2,3]. The prevalence of adult-to-adult LDLT has led to application of a right lobe graft to the procedure for providing a sufficient hepatic mass. Despite impressive results of LDLT, there still is considerable debate concerning donor safety, especially in LDLT using a right lobe graft. Serious postoperative complications resulting from hepatic parenchymal loss occur more frequently in donors undergoing right hepatectomy than in those undergoing left hepatectomy or left lateral segmentectomy [3,4]. Loss of a large part of the liver resulted in hepatic insufficiency or death in several donors [5,6,7]. Precise evaluations of donor liver by imaging modalities before surgery are important for preventing unexpected hepatic insufficiency in the donor.

Biliary complications such as bile leakage and biliary stricture are also frequent and sometimes serious in donors who have undergone right hepatectomy [3,8]. In LDLT using a right lobe graft, precise identification of right biliary duct variants in the donor before the operation is critical for the successfully and safely performing not only donor hepatectomy but also biliary reconstruction in the recipient. We present here results of our evaluations for donors in adult-to-adult LDLT, focusing on preoperative evaluation of liver volume by computed tomography (CT) and of biliary anatomy by CT cholangiography, and outcomes of donors who had undergone right hepatectomy.

Patients and methods

From June 1991 to May 2005, 64 donors underwent donor hepatectomy for adult-to-adult LDLT at Hiroshima University Hospital (Hiroshima, Japan) by a single team. Of them, 52 donors who underwent right hepatectomy without the middle hepatic vein were enrolled in this study. Forty-eight (92%) of the 52 donors had undergone donor hepatectomy in the past 4 years. The donors included 31 men and 21 women with a median age of 29 years (range: 18–61 years). The donors consisted of four parents, 32 children, nine siblings, six spouses and one uncle. Mean and median follow-up periods were 28 and 24 months respectively.

The median age of the recipients was 51 years (range: 20–69 years). Underlying liver diseases of transplant recipients were cirrhosis from hepatitis virus infection in 30 patients (22 with hepatocellular carcinoma), fulminant hepatic failure in seven patients, autoimmune hepatitis in four patients, primary biliary cirrhosis in four patients, alcoholic liver cirrhosis in three patients, retransplantation in two patients and metastatic liver tumors from insulinoma, Wilson disease each in one patient.

Data were obtained from medical record review and follow-up was complete as of 30 July 2005. Postoperative complication was defined as any event satisfying the criteria advocated by Broering *et al.* [9], who modified the classification of Clavian *et al.* [10] to adapt it to a living donor situation.

Donor selection and evaluation

All donors were evaluated before surgery by a hepatologist and psychologist. Acceptance criteria for living donors included age between 18 and 65 years; relation to the recipient within the third degree of consanguinity; negative results of serological tests for hepatitis B and C and human immunodeficiency viruses; adequate psychological support; normal hematologic, liver and renal functions; and normal electronic cardiogram. In terms of ABO blood group compatibility, we had accepted ABO-incompatible donors during our initial experiences. However, we later considered only ABO-identical or ABO-compatible donors to be acceptable as two recipients who received ABO-incompatible grafts died of acute rejection. Eligible donors preceded to imaging studies, including chest and abdominal radiography, abdominal ultrasonography and CT for exclusion of any unrecognized diseases. CT was also used for volumetric study, delineation of vascular anatomy, and evaluation of the degree of fat content. Measurement of graft volume by the method of Heymsfield *et al.* [11] and analysis of CT images has been replaced as case number 6 of our series by a method using Advantage Workstation (version 3.1, GE Medical Systems, Milwaukee, WI, USA) and Zio 900 M (Zio software, Tokyo, Japan) [12].

When estimated liver remnant volume in the donor accounted for <30%, the candidate, in principle, was considered to be unsuitable as a living donor. If it was suspected from results of imaging studies that a potential donor suffered from fatty liver, liver biopsy was performed preoperatively and mild fatty liver (<10% of fat storage) was considered to be acceptable for donation. Other invasive procedures such as hepatic arteriography and endoscopic retrograde cholangiopancreatography were not performed in any donors. CT cholangiography was performed for the evaluation of biliary anatomy for all donors except the initial six cases [12]. The biliary anatomy in donors was classified into four types, based on the tributary from the posterior segment [13] (Fig. 2).

The type of hepatectomy was selected according to the following criteria: ratio of estimated graft volume (GV) to standard liver volume of the recipient exceeding 40% and/or ratio of estimated GV to body weight of the recipient exceeding 0.8%. Standard liver volume of the recipient was calculated according to the formula proposed by Urata *et al.* [14]. Four hundred milliliters of autologous blood was stored routinely before the operation except in the setting of emergent transplantation.

Donor surgical procedure

The abdomen was entered through an inverted L-shaped incision. After cholecystectomy with insertion of a 5-Fr catheter through the cystic duct stump for subsequent intraoperative cholangiography, intraoperative ultrasound was performed to confirm the anatomy of the hepatic vein and to decide the parenchymal transection plane, with special attention given to the sizes of tributaries draining into the middle hepatic vein from the anterior segment. The right hepatic lobe was fully mobilized, preserving the significant (>5 mm) short hepatic veins for later reconstruction. The right hepatic artery was dissected and exposed only to the right side of the common bile duct. Along the demarcation line emerging after transient occlusion of the right hepatic artery and right portal vein, the transection line was determined. Parenchymal transection was performed using an ultrasonic dissector (Sonop 5000; Aloka Co., Ltd., Tokyo, Japan). No inflow or outflow occlusion was applied during the parenchymal transection. After completion of parenchymal transection, intraoperative cholangiography was performed and the presumed point of bile duct division was marked with a stainless clip to confirm adequate residual length, which is 2–3 mm on the proximal side of the bile duct, and to avoid narrowing the common bile duct of the donor. The

biliary stump and the divided hilar plate were closed by continuous 6-0 absorbable surgical sutures. A drain was inserted into the right subphrenic cavity. No dye via the cystic duct catheter was injected for a leak test.

The graft was perfused *ex situ* through the portal vein, initially with cold lactated Ringer's solution and then with cold University of Wisconsin solution (Viaspan; Dupont, Wilmington, DE, USA). Graft weight (GW) was measured on the back table.

Postoperative management

Postoperatively, the donors were observed in the surgical recovery room. To prevent serious complications, including pulmonary embolism and portal vein thrombosis, donors as case number 9 of our series received continuous intravenous infusion of 5000 units of heparin sodium per day for 2 days after hepatectomy. Intermittent mechanical leg compression was performed during the operation and until first mobilization. Liver function tests were performed on postoperative days 1, 2, 3, 7 and 10. CT was performed between postoperative days 6–14 for detecting intra-abdominal or intrathoracic fluid collection or for evaluating regeneration of the liver remnant.

Statistical analysis

Data are presented as medians with ranges in parentheses. Continuous variables were compared using a two-tailed, unpaired *t*-test for independent samples. Categorical data were compared using the chi-square test. A P-value <0.05 was considered to be significant. Correlations between continuous data were identified by linear regression analysis. All statistical analyses were performed using the StatView 5.0 software package for Windows (SAS Institute Inc., Cary, NC, USA).

Results

Fifty-five potential donors were evaluated by our protocol, and three potential donors were considered to be unsuitable as donors because of unacceptable fatty liver, insufficient remnant liver volume <30% or asymptomatic cerebral aneurysm. There was no potential donor considered to be unsuitable as a donor by reason of having vascular or biliary tract variants.

Table 1 shows the demographics of the 52 donors and grafts. The median values of remnant liver volume, estimated GV, and estimated GV-to-standard liver volume ratio were 40.7%, 749 ml and 65.3% respectively. Remnant liver volumes in eight donors were <35% of their total liver volume. The median values of determined GW and GBWR were 616 g and 1.03% respectively. The estimated GVs exceeded the determined GWs in 44 (84.6%) of the 52 donors. The values of GW were significantly correlated with those of estimated GV ($P < 0.0001$). GW was predicted by the following formula: $GW = 155.25 + 0.658 \times GV$; $r^2 = 0.489$ (Fig. 1).

In 45 donors examined by CT cholangiography, type I bile duct was found in 34 donors (66.7%). Type II, type III and type IV bile ducts were found in 3 (6.7%), 4 (8.9%) and 7 (15.6%) donors respectively. One donor had a bile duct of a combination of types III and IV, and the bile duct in this donor was classified as to be type V (Fig. 2). CT cholangiography also revealed one or two small biliary branches from the caudate lobe to the right

Table 1. Donor and graft-related profiles.

No. of case	52
Gender	
Male	31
Female	21
Age (year)*	29 (18–61)
BMI (kg/m^2)*	21.4 (17.4–27.4)
Remnant liver volume (%)*	40.7 (28.9–51.9)
Remnant liver volume <35%	8/52 (15.4%)
Estimated GV (ml)*	749 (506–1221)
Estimated GV/SLV (%)*	65.3 (38.2–95.2)
GW (g)*	616 (478–1142)
GBWR (%)*	1.03 (0.67–2.31)

BMI, body mass index; GV, graft volume; SLV, standard liver volume; GW, graft weight; GBWR, graft-to-body weight ratio.
*Values are expressed as medians with ranges in parentheses.

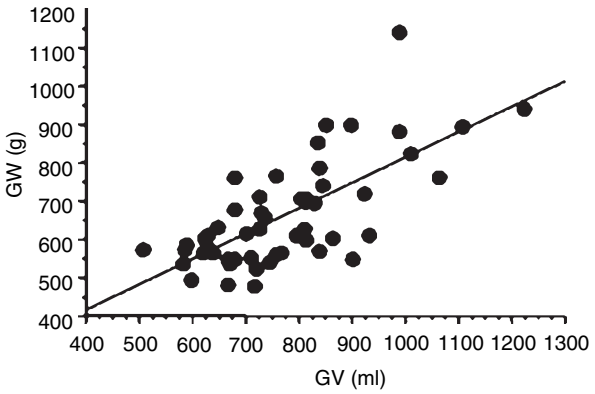

Figure 1 Regression analysis of the correlation between estimated graft volume (GV) by computed tomography and graft weight (GW) measured just after procurement in right lobe donors. The values of GW were significantly correlated with those of estimated GV ($P < 0.0001$). GW was predicted by the following formula: $GW = 155.25 + 0.658 \times GV$; $r^2 = 0.489$.

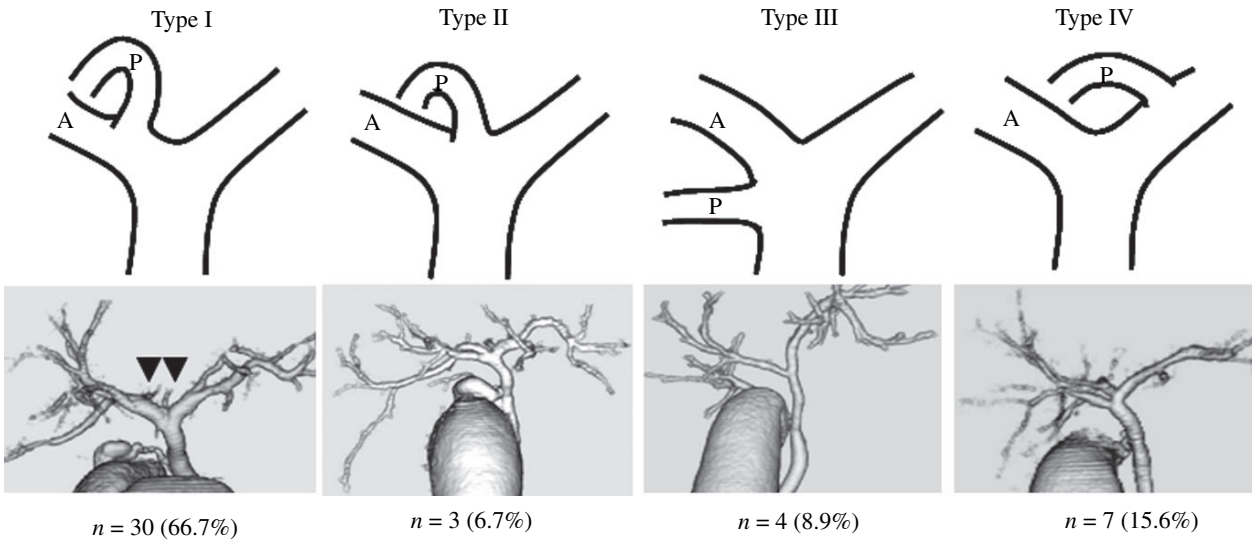

Figure 2 Biliary anatomy determined by CT cholangiography. Bile ducts in 45 donors were classified into four types based on the tributary from the posterior segment according to Nakamura's classification [13]. One donor had a bile duct of a combination of types III and IV. The figure was not shown. One-third of the donors had biliary tract variants. One or two small biliary branches from the caudate lobe to the right hepatic ducts or the confluence (arrowheads) were clearly detectable on images obtained by CT cholangiography.

hepatic ducts or the confluence in 26 (57.8%) of the 45 donors (Fig. 2).

Table 2 shows the outcomes of donor hepatectomy. The median operation time and blood loss were 415 min and 300 ml respectively. Ten (29.4%) of 34 donors whose autologous blood was preserved before the operation received autologous blood during or after the operation. No donors received homologous blood transfusion. However, one donor who suffered from postoperative bleeding followed by the formation of intra-abdominal hematoma received infusion of five units of fresh frozen plasma.

Table 2. Operation-related data and postoperative results.

No. of case	52
Operation time (min)*	415 (320–785)
Blood loss (ml)*	300 (90–2400)
Use of preserved autologous blood (%)	10/34 (29.4)
Homologuos blood transfusion	0/52 (0)
Postoperative complication (%)†	5/52 (9.3)
Intra-abdominal hematoma [*n* (grade‡)]	1 (III)
Bile leakage [*n* (grade‡)]	1 (III)
Pleural effusion [*n* (grade‡)]	1 (II)
Duodenal ulcer [*n* (grade‡)]	2 (II)
Keroid [*n* (grade‡)]	1 (I)
Reoperation rate (%)	1/52 (1.9)
Postoperative hospital stay (day)*	15 (11–24)
Re-admission rate (%)	2/52 (3.8)

*Values are expressed as medians with ranges in parentheses.
†A total of six complications occurred in five donors, resulting in an overall morbidity rate of 9.6%.
‡Postoperative complications were graded according to Broering's classification [9].

Five (9.6%) of the 52 donors had six postoperative complications, including peptic ulcer (grade II) in two donors, and bile leakage with necessity of endoscopic therapy (grade III), postoperative bleeding followed by the formation of hematoma with necessity of reoperation (grade III), pleural effusion (grade II) and keloid (grade I) each in one donor. No infectious complications such as wound infection occurred.

Changes in serum levels of total bilirubin and prothrombin time (INR) are shown in Fig. 3. Significant increases in serum total bilirubin occurred in all donors within 3 days after the operation. Three (5.8%) of the 52 donors suffered from hyperbilirubinemia (serum total bilirubin >5 mg/dl) during their early postoperative periods. However, the elevated total bilirubin level returned promptly to the preoperative value within 2 weeks after the operation in all donors (Fig. 3a). Similarly, INR that were significantly prolonged within several days after the operation returned promptly to the preoperative value within 1 week after the hepatectomies in all donors. In the case of postoperative bleeding, the values of INR were 2.20 and 2.19 on postoperative days 1 and 2 respectively (Fig. 3b). All 52 donors are alive and well for 1 month–13 years. Thirty-five of the 50 recipients are alive and 15 recipients died with a median follow-up period of 23 months.

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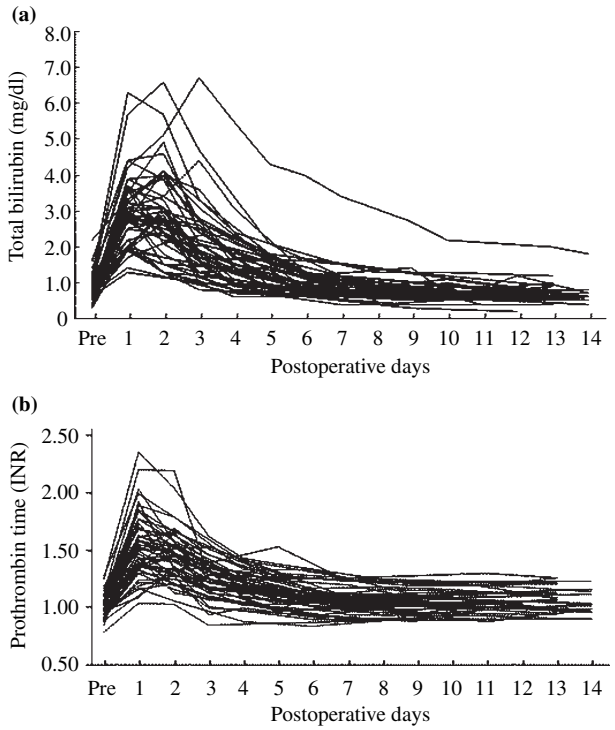

Figure 3 Changes in serum total bilirubin (a) and prothrombin time (INR) (b) before and after right hepatectomy in the 52 donors.

Discussion

Although mortality rate for donors undergoing hepatectomy has been reported to be <0.5% [2,5,8,15], the rate is far higher than that for kidney donation, which has a mortality rate of 0.03% [16]. One report claims that the mortality rate of right lobe donors is probably >1% [17]. However, the exact risk of death for donors remains uncertain because there is no worldwide registry of donor outcomes.

Precise preoperative evaluation of a donor is critical for performing LDLT successfully and safely in both the recipient and donor. Techniques and imaging modalities by which a donor liver have been estimated routinely in our adult-to-adult LDLT program include abdominal ultrasonography, CT with volumetry and CT cholangiography. Except for liver biopsy, which is mandatory for donors with fatty liver, invasive examinations such as hepatic arteriography and endoscopic retrograde cholangiopancreatography have not been performed. CT volumetry is an essential evaluation technique for both the donor and recipient. It has been reported that donor hepatectomies that exceed 70% of total liver volume led to hepatic insufficiency or death and that liver remnant volume should be kept to >30% of total liver volume [6,18]. By adhering to this policy and by precisely estimating the liver remnant volume in our program, there have been no donors in whom hepatic insufficiency occurred after hepatectomies. Several authors have reported that the incidence of hyperbilirubinemia (total bilirubin >5 mg/dl) in donors who underwent right hepatectomy ranged from 3.7% to 18.7% [3,19,20]. In the present study, hyperbilirubinemia (total bilirubin >5.0 mg/dl) occurred in three donors (5.8%) between the first and third postoperative days. None of the eight donors whose remnant liver volume was <35% suffered from postoperative hyperbilirubinemia. It is thought that the infrequent postoperative hyperbilirubinemia in our program was a result of our precise volumetric evaluation for a potential donor, our strict policy for fatty liver and small blood loss during hepatectomies.

Graft-to-body weight ratio has been used when assessing the graft size of a potential donor to be suitable for the recipient and values <0.8% have been associated with increased post-transplantation mortality [21]. As shown in the present study, estimated GV tended to be overestimated compared with GW determined after graft procurement as reported previously [22], whereas estimated GV significantly correlated with GW. The main cause of the overestimation may be related to the difference between the vital liver filled with blood *in vivo* and the graft that is in a state of collapse *ex vivo*. Moreover, since the kind of imaging modality used, the performance, and the method by which GV is measured are different in transplant programs, it is necessary to correct the error using a conversion formula calculated in each transplant program.

A systematic review has shown that reported donor morbidity rates in leading LDLT programs worldwide range from 0% to 67% and has indicated that the differences are likely to be caused by varying definitions of complications [23]. Recently, a new and strict classification of postoperative complications for donor hepatectomy has been advocated to resolve the confusion [9]. Morbidity in the present study according to the strict definition was only 9.6%, and biliary complication occurred in only one donor (1.9%). Complications in donors were more frequent in a center in which small-volume LDLT is performed [5]. In spite of our initial 52 experiences, the results are superior to those in other large series.

Biliary tract complications, including bile leakage and bile duct stricture, are the most frequent cause of morbidity in donor hepatectomy. Recent study showed that postoperative biliary complications occurred in 7–10% of donors who had undergone right hepatectomy [3,8,23]. Postoperative bile leakage can occur in the parenchymal transection surface of the liver, the repair site of the hepatic duct, and the caudate branches in the hilar plate [24]. However, bile leakage from the parenchymal transection surface of the liver rarely occurs in donor hepatectomies because the biliary ducts are not exposed on

the parenchymal transection surface as long as the parenchyma is transected along Cantlie's line. In the setting of hepatectomies except for donor hepatectomy, Lo *et al.* [25] reported that left-sided major hepatectomy was an independent risk factor for the development of postoperative bile leakage because of the risk of damaging the right posterior segment bile duct draining into the left duct. However, in donor hepatectomies, precise preoperative assessments of biliary variants using CT cholangiography make it possible to prevent this type of biliary injury. Actually, this type of variant was confirmed preoperatively by CT cholangiography in 15.6% of our donors, and no biliary injury occurred in these donors. Accordingly, in donor hepatectomies, postoperative bile leakage from caudate branches at the hilar plate is thought to be dominant, because the hepatic ducts are sharply transected very close to the confluence. CT cholangiography enabled us to identify clearly not only various types of biliary tract variant but also small biliary branches from the caudate lobe to the right hepatic ducts or the confluence in the majority of donors. Moreover, preoperative CT cholangiography combined with intraoperative cholangiography has enabled us to divide the right hepatic duct at a suitable portion. Consequently, preoperative CT cholangiography and intraoperative cholangiography resulted in a low biliary complication rate (1.9%) in our program.

Another fatal and serious complication in donors is pulmonary embolism caused by deep vein thrombosis, which can occur following any kind of operation. There has been controversial as to whether it is necessary to administer heparin to a donor during the perioperative period, though prophylactic treatment such as intermittent mechanical leg compression in a donor during the operation and until first mobilization is mandatory. In donor hepatectomy, coagulation abnormalities observed immediately after surgery may be related mostly to blood loss and to the diluting effect of intraoperative infused fluids, although the extent of resection appears to be the most important factor in the extension of the prothrombin time observed until the first postoperative day [26]. The present study showed that significant prolongation of prothrombin time occurred on the first postoperative day and values of INR > 2.0 were observed in 3 donors, although the abnormal values returned to preoperative values within 1 week after the operation. Actually, one donor sustained intra-abdominal bleeding on the first postoperative day, which was not massive but significant, and INR at that time was 2.2. Hemostasis was obtained by discontinuance of heparin administration and by administration of 400 ml banked fresh frozen plasma and 400 ml stored autologous blood. It is necessary to pay special attention to administration of heparin for donors undergoing right hepatectomy.

In conclusion, precise evaluations of liver remnant volume by CT volumetry and biliary variation at the hilum by CT cholangiography are mandatory for performing safe right hepatectomy in a donor, preventing not only serious complications such as hepatic insufficiency but also biliary tract complications. Further efforts should be put into the technical refinements in donor hepatectomy, perioperative management, and precise preoperative evaluation for donor candidates with the goal of achieving a zero complication rate. Moreover, the long-term adverse effect of loss of as much as 60% of the donor's liver on the donor's health remains unknown, and transplant centers should continue their follow-up.

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