Impact of Graft Quality and Fluid Overload on Postoperative Massive Ascites After Living Donor Liver Transplantation

Kentaro Iwaki[a], Shintaro Yagi[a,*], Satoshi Morita[b], Yuhei Hamaguchi[a], Yuki Masano[a], Gen Yamamoto[a], Eri Ogawa[a], Kazuyuki Nagai[a], Naoko Kamo[a], Koichiro Hata[a], Kojiro Taura[a], Hideaki Okajima[a], Toshimi Kaido[a], and Shinji Uemoto[a]

[a]Department of Hepatobiliary, Pancreas and Transplant Surgery, Kyoto University, Kyoto, Japan; and [b]Department of Biomedical Statistics and Bioinformatics, Kyoto University Graduate School of Medicine, Kyoto, Japan

ABSTRACT

After living donor liver transplantation, we encounter cases with massive ascites, which is difficult to manage. We analyzed the risk factors for massive ascites after living donor liver transplantation.

The subjects were 100 adult recipients who underwent living donor liver transplantation at Kyoto University Hospital from 2013 to 2017. We retrospectively assessed patient, graft, operative factors, and percent fluid overload, which were defined as [(weight on the day − preoperative weight)/preoperative weight] × 100%. We defined the massive ascites group as having a14-day average ascites ≥ 2500 mL and the mild ascites group as having a 14-day average ascites < 2500 mL.

Forty-seven patients were included in the massive group, and 53 patients were included in the mild group. There was no difference in short- and long-term survival. In multivariate analysis, the presence of preoperative ascites ($P = .0008$), 14-day average percent fluid overload ≥ 14.5% ($P = .0095$), graft-to-recipient weight ratio < 0.86 ($P = .0253$), and donors' age ≥ 47 years ($P = .0466$) were identified as independent risk factors for massive ascites after living donor liver transplantation. A liver graft with a small graft-to-recipient weight ratio or from an elderly donor, which may indicate poor graft quality, presence of preoperative ascites, and postoperative fluid overload were associated with massive ascites after living donor liver transplantation.

MASSIVE ascites develops with a high frequency after liver transplantation. There are a few studies about massive ascites after liver transplantation that report massive ascites after liver transplantation as a poor prognostic factor [1]. Some risk factors for massive ascites after living donor liver transplantation (LDLT) have been reported, including the following: preoperative ascites, portal hypertension, long operation time, intraoperative blood loss, cold ischemic time, anhepatic time, and poor preoperative liver function [1–4]. However, the impact of graft quality on massive ascites has not been fully studied. Recently, it has been reported that perioperative fluid overload increased complication and mortality [5,6]. However, there has been no study that targeted fluid in-out balance after LDLT. Therefore, the aim of this study was to analyze the risk factors, including graft quality and fluid in-out balance, for massive ascites after LDLT.

PATIENTS AND METHODS

Study Design and Patients

The data of 103 adult patients who underwent LDLT at Kyoto University Hospital from July 2013 to December 2017 were reviewed. Exclusion criteria were death within 14 days postoperatively and retransplantation. After application of these exclusion criteria, 100 patients were analyzed. The median follow-up period was 973 days (range, 25–1691 days). We defined the massive group as patients having an average ascites ≥ 2500 mL and the mild group as < 2500

*Address correspondence to Shintaro Yagi, MD, PhD, Department of Hepatobiliary, Pancreas and Transplant Surgery, Kyoto University, 54 Kawaharacho, Shogoin, Sakyo-ku, Kyoto 606-8507, Japan. Tel: (+81) 75 751 4323; Fax: (+81) 75 751 4348. E-mail: shintaro@kuhp.kyoto-u.ac.jp

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mL on the basis of the median ascites reported over 14 days after LDLT. This study was conducted in accordance with the Declaration of Helsinki following approval from our Institutional Review Board. For evaluating fluid overload, we used percent fluid overload (%FO) defined as following: %FO = [(weight on the day − preoperative weight)/preoperative weight] ×100% [7].

Surgical Procedure

For graft-to-recipient body weight ratio (GRWR), 0.6% was set as the minimum limit for a small graft [8]. A left lobe graft was the first choice. A right lobe graft was considered if the GRWR for a left lobe graft was < 0.6% and the remnant liver volume > 30%. Steatosis of the liver was assessed by the liver-to-spleen computed tomography attenuation value ratio preoperatively. Based on our previous study [9], we used the following criteria for the graft selection: a liver-to-spleen computed tomography attenuation value ratio ≤ 1.1. The biopsy of the liver graft at transplantation showed no steatosis in all patients. The surgical procedures have been described in our previous article [10]. We used a patch plasty method to prevent hepatic venous outflow obstruction [11]. Splenectomy was performed to decrease portal venous pressure (PVP) if PVP was > 15 mm Hg after the graft was put in.

Perioperative Management

Continuous administration of albumin was performed to maintain a serum albumin level ≥ 2.8 mg/dL. Supplementation of sodium was performed to maintain serum sodium level ≥ 120 mEq/dL. Patients were kept on maintenance fluid of 40–50 mL/kg/day. Diuretics were not used routinely. The immunosuppressive regimen consisted of tacrolimus and mycophenolate mofetil [12]. Abdominal drain tubes were removed when the discharge was < 500 mL per day without infection. Doppler ultrasonography was routinely performed to examine blood flow and rule out hepatic venous outflow obstruction**.** If the waveform of the hepatic vein was flat, we performed a computed tomography scan, hepatic venography, and manometry [13]**.**

Supplementation of Ascites

For ascites supplementation, bicarbonate Ringer's solution was administered intravenously in the same amount as total discharge from the drain tubes. We sometimes increased or decreased the ascites supplementation on the basis of clinical findings, such as blood pressure, urine volume, or pulmonary congestion, independently from ascites amount.

Statistical Analysis

Continuous values are expressed as median and interquartile range. Data were analyzed using JMP Pro13 software (SAS Institute, Cary, NC, United States). Student *t* test for continuous data and the χ^2 test for categorical data were used as appropriate. The cutoff values for the univariate analyses were decided using a receiver operating characteristic curve analysis. All *P* values < .05 were considered statistically significant. Data showing a significant difference in the univariate analysis were entered into a stepwise logistic regression analysis. Survival rates were assessed by the log-rank test.

RESULTS

Table 1 shows the patients' characteristics. The 90-day graft loss was 5%, and the 90-day mortality was 4%. Four patients died of infection on postoperative days (PODs) 25, 32, 67, and 90. Surgical complications above grade IIIa according to the Clavien-Dindo classification were found in 36 patients.

There was no significant difference in the prognosis between groups (*P* = .3789). One-year survival was 97.9% in

Table 1. Patients and Graft Characteristics, Operative Factors, and Postoperative Outcomes

Characteristics	Value (N = 100)
Recipient characteristics	
Recipient's age, median (IQR), y	55, 45–62
Recipient's sex, male/female	50/50
Recipient's BMI, median (IQR), kg/m^2	22.1, 20.0–25.3
Hepatitis B/hepatitis C positive, No.	8/22
Autoimmune (AIH, PBC, and PSC), No.	22
Hepatocellular carcinoma, No.	18
MELD score, median (IQR)	16, 12–21
Child-Pugh score C, No.	74
Preoperative eGFR, median (IQR), mL/min/1.73 m^2	81.9, 60.8–100.7
Preoperative albumin, median (IQR), mg/dL	2.5, 2.2–2.9
Presence of preoperative ascites, No.	62
Portosystemic collateral veins ≥ 5mm in diameter, No.	58
Graft characteristics	
Donor's age, median (IQR), y	47, 32–57
Donor's sex, male/female	48/52
Donor's BMI, median (IQR), kg/m^2	22.2, 20.7–24.1
Graft type, right/left/other	55/39/6
Graft volume, median (IQR), g	547, 440–670
GRWR, median (IQR), %	0.89, 0.72–1.04
Operative factors	
Operative time, median (IQR), min	900, 786–987
Blood loss, median (IQR), mL	5405, 3215–9414
Intraoperative fluid infusion, median (IQR), mL	11230, 8427–15305
Intraoperative urine volume, median (IQR), mL	833, 505–1304
Cold ischemic time, median (IQR), min	106, 72–178
Warm ischemic time, median (IQR), min	47, 38–56
Anhepatic time, median (IQR), min	146, 101–212
Pretransplant PVP, median (IQR), mm Hg	18, 15–22
Post-transplant PVP, median (IQR), mm Hg	13, 11–14
Splenectomy, No.	35
Postoperative outcomes	
90-day graft loss, No (%)	5 (5.0)
90-day mortality, No (%)	4 (4.0)
Rejection, No.	26
AKI, No.	9
HVOO, No.	7
Acute congestive heart failure, No.	4
Bacteremia, No.	17
Surgical complication, No.	31
14-day average ascites, median (IQR), mL	2414, 1090–4988
%FO	
14-day average %FO, median (IQR)	13.1, 7.9–18.6

Abbreviations: AIH, [autoimmune hepatitis]; AKI, acute kidney injury; BMI, body mass index; eGFR, estimated glomerular filtration rate; GRWR, graft-to-recipient body weight ratio; HVOO, hepatic vein outflow obstruction; IQR, interquartile range; MELD, model for end-stage liver disease; PBC, [primary biliary cirrhosis]; PSC, [primary sclerosing cholangitis]; PVP, portal venous pressure; %FO, percent fluid overload.

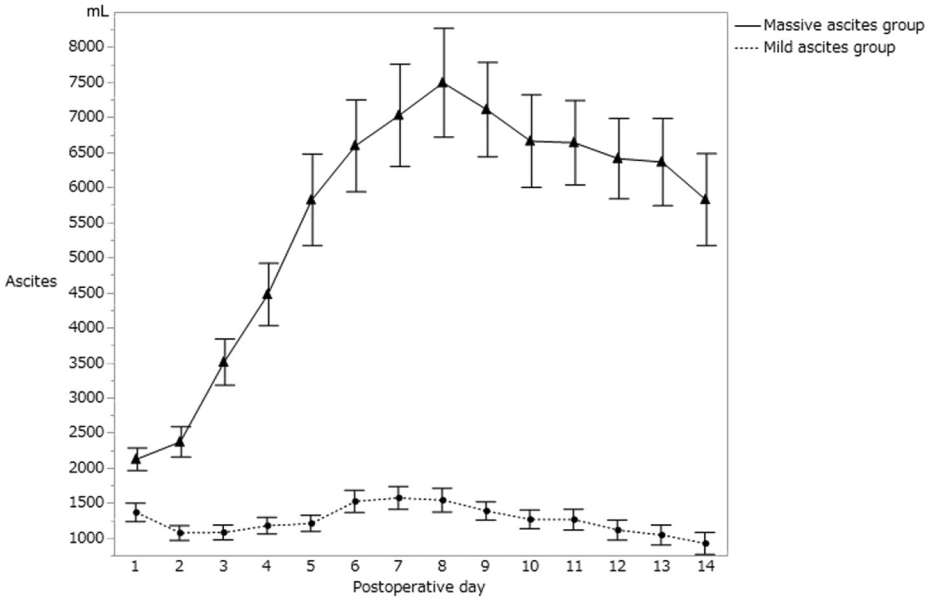

Fig 1. Serial change of the ascites volume in the first 14 days after LDLT. Two-way repeated ANOVA: $P < .0001$. ANOVA, analysis of variance; LDLT, living donor liver transplantation.

the massive group and 94.3% in the mild group. Three-year survival was 97.9% and 94.3%, respectively.

The Serial Change in Postoperative Ascites After LDLT

A total of 47 patients were included in the massive group, and 53 patients were included in the mild group. Figure 1 shows the serial change in each group's ascites until POD 14. The amount of ascites rapidly increased from POD 3, peaked on POD 9, and gradually decreased in the massive group. The serial changes of postoperative ascites showed a significant difference between the groups ($P < .0001$).

The Serial Change in Percentage of Fluid Overload After LDLT

Figure 2 shows the serial change in percentage of fluid overload (%FO) after LDLT until POD 14. The %FO in the massive group rapidly increased until POD 12. However, %FO in the mild group stayed around 10%. The serial

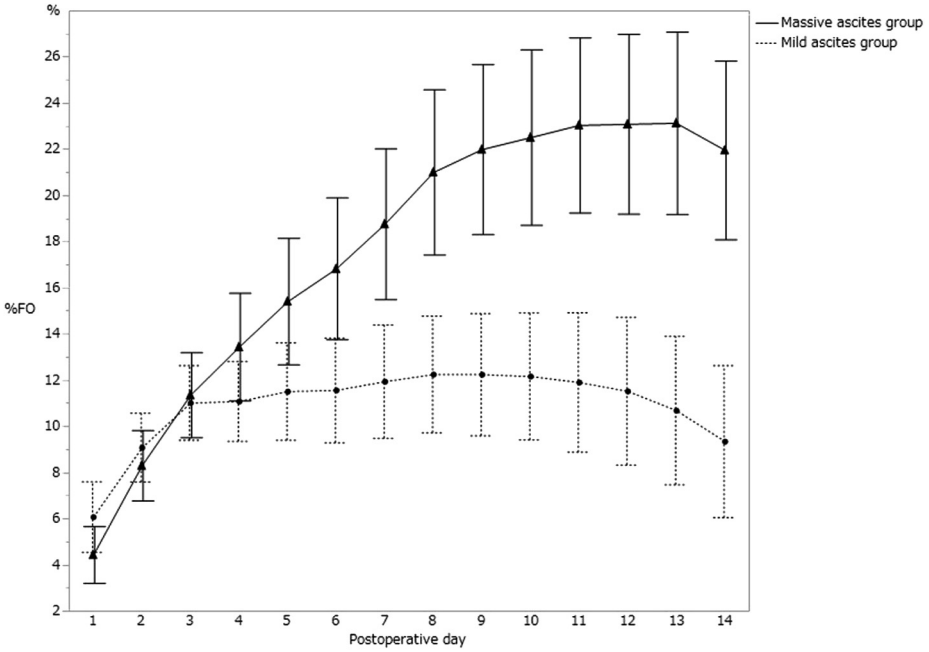

Fig 2. Serial change of %FO in the first after LDLT. Two-way repeated ANOVA: $P < .0001$. %FO, percent fluid overload; ANOVA, analysis of variance; LDLT, living donor liver transplantation.

Table 2. Univariate Analysis for Massive Ascites After LDLT

	Massive Ascites (N = 47)	Mild ascites (N = 53)	*P* Value
Recipient factors			
Recipient's age ≥ 46 y	40	34	.0153*
Recipient's age < 46 y	7	19	
Recipient's sex male/female	26/21	24/29	.3160
Recipient's BMI ≥ 25.1 kg/m^2	9	19	.0609
Recipient's BMI < 25.1 kg/m^2	38	34	
Hepatitis B positive	5	3	.3589
Hepatitis C positive	8	14	.2363
Autoimmune hepatitis	10	12	.8693
MELD score ≥ 14	32	32	.4221
MELD score < 14	15	21	
Child-Pugh score C	38	36	.1384
Preoperative eGFR ≥ 61.7 mL/min/1.73 m^2	30	42	.0861
Preoperative eGFR < 61.7 mL/min/1.73 m^2	17	11	
Preoperative albumin ≥ 2.3 dL	33	36	.8049
Preoperative albumin < 2.3 dL	14	17	
Presence of preoperative ascites	41	21	< .0001*
Presence of preoperative portal-systemic collateral veins ≥ 5 mm in diameter	26	32	.6090
Graft Factors			
Donor's age ≥ 47 y	29	21	.0269*
Donor's age < 47 y	18	32	
Donor's sex, male/female	21/26	27/26	.5314
Donor's BMI ≥ 23.8 kg/m^2	11	18	.2435
Donor's BMI < 23.8 kg/m^2	36	35	
Graft type, right/left	22/24	33/15	.0388*
Graft volume ≥ 525 g	23	37	.0234*
Graft volume < 525 g	24	15	
GRWR ≥ 0.86%	20	36	.0104*
GRWR < 0.86%	27	17	
Operative factors			
Operative time ≥ 1017 min	7	14	.1541
Operative time < 1017 min	40	39	
Intraoperative fluid infusion ≥ 18,330 mL	15	6	.0108*
Intraoperative fluid infusion <18,330 mL	32	47	
Intraoperative urine volume ≥ 563 mL	31	42	.1349
Intraoperative urine volume < 563 mL	16	11	
Cold ischemic time ≥ 190 min	12	7	.0878
Cold ischemic time < 190 min	31	44	
Warm ischemic time ≥ 53 min	14	19	.6342
Warm ischemic time < 53 min	29	32	
Anhepatic time ≥ 193 min	19	13	.1008
Anhepatic time < 193 min	28	39	
Pretransplant PVP ≥ 18 mm Hg	32	23	.0027*
Pretransplant PVP < 18 mm Hg	11	29	
Post-transplant PVP ≥ 14 mm Hg	22	13	.0109*
Post-transplant PVP < 14 mm Hg	22	39	
Splenectomy	16	19	.8500
Postoperative outcome			
90-day graft loss	3	2	.5500
90-day mortality	2	2	.9024
Rejection	14	12	.4164
AKI	3	6	.3839
HVOO	2	5	.3021
Acute congestive heart failure	4	0	.0126*
Bacteremia	6	11	.2847
Surgical complication	17	14	.2926
14-day average ascites, median (IQR), mL	5031, 3386–6524	1106, 700–2011	< .0001*
%FO			
14-day average %FO ≥ 14.5%	30	14	< .0001*
14-day average %FO < 14.5%	17	39	

Abbreviations: AKI, acute kidney injury; BMI, body mass index; eGFR, estimated glomerular filtration rate; %FO, percent fluid overload; GRWR, graft-to-recipient body weight ratio; HVOO, hepatic vein outflow obstruction; IQR, interquartile range; LDLT, living donor liver transplantation; MELD, model for end-stage liver disease; PVP, portal venous pressure.

*$P < .05$.

Table 3. Multivariate Analysis for Risk Factor of Massive Ascites After LDLT

	Odds Ratio	95% Confidence Interval	*P* Value
Presence of preoperative ascites	8.1635	2.4052–27.7081	.0008*
14-day average %FO $\geq$ 14.5%	4.2496	1.4247–12.6758	.0095*
GRWR $<$ 0.86	3.6353	1.1735–11.2612	.0253*
Donor age, $\geq$ 47 y	3.0389	1.0168–9.0827	.0466*
Recipient age $\geq$ 46 y	2.0996	0.6048–7.2885	.2428
Post-transplant PVP at LDLT $\geq$ 14 mm Hg	1.6593	0.5215–5.2798	.3911
Intraoperative fluid infusion $\geq$ 18,330 min	1.3929	0.3723–5.2117	.6225

Abbreviations: %FO, percent fluid overload; GRWR, graft-to-recipient weight ratio; LDLT, living donor liver transplantation; PVP, portal venous pressure.
*$P < .05$.

change of %FO showed significant difference between groups ($P < .0001$).

Risk Factors for Massive Ascites After LDLT

Univariate analysis identified the 11 risk factors of massive ascites after LDLT (Table 2). In the multivariate analysis (Table 3), preoperative ascites, 14-day average %FO $\geq$ 14.5, GRWR $<$ 0.86, and donor age $\geq$ 47 years were identified as independent risk factors for massive ascites after LDLT.

DISCUSSION

Preoperative ascites was an independent risk factor for massive ascites in this study. Recent studies revealed that portal hypertension leads to splanchnic vasodilation and increasing vascular permeability [14]. Additionally, it was shown that the retained fluid accumulates in the peritoneal cavity as ascites [14,15]. Although PVP is decreased after transplantation [16], microvascular changing cannot be improved rapidly after transplantation [17]. In addition, surgical stress induces systemic inflammation. Hence, splanchnic vasodilation may remain after LDLT and induce ascites.

Graft quality "graft volume and donor age" was associated with massive ascites. Ascites after LDLT was identified as a symptom of small-for-size syndrome [18]. Inflow modulation and maximizing graft outflow were reported as the keys for treating small-for-size syndrome [18]. This is the first report to find that donor age is an independent risk factor of massive ascites. Some papers have reported the impact of donor age on the prognosis after transplantation [19,20]. One advantage of younger liver grafts may be a higher regenerative potential [21]. This may be associated with developing ascites. The amount of ascites was far more massive than that at other centers [7,8]. In their cohorts, the mean and standard deviation of the donor age was younger and the graft volume was larger than in ours [3,4]. We speculate that this suggests the impact of graft quality "donor age and graft volume". Donor safety is the most important in our center. Iwasaki et al [22] reported that the donor complication rate was lower for left lobe grafts than for right lobe grafts. Accordingly, we used smaller grafts, with the smallest GRWR being 0.6% [23].

Finally, this is the first report revealing the in-out balance after LDLT. Fluid overload is an independent risk factor for massive ascites. It is difficult to decide the optimal fluid infusion after LDLT because of massive ascites, immunosuppression, drug-induced renal injury, or poor liver synthetic ability. We performed ascites supplementation, the administration of bicarbonate Ringer's solution in the same amount as ascites. Similarly, some other institutions perform the original ascites supplementation [3,4]. We speculated that too much ascites supplementation could cause more ascites after LDLT. In addition to pretransplant systemic permeability due to liver cirrhosis, severe surgical stress would induce new systemic inflammation and increase vascular permeability. Under these situations, a massive infusion of crystalloid solution can cause severe edema and ascites because almost all of the crystalloid solution cannot remain intravascular [24]. Recently, many studies have shown that postoperative fluid overload is associated with poor outcomes [5–7].

This study had several limitations. First, this is a retrospective study in a single institution, and the number of patients was limited. Second, we could not determine the optimal fluid supplementation for ascites. Therefore, further evaluation of adequate fluid intake after LDLT is needed.

CONCLUSION

In summary, preoperative ascites, postoperative fluid overload, small GRWR, and elderly donors were identified as independent risk factors for postoperative massive ascites after LDLT.

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