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Frequent plasma cell hepatitis during telaprevir-based triple therapy for hepatitis C after liver transplantation

To the Editor:

We recently read the article by Coilly *et al.* [1], who used protease inhibitors to treat recurrent hepatitis C after liver transplantation. They described that the side effects, including severe infection and anemia, frequently led to treatment discontinuation or significant dose reduction. They also reported a low sustained viral response (SVR) rate to their telaprevir-based treatment [1]. In our patients, plasma cell hepatitis (PCH) was a frequent complication. We describe our experience of telaprevir-based therapy for hepatitis C after liver transplantation, with special references to PCH.

We treated 9 patients with recurrent hepatitis C (genotype 1b) after living donor liver transplantation. The doses of telaprevir, pegylated interferon alpha 2b (PegIFNα2b) and ribavirin were 1500 mg/day, 1.5 μg/week, and 200–800 mg/day, respectively. After starting telaprevir, the cyclosporine A (CsA) dose was reduced by one-quarter to one-half from the maintenance dose [2]. CsA level was monitored 2 times a week during the introduction and completion phase of telaprevir and on a biweekly basis during other periods. One patient discontinued treatment because of viral breakthrough. Thus, rapid viral response (RVR), EVR, end-of-treatment response (ETR) and SVR_{12} were 33.3% (3/9), 88.9% (8/9), 88.9% (8/9), 88.9% (8/9), respectively.

Anemia requiring ribavirin dose reductions was observed in 55.5% (5/9) of patients, and red blood cell transfusion was performed in 44.4% (4/9) of patients. None of the patients experienced infections. However, 33.3% (3/9) of patients developed PCH during or after telaprevir-based triple therapy (Table 1). Criteria for PCH followed those established from recent reports [3–5]. Histological features of PCH are centrilobular and portal necrosis and a prominent (>30%) plasma cell aggregation [3]. Because only 6.7% (7/105) of the patients who received dual therapy using PegIFN and ribavirin developed PCH, the frequency of PCH was significantly higher ($p = 0.007$) in the patients with triple therapy. In all the patients receiving triple therapy, pre-treatment graft biopsies were obtained and ruled out for PCH and acute cellular rejection (ACR).

Case #1 had increased liver enzymes at week 21 and was treated with PegIFN-α2b and ribavirin after completing 12 weeks of telaprevir. Liver biopsy showed plasma cell aggregations around the portal triads with lymphocyte infiltration, bile duct injury, and endotheliitis, suggesting a combination of PCH and ACR. PegIFN-α2b and ribavirin were discontinued. The patient received a steroid pulse, 2000 mg/day mycophenolate mofetil (MMF), and the CsA dose level was increased to 150–250 ng/ml. The steroid pulse consisted of 1 g of methylprednisolone, followed by tapering from 200 mg to 40 mg over 5 days, and was then switched to 20 mg/day of oral prednisolone. The liver enzymes promptly stabilized and hepatitis C RNA remained negative, resulting in SVR_{12}.

Case #2 had increased liver enzymes at 31 weeks after completing triple therapy with ETR. Because a biopsy showed moderate PCH, the patient was treated similarly to Case #1. The outcomes were satisfactory, with normalization of liver enzymes and SVR_{12}.

Cases #3 and #4 had increased liver enzymes during PegIFN-α2b and ribavirin therapy. Because biopsies showed mild PCH and only a short time had elapsed after completing telaprevir, these patients were prescribed 5 mg/day of oral prednisolone, with satisfactory outcomes with SVR_{12}.

PCH is characterized by the infiltration of plasma cells around the portal triads, without apparent bile duct injury or endotheliitis. PCH was also referred to as *de novo* autoimmune hepatitis after liver transplantation [4]. However, Levitsky *et al.* [5] recently proposed the term interferon-induced graft dysfunction (IGD) for interferon-induced liver graft damage pathologically characterized by PCH, ACR, chronic rejection, or a combination of these. One of their most important findings was the poor survival of grafts with IGD and SVR, even compared with grafts without SVR. PCH, a common feature of IGD, is a serious complication during or after interferon-based treatment for hepatitis C after liver transplantation.

Levitsky *et al.* [5] reported that no prior interferon treatment, the use of PegIFNα-2a, and features consistent with PCH in pre-treatment liver biopsy were risk factors for PCH. However, Fiel *et al.* [5] reported that 80% of patients with PCH had a recent lowering of their immunosuppression protocol. Kugelmas *et al.* [6] reported that the clearance of hepatitis C virus improved hepatic microsomal function, resulting in lower immunosuppression levels [6], and that the mean decrease in the calcineurin inhibitor level after viral clearance was 32% in responders and <1% in non-responders. In fact, in Cases #3 and #4 the CsA level declined spontaneously, by 50–60%, after viral clearance, which probably caused PCH. However, the CsA levels were stable (100–150 ng/ml) in Cases #1 and #2. It is likely that the loss of the therapeutic target increased the sensitivity of the host's immune system to the transplanted graft [3]. In triple therapy including telaprevir, which has potent viral clearance activity and strong interference with calcineurin inhibitor metabolism, there might be more chances to have interferon induced PCH and IGD.

Although the accumulation of more cases is essential, we wish to highlight the possibility of PCH in patients treated with protease inhibitors for hepatitis C after liver transplantation. Because of the potential severity of PCH, close monitoring and careful adjustment of the CsA level is necessary at the start of treatment and after viral clearance. Hepatologists should be aware of this complication, and its diagnosis and treatment.

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Table 1. Characteristics of the cases with plasma cell hepatitis.

Case #	#1	#2	#3
Age, sex	52 M	64 F	55 F
HCV genotype	1b	1b	1b
Recipient/donor rs8099917	TT/TT	TG/TG	TT/TT
Outcome of previous treatment	Relapsed	Relapsed	No respond
PegIFNα2b (μg/kg/wk)	1.5	1.5	1.5
Telaprevir (mg/d)	1500	1500	1500
Ribavirin (mg/d)	400	400	200
HCV-RNA at induction (log IU/L)	6.4	5.7	6.7
Negative HCV-RNA (wk)	5	4	4
Pre-treatment graft biopsy	CH-C, G2S1	CH-C, G2S1	CH-C, G2S1
Immunosuppression regimen	CsA + MMF	CsA + MMF	CsA
CsA trough level (ng/ml)			
Before induction	102	125	160
1-12 wk	102 ± 41	128 ± 19	108 ± 24
13-24 wk	125 ± 34	110 ± 16	53 ± 9
25 wk -	153 ± 14	177 ± 62	86 ± 29
Onset of PCH (wk)	21	31	14
AST (IU/L)	168	214	113
ALT (IU/L)	161	127	97
γGTP (IU/L)	158	90	150
Total bilirubin (mg/dl)	1.3	0.8	0.8
Pathology	PCH, moderate ACR, moderate	PCH, moderate	PCH, mild
Treatment	Discontinue IFN Steroid pulse Increase CsA Add MMF	Steroid pulse Increase CsA Add MMF	Increase CsA Add steroid
Treatment response	Good	Good	Good
One month after treatment (wk)	25	35	18
AST (IU/L)	16	19	34
ALT (IU/L)	10	9	28
γGTP (IU/L)	29	45	85
Total bilirubin (mg/dl)	1.2	1.1	0.6
HCV RNA	Negative	Negative	Negative
Maintenance immunosuppression	CsA + MMF + steroid	CsA + MMF + steroid	CsA + steroid
Anti-viral treatment outcome	EVR, SVR_{12}	EVR, SVR_{12}	RVR, SVR_{12}

M, male; F, female; HCV, hepatitis C virus; CH-C, chronic hepatitis C; G, grade; S, stage; PegIFN, pegylated interferon; CsA, cyclosporine A; MMF, mycophenolate mofetil; PCH, plasma cell hepatitis; ALT, alanine aminotransferase; AST, aspartate aminotransferase; γGTP, gamma-glutamyl transpeptidase; ACR, acute cellular rejection; IFN, interferon; EVR, early viral response; SVR, sustained viral response; RVR, rapid viral response; ETR, end-of-treatment response.

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Conflict of interest

The authors who have taken part in this study declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

Authors' contribution

Toru Ikegami: study conception, design, and drafting of the manuscript.
Tomoharu Yoshizumi: study conception and design.
Ken Shirabe: critical revision of the manuscript.
Yoshihiko Maehara: final approval of the manuscript.

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Toru Ikegami*
Tomoharu Yoshizumi
Ken Shirabe
Yoshihiko Maehara
Department of Surgery and Science, Graduate School of Medical Science, Kyushu University, 3-1-1, Higashi-ku, Fukuoka 812-8582, Japan
*Corresponding author.
E-mail address: tikesurg@surg2.med.kyushu-u.ac.jp

Reply to: "Frequent plasma cell hepatitis during telaprevir-based triple therapy for hepatitis C after liver transplantation"

To the Editor:

We much appreciate Dr Ikegami and colleagues' comments on our study on the use of a first generation protease inhibitor-based regimen to treat hepatitis C (HCV) recurrence after liver transplantation (LT) [1]. One comment concerned the lack of occurrence of plasma cell hepatitis (PHC) in our series of 37 patients. Dr Ikegami reported on 9 patients treated with telaprevir (TVR), peginterferon α2b (PegIFN) and ribavirin (RBV) in a context of HCV recurrence after living donor LT. PHC occurred in 33.3% of patients (3/9) during triple therapy, compared with 6.7% (7/105) during standard PegIFN/RBV. We have developed some arguments to explain the difference between these two different findings.

A low immunosuppressive regimen is a risk factor for the development of PCH [2]. All patients in Dr Ikegami's letter received cyclosporine (CsA) ± mycophenolate mofetil (MMF). Data concerning targeted trough blood concentrations (TBC) of CsA, and the delay between triple therapy and LT, were lacking. All PHC cases reported by Dr Ikegami occurred after the discontinuation of TVR (weeks 21, 31, and 12). Despite biweekly monitoring, the mean CsA TBC in patient 3 was low after week 12 (from 53 to 86 ng/ml). Drug-drug interactions between PI and calcineurin inhibitors have always been the main challenge when using PI after LT. In the first instance, we focused on the PI initiation period to demonstrate its feasibility in terms of practical management [3]. We also looked carefully at the time of PI discontinuation. In our study, TBC were monitored daily and CsA doses were also adjusted daily to reach the target range. It was necessary to increase the CsA doses by 47% after TVR discontinuation [1]. In this context, HCV clearance might have an impact on PHC occurrence with triple therapy, but drug-drug interactions are more likely to be responsible for the excess risk found by Ikegami *et al.*

One observation in Dr Ikegami's letter was particularly surprising, and concerned the favorable outcome of PHC in all patients. This contrasted with the usually poor prognosis of PHC in a context of HCV recurrence. According to Fiel *et al.*, patients who were not treated or were receiving corticosteroids had a negative outcome. Cirrhosis was seen to develop in 60% of patients (4). According to Dr Ikegami, patients 1 and 2 were treated with steroid pulses and an increase in or addition of mycophenolate mofetil (MMF). For patient 1, we could hypothesize that acute cellular rejection (ACR) justified such a treatment. And as for patient 3, MMF and low-dose corticosteroids (5 mg) were added to CsA.

The prevalence of PHC may vary, depending on the diagnosis criteria applied. Most studies on PHC have considered that this diagnosis is based on three criteria: (1) abnormality of liver tests, (2) increased levels of immunoglobulin G and/or specific antibodies of auto-immune hepatitis, (3) compatible histological features. Dr Ikegami does not mention any serological data. Furthermore, we have some concerns about the histological findings. The authors considered that the diagnosis was based on the presence of centrilobular and portal necrosis and a prominent (>30%) plasma cell (PC) aggregation, as previously described by Fiel *et al.* [4]. In patient 1, PHC was associated with ACR. The differential diagnosis between these entities can be difficult. In severe ACR, a severe portal necro-inflammatory activity may mimic hepatitis. The infiltrate may be made up of PC, but without proper PCH. In order to clarify the histological features of PCH, we recently reported on a scoring system based on centrilobular changes such as necro-inflammatory activity (NIA) and the centrilobular PC ratio. The positive predictive value of the association of severe centrilobular NIA and a PC ratio of up to 30% was >90% [5]. In fact, we currently use these criteria to diagnose PCH.

To conclude, we agree with Dr Ikegami that PCH is a potential complication of a TVR-based antiviral regimen. For as long as an interferon-based regimen is used after LT, hepatologists should be alert to possibilities of PHC occurrence. Close monitoring of drug-drug interactions is warranted, particularly soon after PI initiation and also at the time of PI discontinuation. We also think that using stringent criteria based on serological markers and histological features is crucial to preventing a misdiagnosis of PHC.

Small Upper Midline Incision for Living Donor Hemi-Liver Graft Procurement in Adults

Toru Ikegami, MD, FACS, Ken Shirabe, MD, FACS, Yo-ichi Yamashita, MD, Tomoharu Yoshizumi, MD, FACS, Norifumi Harimoto, MD, Kazuki Takeishi, MD, Eiji Tsujita, MD, Shinji Itoh, MD, Yoshihiko Maehara, MD, PhD, FACS

Less invasiveness, including laparoscopic approaches, has been more frequently used for major surgical procedures.[1] The use of less invasive methods for living donor hemi-liver procurement (LDHP) for living donor liver transplantation (LDLT), however, is regarded as controversial because donor safety is of paramount importance and morbidity and mortality have been reported, even when LDHP is performed by expert surgeons.[2] For example, one report described an intraoperative death during laparoscopic LDHP of a living donor because of uncontrolled bleeding from the inferior vena cava (IVC).[3] Right lobe LDHP using an upper midline incision (UMI) was first reported in 2009.[4] In 2011, we began to use small UMI as a standard procedure for LDHP, not only for the right lobe, but also for left and caudate lobe LDHP. We found that this method was safe, feasible, and less invasive, and could be standardized.

METHODS

The abdomen was opened by an UMI, extending from the xiphoid to 3 to 5 cm above the umbilicus (Video 1). Although the incision was intended to be 12 cm long, it ranged from 11 to 15 cm in length depending on the sizes of the donor's abdomen and graft. Self-retaining retractors were applied to the rib edges (Kent retractor, Takasago Medical Industry Co., Ltd.) and the middle abdominal wall (Gosset retractor, Takasago Medical Industry Co, Ltd.) (Fig. 1A). The rib edges were lifted anteriorly to provide sufficient space between the abdominal wall and the liver surface for the surgeon's hands and the mobilized liver. The first assistant retracted the liver to expose the right coronary and right triangular ligaments to be dissected (Fig. 1B). The right liver was gradually rotated underneath the counter abdominal wall. At the hilum, the first Glissonean pedicle was controlled and the arterial and portal systems were dissected.

We routinely procured the caudate lobe for left lobe LDHP.[5] The lead surgeon's left hand retracted the Spiegel lobe to expose the IVC, which was counter-retracted by the 2 forceps held by the first assistant. This maneuver was essential to provide sufficient space for safe retrohepatic dissection. After controlling the conduit of the left and middle hepatic veins, a hanging tape was passed between the right and middle hepatic veins to the anterior surface of the IVC (Fig. 1C). During right lobe graft procurement, 5 mm or more of the inferior right hepatic vein was preserved. A hanging tape was passed between the anterior surface of the IVC and the liver on the left side of the right and right inferior hepatic veins (Fig. 1D).

The caudal edge of the hanging tape was subsequently passed up over the first Glissonean pedicle to lift the parenchyma for transection (Fig. 2A). The parenchyma was transected along the demarcation line using a Cavitron Ultrasonic Surgical Aspirator (CUSA; Valleylab Inc) and a saline-linked radiofrequency dissecting sealer (Tissuelink; Tissuelink Medical Inc). The traction sutures placed on both ends of the tissue to be transected were lifted, as were both ends of the hanging tape, to ensure that the transection plane was lifted sufficiently (Fig. 2B). As the parenchymal transection proceeded, the surgeon manipulated the divided parenchyma to expose the surgical field and to achieve parenchymal hemostasis. The airway pressure and central venous pressure were maintained at <15 mmHg and <5 mmHg, respectively, during parenchymal transection. Real-time cholangiography was performed after parenchymal transection, followed by the division of the hepatic duct and closure of the stump.[6] The hepatic arteries on the left lobe were ligated and divided, vascular clamps were applied to the portal and venous systems, and the graft, consisting of the left and caudate lobes, was procured. On follow-up as outpatients, all donors showed adequate wound healing (Fig. 2C). Values are expressed as means $\pm$ standard deviation.

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From the Department of Surgery and Science, Graduate School of Medical Science, Kyushu University, Fukuoka, Japan.

Correspondence address: Toru Ikegami, MD, FACS, Department of Surgery and Science, Graduate School of Medical Sciences, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka 812-8582, Japan. email: tikesurg@surg2.med.kyushu-u.ac.jp

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Abbreviations and Acronyms

IVC = inferior vena cava
LDHP = living donor hemi-liver graft procurement
LDLT = living donor liver transplantation
UMI = upper midline incision

RESULTS

Between August 2012 and October 2013, LDHP by UMI was performed in 41 donors, with left plus caudate lobes procured from 22 and right lobes from 19, as the standard approach at Kyushu University Hospital. Mean donor age was 36.7 ± 11.8 years, and 24 (58.5%) donors were male. The mean height, body weight, body mass index, and graft volume of the donors were 165.4 ± 7.8 cm, 58.2 ± 9.4 kg, 21.2 ± 2.4 kg/m^2, 479 ± 113 g, respectively. The mean length of the incision was 12.4 ± 1.3 cm (range 11 to 15 cm). Mean operative time was 298 ± 36 minutes and mean blood loss was 284 ± 189 mL, with 3 donors (7.3%) receiving auto-transfusions. Mean postoperative hospital stay was 9.3 ± 1.7 days.

Complications were observed in 4 donors, classified as Clavien–Dindo Grade II in 3 (1 each with wound infection, bronchial asthma, and intra-abdominal fluid collection) and Grade IIIb in 1 (immediate postoperative bleeding, which was treated by relaparotomy via UMI). Although all of the grafts were successfully transplanted surgically, 1 graft failed due to advanced donor age. So the cumulative 1-year graft survival rate was 96.6%.

Donors of left plus caudate lobes were significantly taller (167.5 ± 6.9 cm vs 162.9 ± 8.1 cm, p = 0.079) and heavier (62.8 ± 8.6 kg vs 52.9 ± 7.5 kg, p < 0.001) than right lobe donors. Additionally, graft volume was significantly lower (413 ± 86 g vs 555 ± 90 g, p < 0.001) and operation time was significantly longer (313 ± 24 minutes vs 287 ± 44 minutes, p = 0.048) for left plus caudate than for right lobe donors. In contrast, incision length (12.7 ± 1.5 cm vs 12.2 ± 1.6 cm, p = 0.363), operative blood loss (294 ± 230 mL vs 273 ± 131 mL, p = 0.600), and postoperative hospital stay (9.2 ± 1.6 days vs 9.3 ± 1.9 days, p = 0.957) were similar in these 2 donor groups.

Surgical outcomes of the 41 donors who underwent UMI for LDHP were compared with outcomes of 43 donors who had hockey stick incisions for LDHP between October 2011and July 2012 (Table 1). Operative time was significantly shorter in the UMI than in the hockey stick incision group (298 ± 36 minutes vs 351 ± 59 minutes, p < 0.001), but other operative factors did not differ significantly. Total postoperative fentanyl dosage for patient controlled analgesia was significantly lower

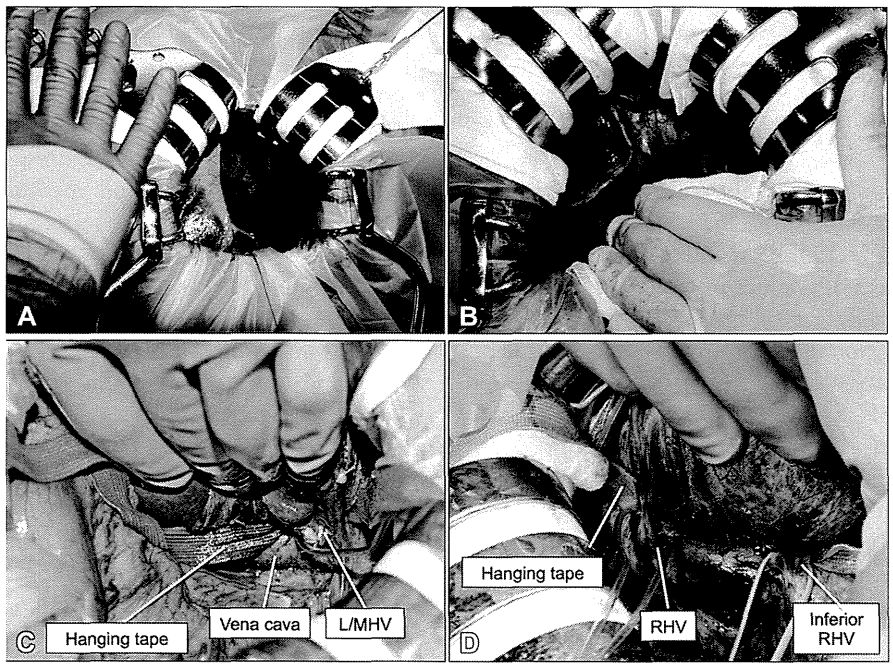

Figure 1. Initial method of upper midline incision for living donor hemi-liver graft procurement. (A) After the small upper midline incision was exposed by retractors, (B) the right lobe was mobilized. (C, D) Tapes for the hanging maneuver for obtaining grafts of the (C) left and caudate lobes and (D) the right lobe. L/MHV, left and middle hepatic vein; RHV, right hepatic vein.

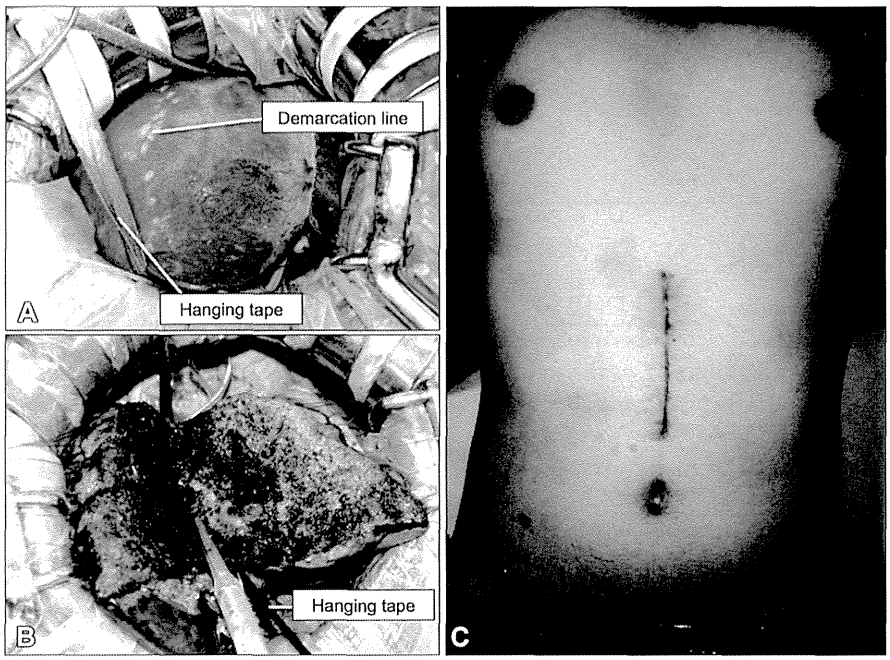

Figure 2. Later method of upper midline incision for living donor hemi-liver graft procurement. (A) The complete hanging tape was set up before parenchymal transection, and (B) parenchymal transection was performed by the hanging maneuver with traction sutures placed on both edges of the transected parenchyma. (C) View of an upper midline incision, 11 cm in length, 1 month after procurement of a left plus caudate lobe graft.

(17.2 ± 5.1 mg vs 21.1 ± 3.8 mg, $p < 0.001$) and length of hospital stay was significantly shorter (9.3 ± 1.7 days vs 11.9 ± 2.6 days, $p < 0.001$) in the UMI than in the hockey stick incision group.

DISCUSSION

Liver donation carries an inherent and considerable risk of morbidity and mortality for healthy donors.[1-3] Although laparoscopic LDHP involves smaller surgical incisions, it introduces difficulties in managing intraoperative emergencies.[1] The use of smaller UMI for LDHP may provide better potential for treating intraoperative emergencies than conventional LDHP.[4] The most important features of UMI for LDHP include its safety and feasibility, inasmuch as critical stages of the procedure, including retrohepatic venous dissection, hilar dissection, parenchymal transection, division of the hepatic duct, and organ retrieval, are performed under direct vision.

The most dangerous aspect of LDHP is retrohepatic dissection of the short hepatic veins followed by control of the major hepatic veins, because massive bleeding during the procedure is potentially fatal. During UMI-LDHP, the retrohepatic IVC could be directly observed just under the incision, making possible the control of bleeding in this area by direct holdings or suturing. The IVC can be directly and easily visualized by handling the soft donor liver. Higher positioning of the self-retaining rib retractors is key to providing sufficient space for handling or mobilizing the right lobe.[4] Although recent studies described totally laparoscopic right lobe LDHP, those studies did not include technical details about dissecting peri-IVC structures, the risks of massive bleeding from the IVC, and methods taken to reduce these risks.[7,8] Despite recent reports regarding the feasibility of a magnified laparoscopic approach around the IVC and major hepatic veins,[9,10] there are still risks of massive bleeding and gas emboli.

Mobilization of the Spiegel lobe is the most technically demanding aspect of left plus caudate lobe LDHP by UMI, because the retrohepatic space is very deep and narrow, limiting the access. However, the counter traction between the surgeon's left hand on the Spiegel lobe and the retracted IVC held by the first assistant's 2 forceps provided sufficient space for safe retrohepatic dissection. To date, laparoscopic LDHP of the left and caudate lobes has not been been reported,[11,12] although additional procurement of the caudate lobe during adult LDLT increases the graft volume.[5]

Major problems associated with total laparoscopic LDHP are the limited potential for treating bleeding from the IVC or its branches, along with possible air

Table 1. Recipient and Donor Characteristics in Cases of Living Donor Hemi-Liver Graft Procurement by Upper Midline Incision or Hockey Stick Incision

Variables	Upper midline incision (n = 41)	Hockey stick incision (n = 43)	p Value
Recipients			
Age, y	54.3 ± 11.3	50.8 ± 14.5	0.397
Sex, male, n (%)	19 (46.3)	16 (37.2)	0.396
Height, cm	166.4 ± 7.8	165.8 ± 8.4	0.667
Body weight, kg	62.4 ± 11.2	59.9 ± 12.1	0.294
MELD score	18.9 ± 7.9	17.7 ± 7.2	0.451
Donors			
Age, y	36.7 ± 11.8	38.4 ± 10.7	0.428
Sex, male, n (%)	24 (58.5)	27 (62.8)	0.689
Height, cm	165.4 ± 7.8	165.8 ± 8.4	0.667
Body weight, kg	58.2 ± 9.4	61.5 ± 9.1	0.159
Body mass index, kg/m^2	21.2 ± 2.4	22.3 ± 2.3	0.285
Left lobe graft, n (%)	22 (53.7)	23 (53.5)	0.987
GV, g	479 ± 113	478 ± 123	0.754
GV/SLV ratio, %	40.7 ± 8.0	41.7 ± 8.8	0.771
Operative time, min	298 ± 36	351 ± 59	<0.001
Blood loss, mL	284 ± 189	384 ± 276	0.077
Auto-transfusion after surgery, n (%)	3 (7.3)	1 (2.3)	0.283
Donors, postoperative			
Peak T.Bil, mg/dL	1.8 ± 0.7	2.1 ± 0.8	0.143
Peak AST, IU/L	434 ± 144	408 ± 192	0.156
Peak ALT, IU/L	470 ± 181	441 ± 176	0.582
Complications, n (%)	4 (9.8)	9 (20.9)	0.157
Wound infection, n (%)	1 (2.4)	5 (11.6)	0.078
Total fentanyl dose, mg	17.2 ± 5.1	21.1 ± 3.8	<0.001
Hospital stay, d	9.3 ± 1.7	11.9 ± 2.6	<0.001

Data are presented as mean ± SD.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; GV, graft volume; MELD, Model for End-Stage Liver Disease; SLV, standard liver volume; T.Bil, total bilirubin.

embolism.[7-12] Although total laparoscopic LDHP interests surgeons because of its technical features, several hurdles must be overcome to ensure perfect safety before it can become a standard LDHP procedure. During hybrid LDHP, however, the liver is mobilized laparoscopically, with or without dissection of the retrohepatic IVC.[13-16] Mobilization of the right liver followed by retrohepatic dissection and control of the major hepatic veins under hand-assisted laparoscopic procedures has been reported[13,14]; another group mobilized only the liver under hand-assisted laparoscopy.[15] These procedures could be performed by UMI, without any special instruments, by extending the incision a few centimeters. Right lobe LDHP via a midline incision has been reported for smaller donors, with laparoscopic assistance required only for right lobe mobilization from larger donors.[16]

In UMI-LDHP, bloodless parenchymal transection can be achieved with low intrahepatic venous pressure, with hemostasis made effective using a dissecting sealer. Low intrahepatic venous pressure can be realized by pulling up the liver (eg, inserting pads into the subphrenic space, using traction sutures on the transected liver edges, and/or using a hanging maneuver) and by keeping airway and central venous pressure low. Such tactics are important in UMI because the liver cannot be manually held up as high as it can in a conventional J-shaped incision.[17] These technical refinements may enable UMI-LDHP to be performed with a blood loss <300 mL.

During totally laparoscopic LDHP, the possible cutting lines of the hepatic duct are very limited.[11] During hilar dissection in UMI-LDHP, however, the hepatic duct is controlled by subtracting the hepatic artery and portal vein from the corresponding Glissonean pedicle, followed by intraoperative cholangiography using a high-definition C-arm unit and division of the hepatic duct, as in conventional LDHP.[6] The cut edge of the hilar plate, including the hepatic duct and several caudate biliary branches, is closed by carefully placing continuous

sutures to prevent biliary leakage.[6] Indeed, none of the 41 donors who underwent LDHP by UMI experienced biliary complications. The vessels are clamped and then divided, and the hemi-liver graft is retrieved from the UMI. So performance of these critical procedures in UMI-LDHP is similar to that in conventional LDHP.

CONCLUSIONS

In conclusion, LDHP by UMI is a secure, feasible, and less invasive surgical technique for adult-to-adult LDLT, and may become a standardized approach.

Author Contributions

Study conception and design: Ikegami, Shirabe, Yamashita
Acquisition of data: Harimoto, Takeishi, Tsujita
Analysis and interpretation of data: Ikegami, Yoshizumi, Itoh
Drafting of manuscript: Ikegami
Critical revision: Shirabe, Yamashita, Maehara

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D-MELD as a Predictor of Early Graft Mortality in Adult-to-Adult Living-Donor Liver Transplantation

Toru Ikegami,[1,2] Daisuke Imai,[1] Huanlin Wang,[1] Tomoharu Yoshizumi,[1] Yo-ichi Yamashita,[1] Mizuki Ninomiya,[1] Tomohiro Iguchi,[1] Yuki Bekki,[1] Ken Shirabe,[1] and Yoshihiko Maehara[1]

Background. Ensuring a good match between donor and recipient is critically important to achieve acceptable graft outcomes after living-donor liver transplantation (LDLT). Our objective was to evaluate the product of donor age and Model for End-stage Liver Disease score (D-MELD) as a predictor of graft survival after LDLT.

Methods. We retrospectively evaluated the records of 355 adults who underwent LDLT for chronic liver disease and explored the relationship between D-MELD and graft outcome.

Results. High MELD score and advanced donor age were significantly associated with graft survival; D-MELD had the strongest association with in-hospital mortality. Receiver operating characteristic curve analysis showed that a D-MELD score of 462 had the highest sensitivity for predicting in-hospital mortality. Patients were allocated to three groups based on D-MELD (Class A [≤449; n=142], Class B [450–899; n=163], and Class C [≥900; n=50]) and were found to have stratified cumulative 2-year graft survivals of 94.1%, 85.3%, and 63.1%, respectively ($P<0.01$). Although D-MELD Class C patients had larger graft volume-to-standard liver volume ratio ($P<0.01$) and received right lobe grafts more often ($P<0.01$), they still exhibited significantly higher rates of primary graft dysfunction ($P<0.01$) and in-hospital mortality ($P<0.01$). Outcomes in D-MELD Class C were significantly worse in hepatitis C–positive patients ($P<0.05$).

Conclusions. The D-MELD score is a simple and reliable predictor of early graft survival that assists the matching of donors and recipients in LDLT in adults.

Keywords: Living-donor liver transplantation, Donor age, MELD, Primary graft dysfunction.

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There are a number of factors that influence graft outcome after liver transplantation (*1–3*). In living-donor liver transplantation (LDLT), these include poor recipient condition, smaller graft volume (GV), and advanced donor age (*4–7*). When planning a procedure, however, these factors need to be considered together rather than individually (*4*). The decision to undertake LDLT can be difficult when the living-donor graft is marginal and the recipient is judged to be at high risk of complications.

In the United States, the Model for End-stage Liver Disease (MELD) score has been used to quantify the severity of recipient disease objectively and to prioritize organ allocation in patients awaiting deceased-donor liver transplantation (DDLT) (*8*). In recognition that donor factors also affect outcome after liver transplantation, Halldorson et al. used the product of MELD score and donor age (D-MELD) to predict outcome after DDLT and reported that a D-MELD score in excess of 1600 was associated with poor graft outcome (*3*). In LDLT, there is, as yet, no simple means of predicting graft survival during donor–recipient matching, although this is a critical step in achieving the most favorable graft outcomes.

We hypothesized that the D-MELD score could also be used to quantify an incremental gradient of risk of graft dysfunction and mortality after LDLT.

RESULTS

Factors Associated with Short-term Graft Survival

Factors that could be evaluated preoperatively to predict short-term outcome after LDLT are shown in SDC 1

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[1] Department of Surgery and Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan.

[2] Address correspondence to: Toru Ikegami, M.D., Department of Surgery and Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka 812-8582, Japan.

E-mail: tikesurg@surg2.med.kyushu-u.ac.jp

T.I. participated in the study concept and design and drafting of the article. D.I., T.Y., and K.S. participated in the critical revision of the article. H.W. participated in the statistical analyses. Y.Y., M.N., T.I., and Y.B. participated in the data collection. Y.M. participated in the final approval of the article.

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