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Risk factors for acute renal injury in living donor liver transplantation: evaluation of the RIFLE criteria

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Keywords
acute renal failure, liver transplantation, living donor, RIFLE criteria.

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Summary

Acute renal injury (ARI) is a serious complication after liver transplantation. This study investigated the usefulness of the RIFLE criteria in living donor liver transplantation (LDLT) and the prognostic impact of ARI after LDLT. We analyzed 200 consecutive adult LDLT patients, categorized as risk (R), injury (I), or failure (F), according to the RIFLE criteria. ARI occurred in 60.5% of patients: R-class, 23.5%; I-class, 21%; and F-class, 16%. Four patients in Group-A (normal renal function and R-class) and 26 patients in Group-B (severe ARI: I- and F-class) required renal replacement therapy ($P < 0.001$). Mild ARI did not affect postoperative prognosis regarding hospital mortality rate in Group A (3.2%), which was superior to that in Group B (15.8%; $P = 0.0015$). Fourteen patients in Group B developed chronic kidney disease (KDIGO stage 3/4). The 1-, 5- and 10-year survival rates were 96.7%, 90.6%, and 88.1% for Group A and 71.1%, 65.9%, and 59.3% for Group B, respectively ($P < 0.0001$). Multivariate analysis revealed risk factors for severe ARI as MELD ≥20 [odds ratio (OR) 2.9], small-for-size graft (GW/RBW <0.7%; OR 3.1), blood loss/body weight >55 ml/kg (OR 3.7), overexposure to calcineurin inhibitor (OR 2.5), and preoperative diabetes mellitus (OR 3.2). The RIFLE criteria offer a useful predictive tool after LDLT. Severe ARI, defined beyond class-I, could have negative prognostic impact in the acute and late postoperative phases. Perioperative treatment strategies should be designed and balanced based on the risk factors for the further improvement of transplant prognosis.

Introduction

Acute renal injury (ARI) is a serious complication after liver transplantation. Several studies have demonstrated an association between ARI and increased mortality rates after cadaveric liver transplantation [1–3]. The incidence of postliver transplant ARI has been reported with a wide range in the literature, because of the use of different definitions and parameters [4–8]. Until recently, more than 30 different definitions of ARI have been used in the literature. This lack of common reference points has created confusion and complicated the interpretation of findings. It has also led to strong advocacy for a consensus definition. In response to the need for common definitions and classifications of ARI, the Acute Dialysis Quality Initiative group of experts (http://www.adqi.net) developed a consensus definition for ARI in critically ill patients (the RIFLE criteria) based on changes in glomerular filtration rate (GFR) and/or urine output. RIFLE is an acronym for "risk of renal dysfunction, injury to the kidney, failure of the kidney, loss of the kidney and end-stage kidney disease" [9]. These criteria have been evaluated in several studies, showing that acute kidney disease is associated with significantly higher mortality rates [10–12]. Several studies have also demonstrated that ARI is associated with the development of chronic kidney disease (CKD) [13,14].

These criteria can be suitable for cadaveric liver transplantation [13,15,16]. In living donor liver transplantation (LDLT), graft size seems to be an indispensable factor for predicting post-transplant ARI and prognosis, in addition to the conventional risk factors [17]. Despite the important implications of the RIFLE criteria for cadaveric liver transplantation, no studies have yet dealt with LDLT; however, the RIFLE criteria are also expected to serve as a useful prognostic predictor after LDLT. The aim of this study was to clarify the usefulness of the RIFLE criteria in LDLT and to determine risk factors for ARI after LDLT. This study also focused on evaluating the relationship between ARI and post-transplant mortality, the influence of ARI on CKD, and late postoperative phase prognosis.

Materials and methods

Patients

In this retrospective analysis, we reviewed 200 consecutive adult patients undergoing LDLT at Okayama University Hospital between August 1996 and January 2011. The study subjects comprised 57.8% men (overall mean age, 49.2 ± 11.8 years). Indications for LDLT in these patients included postnecrotic liver cirrhosis (n = 126; 63%), cholestatic disease (n = 39; 19.5%), acute liver failure (n = 24; 11.9%), and metabolic disorder (n = 11; 5.5%). Among the patients with postnecrotic liver cirrhosis, hepatitis C virus (HCV) was the predominant etiology (n = 62; 49.2%). Hepatocellular carcinoma (HCC) accounted for 48.4% (n = 61) of all cirrhotic patients.

In terms of surgical technique and postoperative care, the procedures and protocols were followed as described previously, with minor modifications [18–21]. In the donor procedure, parenchymal dissection was performed without hepatic inflow occlusion, followed by graft procurement. In the recipient procedure, the native liver was resected, preserving the inferior vena cava. After reconstructing the hepatic and portal veins, the hepatic artery was anastomosed under microscopy. The biliary tract was reconstructed. During the postoperative period, the initial immunosuppressive regimen consisted of tacrolimus or cyclosporine and a short course of steroids, tapering over 3–6 months. The dosage was carefully adjusted according to the drug trough level, targeting trough levels of 10–12 ng/ml for tacrolimus and 150–200 ng/ml for cyclosporine. Whole-blood tacrolimus or cyclosporine drug trough levels were measured at 12 h after administration of the drug during the postoperative acute phase. Averaged calcineurin inhibitor (CNI) trough level represented the whole blood concentration within the first month or prior to develop ARI. The measurement protocol for CNI which had undergone the following changes is now affinity column-mediated immunoassay method. During the period between 1998 and 2003, both agents were measured by enzyme-linked immunosorbent assay method which was substituted by microparticle enzyme immunoassay method in tacrolimus and by monoclonal fluorescence polarization immunoassay method up to 2008. Concerning measurement protocol for CNI, new measurement technologies have been developed within the study period. In this study, the historical bias between the measurement protocols could seem to be allowable [22–26]. We introduced mycophenolate mofetil (MMF) in August 2002 and used MMF for every patient for initial immunosuppression. The main purpose of the MMF was to diminish the CNI dosage and lower the CNI trough levels to avoid any adverse events related to CNI. MMF was administered to some patients in whom the trough levels of CNI diminished to 70–80%. In our protocol, MMF is started from 5 to 7 days after LDLT. In cases of ARI, early renal replacement therapy (RRT) was introduced as support until the kidneys recovered function. The choice of intermittent hemodialysis or continuous RRT was based on the hemodynamic stability of the patient.

All 200 LDLT recipients were classified according to these RIFLE criteria using the worst value of renal function within 28 days after LDLT. Because classes L and E should be used to denote persistent disease for more than 4 weeks, all patients were classified in classes R to F rather than classes L or E in this study. After follow-up for 1 year following LDLT, patients with persistent chronic kidney dysfunction were classified according to the KDIGO Clinical Practice Guidelines as CKD stage 3 if the GFR was 30–59 ml/min; CKD stage 4 if the GFR was 15–29 ml/min; and CKD stage 5 if GFR was <15 ml/min or dialysis, depending on the last value of the GFR [27,28].

Statistical analysis

Nonparametric methods were used for inferential analysis. Continuous variables were evaluated using the Mann–Whitney test, and categorical data were compared by the chi-squared test. Overall survival rates were estimated by the Kaplan–Meier method and compared using the log-rank test. Sixteen clinical variables potentially associated with the occurrence of severe ARI were adopted for multivariate logistic regression analysis, after employment of cut-off values for continuous variables using ROC analysis. Cutoff values of concentration for the overexposure to CNI were determined by ROC analysis for ARI, referring to previous reports [29–32]. And the rate of overexposure to CNI was defined as patient proportion with averaged tacrolimus trough >10 ng/ml or with cyclosporine trough >200 ng/ml. The variables examined were age, sex, background disease, Model for End-stage Liver Disease (MELD) score, pre-existence of insulin-controlled diabetes mellitus and hypertension at transplantation, donor age, graft and graft volume,

blood loss, operative time, graft ischemic time, initial immunosuppressive agent, overexposure to CNI, and combined use of MMF. All 16 variables were entered into the multivariate analysis, even if deemed insignificant on univariate analysis, because of the potential importance of each variable [33]. All statistical analyses were performed using JMP software (release 6.0.3; SAS Institute Japan, Tokyo, Japan). Values of $P < 0.05$ were regarded as significant.

Results

Pre- and postoperative renal function and postoperative course

During the 28 days of postoperative follow-up, ARI, as determined by the RIFLE criteria, occurred in 121 (60.5%) of the study patients. The numbers of patients with ARI in the R-class, I-class, and F-class were 47 (38.8%), 42 (34.7%), and 32 (26.4%), respectively. The 1- and 5-year survival rates were 97.5% and 90.6% in the N-class, 95.7% and 89.2% in the R-class, 85.7% and 81.8% in the I-class, and 50.0% and 46.7% in the F-class, respectively (Fig. 1). Fatal outcomes in early post-transplant phase were seen in two cases in the N-class, two cases in the R-class, two cases in the I-class, and 10 cases in the F-class. Overall survival rates in the R-class were comparable to the rates in the N-class, and the survival rates in these groups were superior to those in the other classes. We therefore defined the combination of the N- and R-classes as the normal kidney function or mild ARI group (Group A, $n = 126$) and the combination of the I- and F-classes as the severe ARI group (Group B, $n = 74$). The 30 patients (15%) who required postoperative RRT in the acute postoperative phase comprised four Group A patients and 26 Group B patients. Every patient recovered from ARI, and no recipient required permanent RRT at 1-year follow-up. However, the rates of development to stage 3/4 CKD were 0.8% (1 of 126 patients) in Group A and 19% (14 of 74 patients) in Group B, respectively.

The in-hospital mortality rate was significantly lower for Group A (3.2%) than for Group B (15.8%; $P = 0.0015$). All cases of hospital mortality resulted from postoperative sepsis and/or graft perfusion obstruction, which were followed by graft failure. The 1-, 5- and 10-year survival rates were 96.7%, 90.6%, and 88.1% for Group A and 71.1%, 65.9%, and 59.3% for Group B, respectively. Group A showed more favorable post-transplant outcomes than Group B ($P < 0.0001$; Fig. 1). Late-phase mortality after follow-up for 1 year following LDLT was seen in nine patients (7%) in Group A and 14 patients (22%) in Group B as a result of HCV relapse, HCC recurrence, heart failure, *de novo* cancer, and chronic rejection. Forty-three percent of recipients with stage 3/4 CKD (6 of 14 patients) in Group B showed fatal outcomes in the chronic-phase, compared with uniformly satisfactory prognosis in Group A (Fig. 1). Unfortunately, each of these patients would have limited options for treatment modalities because of poor renal function, although the patients with chronic-phase deaths in Group A had a similar situation.

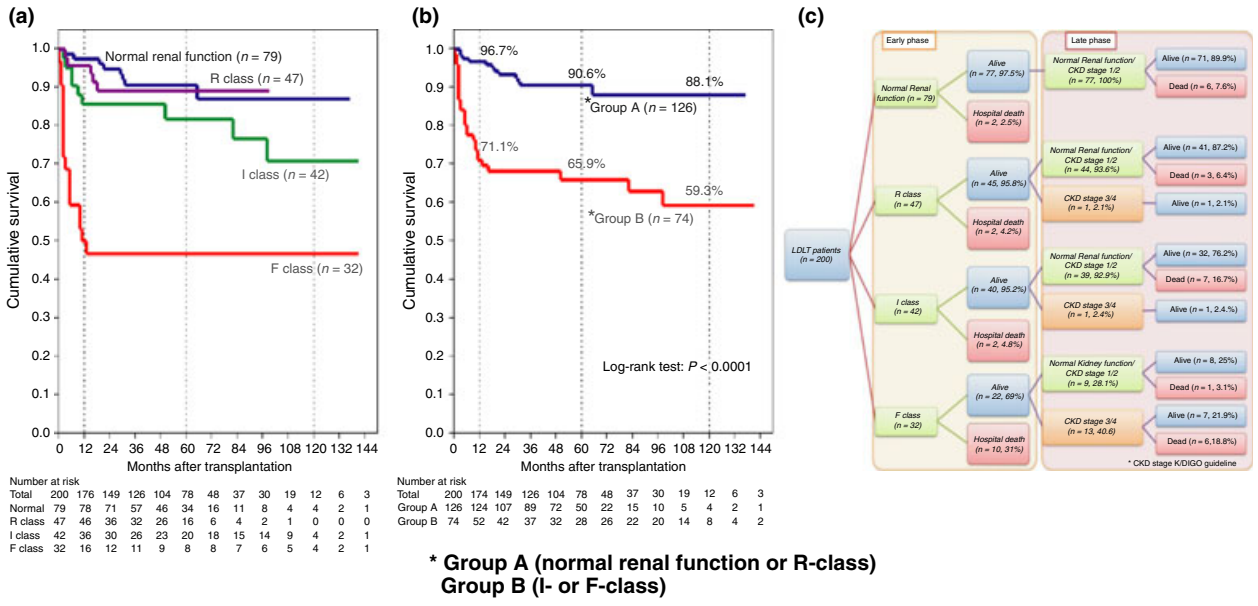

Figure 1 Overall survival curves and diagram of post-transplant prognosis. (a) Comparison of cumulative overall survival curves stratified by RIFLE criteria. (b) The patients were divided into two groups: Group A (normal renal function or R-class); and Group B (I- or F-class). Comparison of cumulative overall survival curves between Group A and Group B. (c) Diagram of prognosis for all patients after LDLT. LDLT, living donor liver transplantation.

Risk factors for severe ARI after LDLT

The background data for patients relevant to the RIFLE criteria are shown in Table 1. The results of univariate analysis of the studied variables for Groups A and B are summarized in Table 2. The patients in Group B had significantly higher MELD scores and higher frequency of insulin-controlled diabetes mellitus, but no other preopera-

Table 1. Demographic characteristics of patients according to RIFLE criteria.

	Normal renal function (n = 79)	R-class (n = 47)	I-class (n = 42)	F-class (n = 32)
Preoperative factors				
Age (years)	49.6 ± 1.3	51.0 ± 1.7	48 ± 1.6	47.9 ± 2.01
Sex				
Male/female (%)	54 (68)/25 (32)	24 (51)/23 (49)	21 (50)/21 (50)	16 (50)/16 (50)
Background disease				
Postnecrotic liver cirrhosis	50 (63%)	32 (68%)	26 (62%)	18 (56%)
HCV	22	16	13	11
HBV	22	4	7	2
Alcohol or non-HBV/HCV	6	12	6	5
Cholestatic disease	16 (20%)	8 (17%)	6 (14%)	9 (28%)
Acute liver failure	7 (9%)	6 (13%)	6 (14%)	5 (16%)
Metabolic disease	6 (8%)	1 (2%)	4 (10%)	0
MELD score	15.2 ± 0.8	15.4 ± 0.8	17.1 ± 0.9	18.2 ± 1.2
HCC (%)	25 (32)	13 (28)	15 (36)	8 (25)
Serum creatinine level (mg/dl)	0.85 ± 0.05	0.71 ± 0.05	0.71 ± 0.04	0.89 ± 0.13
GFR (ml/min)	75.9 ± 4.4	74.1.1 ± 4.5	70.5 ± 4.3	70.9 ± 6.9
Serum albumin level (g/dl)	3.0 ± 0.07	2.9 ± 0.07	2.8 ± 0.08	2.7 ± 0.11
Hypertension (%)	12 (15)	2 (4)	5 (12)	3 (9)
Diabetes mellitus (%)	4 (5)	7 (15)	9 (21)	3 (9)
Donor/graft factors				
Age (years)	38.3 ± 1.5	39.7 ± 1.8	39.2 ± 1.8	43.0 ± 2.3
Right/left lobe graft (%)	57 (72)/22 (28)	24 (51)/23 (49)	23 (55)/19 (45)	20 (62)/12 (38)
GW/RBW (%)	0.98 ± 0.03	0.87 ± 0.03	0.95 ± 0.05	0.91 ± 0.04
Operative factors				
Operative time (min)	567 ± 12.5	571 ± 13.6	674 ± 24.3	712 ± 79.1
Blood loss (ml/kg)	97.0 ± 18.2	91.0 ± 12.4	164.7 ± 22.8	130 ± 31.2
Cold ischemic time (min)	61.9 ± 4.2	60.2 ± 6.5	71.6 ± 10.2	82 ± 9.1
Warm ischemic time (min)	42.3 ± 1.6	44.2 ± 2.5	43.6 ± 2.2	43.1 ± 2.8
Transplant period				
Early/late period (%)*	42(53)/37(47)	17(36)/30(64)	23(55)/19(45)	18(56)/14(44)
Postoperative factors				
Initial induction of CNI				
Tacrolimus/cyclosporine (%)	61 (77)/18 (23)	33 (70)/14 (30)	32 (76)/10 (24)	27 (84)/5 (16)
Average CNI trough (ng/ml)				
Tacrolimus	9.6 ± 0.2	9.7 ± 0.46	10.5 ± 0.49	10.8 ± 0.59
Cyclosporine	188.6 ± 10.9	179.2 ± 11.0	177.0 ± 37.4	157.5 ± 16.4
Overexposure to CNI†	29 (36%)	18 (38%)	25 (59%)	18 (56%)
MMF use (%)	54 (68)	42 (89)	21(50)	19 (59)
Biopsy-proven rejection (%)	26 (13)	12 (6)	9 (4.5)	9 (4.5)
Clinical outcomes				
RRT (%)	2 (2.5)	2 (4.2)	6 (14)	20 (63)
Progression to L/E class	0	0	0	2 (6%)
Hospital stay (days)	56 ± 4.2	63 ± 6.0	76 ± 7.8	80 ± 10.5
Hospital mortality (%)	2 (2.5)	2 (4.2)	2 (4.8)	10 (31)
Progression to CKD (%)‡	0	1 (2)	1 (3)	13 (59)
Late-phase mortality (%)	6 (8)	3 (7)	7 (18)	7 (32)

CNI, calcineurin inhibitor; GW/RBW, graft weight-to-recipient body weight ratio; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; MMF, mycophenolate mofetil; RRT, renal replacement therapy.

*The first and second half of 200 cases.

†Averaged concentration: tacrolimus trough >10 ng/ml or cyclosporine trough >200 ng/ml within the first month.

‡Chronic kidney disease (KDIGO stage 3/4).

Table 2. Univariate analysis of variables between Group A and Group B.

	Group A (n = 126)	Group B (n = 74)	P-value
Preoperative factors			
Age (years)	49.6 ± 12.72	48.5 ± 10.8	0.530
Sex			
Male/female (%)	78 (62)/48 (38)	37 (50)/37 (50)	0.100
Body mass index (kg/m^2)	23.8 ± 3.3	24.0 ± 4.2	0.750
Background disease			
Postnecrotic liver cirrhosis	82 (65%)	44 (59%)	0.711
Cholestastic disease	24 (19%)	15 (20%)	
Acute liver failure	13 (10%)	11 (15%)	
Metabolic disease	7 (5%)	4 (5%)	
MELD score	15.1 ± 7.6	19.1 ± 0.8	<0.001
HCC (%)	38 (30)	23 (32)	0.843
Serum creatinine level (mg/dl)	0.79 ± 0.4	0.78 ± 0.5	0.870
GFR (ml/min)	75.1 ± 3.1	73.7 ± 3.9	0.388
Serum albumin level (g/dl)	2.98 ± 0.6	2.82 ± 0.6	0.078
Hypertension (%)	14 (11)	8 (11)	0.948
Diabetes mellitus (%)	10 (8)	13 (18)	0.039
Donor/graft factors			
Age (years)	38.5 ± 12.8	41.1 ± 12.5	0.156
Right/left lobe graft (%)	81 (64)/45 (36)	43 (58)/31 (42)	0.385
GW/RBW (%)	0.94 ± 0.27	0.92 ± 0.26	0.727
Operative factors			
Operative time (min)	565.3 ± 105.7	662.9 ± 156.6	<0.001
Blood loss (ml/kg)	95.5 ± 136.2	147.2 ± 153.9	0.017
Cold ischemic time (min)	63.5 ± 38.3	78.8 ± 55.6	0.039
Warm ischemic time (min)	42.2 ± 15.2	44.4 ± 14.7	0.465
Transplant period			
Early/late period (%)*	59 (47)/67 (53)	41 (55)/33 (44)	0.241
Postoperative factors			
Initial induction of CNI			
Tacrolimus/Cyclosporine (%)	94 (75)/32 (25)	59 (80)/15 (20)	0.409
Average CNI trough (ng/ml)			
Tacrolimus	9.4 ± 0.2	10.6 ± 0.3	0.008
Cyclosporine	182.0 ± 6.9	171.4 ± 8.9	0.315
Overexposure to CNI†	47 (37%)	43 (58%)	0.004
MMF use (%)	96 (76)	40 (54)	0.001
Biopsy-proven rejection (%)	37 (18.5)	19 (9.5)	0.574
Biliary fistula (%)	17 (13.5)	6 (8.1)	0.249
Major vascular complication (%)‡	11 (8.7)	10 (13.5)	0.287
Clinical outcomes			
RRT (%)	4 (3)	26 (35)	<0.001
Hospital stay (days)	69.7 ± 48.5	101.5 ± 68.8	<0.001
Hospital mortality (%)	4 (3)	12 (16)	0.001
Progression to CKD (%)§	1 (1)	14 (19)	<0.001
Late-phase mortality (%)	9 (7)	14 (22)	0.004

CNI, calcineurin inhibitor; GW/RBW, graft weight-to-recipient body weight ratio; HCC, hepatocellular carcinoma; MMF, mycophenolate mofetil; RRT, renal replacement therapy.

*The first and second half of 200 cases.

†Averaged concentration: tacrolimus trough >10 ng/ml or cyclosporine trough >200 ng/ml within the first month.

‡Hepatic artery, portal and hepatic vein stenosis needed surgical or radiological intervention.

§Chronic kidney disease (KDIGO stage 3/4).

tive factors appeared significant. Despite higher MELD score in Group B, preoperative serum creatinine (sCr) and GFR did not differ between the two groups. Among donor/graft and operative factors, operative time, blood loss, graft cold ischemic time, and use of MMF seemed to be significant factors related to severe ARI in univariate analysis. In

Table 3. Multivariate logistic regression analysis of variables associated with severe ARI.

	Number	Odds ratio	95% CI	*P*-value
Recipient age (years)				
<50	80	1	–	
≥50	120	0.58	0.22–1.45	0.247
Sex				
Male	115	1	–	
Female	85	1.91	0.79–4.71	0.149
Background disease				
Postnecrotic liver cirrhosis	126	1	–	–
Cholestatic disease	39	0.66	0.20–2.03	0.475
Acute liver failure	24	2.65	0.72–10.2	0.138
Metabolic disease	11	0.30	0.41–1.77	0.475
MELD score				
<20	158	1	–	
≥20	42	2.96	1.19–7.63	0.019
Hypertension				
No	178	1	–	
Yes	22	1.01	0.27–3.58	0.993
Diabetes mellitus				
No	177	1	–	
Yes	23	3.23	1.02–10.7	0.044
Donor age (years)				
<50	142	1	–	
≥50	58	0.91	0.38–2.12	0.839
Graft				
Right lobe graft	124	1	–	
Left lobe graft	76	1.56	0.64–3.81	0.321
Graft volume (GW/RBW, %)				
≥0.7	164	1		
<0.7	36	3.10	1.04–9.79	0.042
Operative time (h)				
<10	105	1	–	
≥10	95	1.13	0.47–2.69	0.776
Blood loss/body weight (ml/kg)				
<55	82	1	–	
≥55	118	3.70	1.53–9.53	0.003
Cold ischemic time (min)				
<80	149	1	–	
≥80	51	2.32	0.96–5.72	0.058
Warm ischemic time (min)				
<50	152	1	–	
≥50	48	1.00	0.39–2.47	0.995
Immunosuppressive induction of CNI				
Cyclosporine	47	1	–	
Tacrolimus	153	1.35	0.47–3.94	0.570
Overexposure to CNI*				
No	110	1	–	
Yes	90	2.59	1.14–6.11	0.022
Combined use of mycophenolate mofetil				
Yes	136	1	–	
No	64	2.50	0.957–6.67	0.061

ARI, acute renal injury; GW/RBW, graft weight-to-recipient body weight ratio; CNI, calcineurin inhibitor.

*Averaged concentration: tacrolimus trough >10 ng/ml or cyclosporine trough >200 ng/ml within the first month.

immunosuppressive therapy, the proportions of CNI were divided equally for two groups. The rate of overexposure to CNI was significantly higher in Group B. Furthermore, Group B also showed the higher average trough level for tacrolimus prior to develop renal dysfunction. As regards MMF-use, MMF was administered to 136 of all 146 patients after the introduction of MMF into our immunosuppression protocol, and in the other 10 patients MMF was stopped because of persistent afebrile diarrhea and bone marrow suppression. However, from another point of view, the average trough levels of tacrolimus in the MMF group were significantly lower than the levels in the non-MMF group (9.02 ± 0.2 ng/ml vs. 10.4 ± 0.26 ng/ml, $P < 0.0001$). And MMF showed the same efficacy in cyclosporine (173.0 ± 5.4 ng/ml vs. 212.7 ± 20 ng/ml, $P = 0.063$). Concerning clinical events, there were no differences between the two groups in biopsy-proven rejection episodes requiring rescue therapy, major biliary and vascular complications, and the transplant period; the first and second half of 200 cases. As a result, the patients in Group B were inferior in rates of requiring RRT, hospital stay and mortality, progression rates of CKD, and late-phase mortality.

On multivariate logistic regression analysis, independent risk factors associated with severe ARI were MELD ≥20 [odds ratio (OR), 2.96; $P = 0.019$], small-for-size graft [graft weight-to-recipient body weight ratio (GW/RBW) <0.7%; OR, 3.10; $P = 0.042$], blood loss/body weight >55 ml/kg (OR, 3.70; $P = 0.042$), overexposure to CNI (OR, 2.59; $P = 0.022$), and preoperative diabetes mellitus (OR, 3.23; $P = 0.044$). Graft size did not appear to be a significant factor in univariate analysis, but was identified as a significant factor after categorization with cutoff value of 0.7% for GW/RBW and consideration of confounding factors in multivariate analysis (Table 3).

A simple scoring system for all patients was then developed, with 1 point assigned to each significant patient-background factor: MELD ≥20; GW/RBW <0.7%; blood loss/body weight >55 ml/kg; overexposure to CNI; and preoperative diabetes mellitus, using a similar odds ratio to that used in multivariate analysis. The patients were divided into four groups according to the number of risk factors (R): R0 ($n = 22$); R1 ($n = 80$); R2 ($n = 61$); R3 ($n = 35$); R4 ($n = 2$); and R5 ($n = 0$). According to this risk classification scoring system, in which R4 was combined with R3, the proportion of postoperative ARI grade in each group was well categorized (Fig. 2).

Discussion

Acute renal injury is a common and important complication of orthotopic liver transplantation, representing a major cause of morbidity and mortality in the postopera-

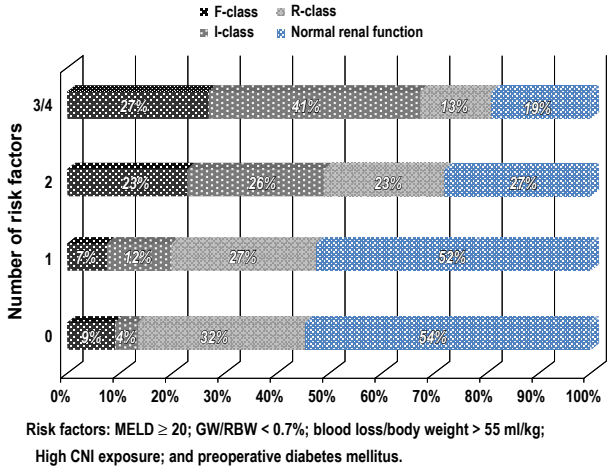

Figure 2 Proportion of acute renal injury after LDLT according to the risk-scoring system. A simple scoring system was developed with one point assigned to each significant risk factor: MELD ≥20; GW/RBW <0.7%; blood loss/body weight >55 ml/kg; high trough concentrations of CNI; and preoperative diabetes mellitus. It categorizes the proportion of ARI after LDLT. LDLT, living donor liver transplantation; MELD, Model for End-stage Liver Disease; GW/RBW, graft weight-to-recipient body weight ratio; CNI, calcineurin inhibitor; ARI, acute renal injury.

tive period [1–3,34]. ARI has been associated with an eightfold increase in mortality risk [34], prolonged stay in the intensive care unit, and higher hospital costs [35]. Although mortality rates with ARI after OLT have been reported as high (45.1–67%), patients with ARI can have a good prognosis, with a recovery rate of 97% [7,36]. Previous studies have demonstrated preoperative renal injury [2,5,6,8], recipient age, male sex, HCV, preoperative hypertension, diabetes [37], red blood cell transfusion [15], use of vasopressors, overexposure to CNI [30,31,38], and hypoalbuminemia as risk factors for postoperative ARI [16]. However, early postoperative renal function after LDLT has rarely been investigated. This study therefore focused on the relationships between ARI after LDLT and prognosis, as well as on risk factors predicting this serious complication.

Using the RIFLE criteria, ARI after LDLT could be categorized into the R-, I-, or F-class. In our study, the incidence of ARI was 60%, which is a relatively high rate compared with previous reports. However, depending on the definition used for ARI, the incidence of ARI would have different rates. The occurrence of postliver transplant ARI has been reported as 51.5% using the definition of sCr >1.5 mg/dl [5], and as 39.2% using the definition of sCr >2 mg/dl [39]. In the RIFLE criteria, the R-class is defined as a 1.5-fold increase in the sCr and/or >25% decrease in the GFR. This comprehensive definition used in our study accounts for the high incidence of ARI that we observed. Using the definition of doubling in creatinine postliver transplant, the incidence of ARI rises to 37%, which is similar to values previously reported. We also divided the patients into two groups: Group A (normal renal function or R-class); and Group B (I- or F-class). The reason for this grouping related to the comparability and differences in post-transplant prognosis: the overall survival rate in the R-class was comparable to that in the normal renal function group, with survival in both the R-class and the normal renal function group significantly superior to that in the other classes, and with almost all patients in the R-class recovering renal function in the chronic phase. In other words, ARI in the R-class could be within the permissible range. On the other hand, ARI beyond the I-class led to higher hospital mortality rates and poor prognosis in the late phase. The 1- and 5-year overall survival rates were 95.7% and 89.0% in the R-class and 85.7% and 81.8% in the I-class, respectively. It is possible to speculate that ARI in the I-class could affect the lower survival rate in the late phase. We also focused on obvious perioperative ARI impact and simple risk analysis to derive and construct treatment strategies. Therefore, we decided to divide the study patients between the R- and I-class. ARI in Group B tended to progress to CKD and subsequent poor prognosis in the late phase. CKD after liver transplantation has been reported as an independent risk factor of lower patient survival in the late phase [40,41]. Our patients with stage 3/4 CKD had worse prognosis, which could have resulted from infectious episodes and poor tolerance of other treatment modalities for the adverse pathological episodes compared with Group A. The RIFLE criteria were also useful as a prognostic tool for ARI in LDLT. We emphasize that progression beyond the I-class could be a particularly hazardous sign, and may indicate irreversible renal injury after LDLT.

Multivariate analysis revealed that risk factors for severe ARI included preoperative diabetes mellitus, MELD ≥20, small-for size graft (GW/RBW <0.7%), blood loss/body weight >55 ml/kg, and overexposure to CNI. With regard to preoperative factors, diabetes mellitus was reported in 12.5% of pretransplant recipients, and 19.2% developed new-onset diabetes within 1 year after liver transplantation [42], along with increased risk of vascular disease, infection and CKD [43,44]. Some studies have identified pretransplant diabetes as a risk factor for the occurrence of ARI [42,45]. In our study, patients who had insulin-controlled diabetes prior to LDLT showed a significant increase in the incidence of severe ARI. Preoperative creatinine level, which can be used to indicate renal function, is a key component of the MELD calculation. An association between a higher MELD score and post-transplant ARI has been reported [46–48]. Our results support these previous findings that pretransplant renal impairment could have a negative influence on post-transplant renal function. Concerning operative factors, our study indicated that

surgical blood loss, which exerts a major effect on systemic hemodynamics, is a risk factor for severe ARI. Intraoperative hemodynamic instability resulting from blood loss is a well-recognized phenomenon during liver transplantation [49,50]. Vasopressors are known to constrict the renal vasculature, resulting in reductions in renal blood flow. Blood loss and hemodynamic instability are related to a certain extent, but could affect postoperative renal function through different mechanisms. This theory is supported by the fact that blood loss has been identified as an independent risk factor for severe ARI.

Compared to deceased donor liver transplantation, partial liver grafts sometimes cause serious complications. Particularly in adult LDLT, graft size mismatching with partial liver transplantation can cause various problems that may affect the prognosis when the graft cannot sustain excessive portal blood perfusion. This is defined as small-for-size syndrome (SFSS), characterized clinically by large-volume ascites, hyperbilirubinemia, coagulopathy, and ARI [17,51,52]. Some studies have found a significant relationship between small-for-size grafts (GW/RBW <0.8) and ARI after LDLT [52–54]. This condition affects the balance between vasoconstriction and vasodilatory factors and leads to renal dysfunction. ARI after adult LDLT may thus occur because of persistent portal hypertension and a hyperdynamic state in patients with a small-for-size graft [5]. Recent treatment strategies for SFSS, such as portosystemic shunt, splenectomy, and splenic artery ligation or embolization, could improve prognosis [20,55–60]. Furthermore, the lower limit of GW/RBW 0.8% could be reduced to <0.8% through these treatments [58,61]. In our institution, after the introduction of splenic artery ligation and preoperative embolization as portal modulation techniques, a risk cutoff value of 0.7% was set for the risk of SFSS and ARI. Multivariate analysis shows that use of this value has had a significant impact on the occurrence of severe ARI.

Nephrotoxicity resulting from use of a CNI has been well established as a cause of renal dysfunction, resulting from an imbalance in vasoactive substance release [62–64]. The direct toxic effects represent acute microvascular disease with a pattern of thrombotic microangiopathy resembling hemolytic uremic syndrome/thrombotic thrombocytopenic purpura [65]. A toxic concentration of CNI is a noticeable problem. The cutoff value of 10.4 ng/ml for tacrolimus trough and 198 ng/ml for cyclosporine trough for ARI after LDLT were calculated in ROC analysis. These data are in agreement with previous reports [30,38]. Recent studies in liver transplantation have shown that the use of MMF in combination with low CNI levels improves renal function while maintaining adequate immunosuppression [13,38,66]. In this analysis, MMF was less introduced for the patients in Group B, than Group A. As a result, the average trough level of tacrolimus in Group B was significantly higher than Group A. And CNI trough levels in immunosuppressive protocol with MMF were lower than those without MMF in all cases. So we speculated that the factor of MMF could be indicated as significant by an actually lowered CNI level and contribute to prevention of severe ARI. Thus, a reduced CNI exposure by adding MMF is beneficial in terms of renal impairment after LDLT and should be preferred to conventional dosage. Modification in nephrotoxic immunosuppressive regimens with MMF to avoid postoperative ARI could lead to favorable renal outcomes.

Concerning the treatment strategies for prophylaxis of severe ARI after LDLT, our scoring system that focuses on significant risk factors could offer a useful tool. For example, a recipient with a high MELD and insulin-controlled preoperative diabetes mellitus initially has a substantial risk of progressing to severe ARI. A systematic plan for perioperative and postoperative care should thus be considered, comprising a donor liver with sufficient graft volume, use of MMF in combination with reduced CNI use, transfusion in the perioperative phase, and early introduction of RRT to arrest progression toward severe ARI.

Severe ARI after LDLT is a risk factor for poor prognosis, which is associated with increased hospital mortality and which predicts the development of advanced CKD. We conclude that the RIFLE classification offers a simple and useful tool for stratifying the severity of ARI after LDLT. Discretionary choices in transplant surgery and the subsequent medical care are very restricted. So in these complicated situations, RIFLE is a very simple and useful predictive tool after LDLT and could contribute toward improved transplant prognosis in terms of medical care. However, the determination of RIFLE criteria after transplantation might be useful only with respect to the laboratory results and prediction made at that particular time in the patient's postoperative course. The essential point is the benefit of constructing suitable preventive and treatment strategies for ARI after LDLT. Such strategies should be based on the patient's etiology and risk factors for ARI. Our results suggest five risk factors for ARI after LDLT: MELD ≥20; GW/RBW <0.7%; blood loss/body weight >55 ml/kg; overexposure to CNI; and preoperative diabetes mellitus. Furthermore, the scoring system for these risk factors could categorize the grade of ARI severity after LDLT according to the RIFLE criteria. These risk factors could be mitigated through intentional care management: (i) strict therapeutic drug monitoring for CNI and (ii) accepting only donor livers with sufficient graft volume (i.e., GW/RBW more than 0.7% in high-risk recipients with MELD more than 20 and/or diabetes mellitus). The immunosuppressive regimen should be modified by MMF and any other agent for the sake of lowering CNI dose, especially in tacrolimus [38,67]. Perioperative treatment strategies should be designed and balanced based on the

risk factors for the further improvement of transplant prognosis.

Authorship

MU: participated in data analysis and writing of the paper. YU: participated in research design and writing of the paper. TY and TF: participated in research design. HS, TN, HM, AT, SS, RY, DS, DN and TF: participated in data analysis.

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