Does the Development of Chronic Kidney Disease and Acute Kidney Injury Affect the Prognosis after Living Donor Liver Transplantation?

Yusuke Inoue, Akihiko Soyama, Mitsuhisa Takatsuki, Masaaki Hidaka

Ayaka Kinoshita, Koji Natsuda, Zhassulan Baimakhanov, Tota Kugiyama,

Tomohiko Adachi, Amane Kitasato, Tamotsu Kuroki, Susumu Eguchi

Department of Surgery, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan

Running title CKD and AKI after LDLT

Address correspondence to:

Susumu Eguchi, MD, PhD.

Department of Surgery, Nagasaki University Graduate School of Biomedical Sciences,

1-7-1 Sakamoto, Nagasaki 852-8501, Japan

TEL: 81-95-819-7316, FAX: 81-95-819-7319

E-mail: sueguchi@nagasaki-u.ac.jp

(Abstract page)

Inoue Y

Does the Development of Chronic Kidney Disease and Acute Kidney Injury Affect the Prognosis after Living Donor Liver Transplantation?

Abbreviations

AKI, acute kidney injury

AKIN, acute kidney injury network

CKD, chronic kidney disease

CMV, cytomegalovirus

CNI, calcineurin inhibitor

eGFR, estimated glomerular filtration rate

ESKD, end-stage kidney disease

GV/SLV ratio, graft volume/standard liver volume ratio

ICU, intensive care unit

IL-18, interleukin-18

KIM-1, kidney injury molecule-1

KDIGO, Kidney Disease: Improving Global Outcomes

LC-B, hepatitis B virus-related cirrhosis

LC-C, hepatitis C virus-related cirrhosis

L-FABP, L-type fatty acid binding protein

LDLT, living donor liver transplantation

MELD, model for end-stage liver disease

MMF, mycophenolate mofetil

NGALZ, neutrophil gelatinase-associated lipocalin

POY, postoperative year

SFSS, small-for-size syndrome

Key words

HCV, diabetes, intraoperative bleeding, sepsis, age, AKI, CKD

Yusuke Inoue, MD.

Department of Surgery, Nagasaki University Graduate School of Biomedical Sciences,

1-7-1 Sakamoto, Nagasaki 852-8501, Japan

TEL: 81-95-819-7316, FAX: 81-95-819-7319

E-mail: inoue17@live.jp

ABSTRACT

【Background and aims】Chronic kidney disease (CKD) and acute kidney injury (AKI) have been discussed as complications following living donor liver transplantation (LDLT). The aim of this study was to clarify the relationships among CKD, AKI and the prognosis after LDLT.

【Methods】This study included 118 patients who underwent LDLT in our department. A low eGFR (<60 ml/min/1.73m^2) was regarded to indicate CKD. AKI 1 and 2 were characterized by an increase in the serum creatinine level of 0.5 and 1.0 mg/dL, respectively, within one week after LDLT. We investigated the risk factors for and the relevance of CKD and AKI on the prognosis.

【Results】AKI 1 was associated with sepsis and intraoperative bleeding (p=0.0032, p=0.001). AKI 2 was associated with sepsis and hepatitis C infection (p<0.001, p=0.027). A preoperative eGFR of 60-89 and diabetes were risk factors for the development of CKD in POY2 (p=0.018, p=0.002). AKI 2, sepsis and diabetes were risk factors for patient death within one year after LDLT (p=0.010, p=0.002, p=0.022). AKI 2 and sepsis were risk factors for death within two years after LDLT (p=0.005, p=0.018).

【Conclusions】Recognizing the risk factors and careful management for preventing

both AKI and CKD may improve the prognosis of patients following LDLT.

Introduction

Acute kidney injury (AKI) was recently revealed to be a risk factor for end-stage renal disease and long-term mortality (1-4). Chronic kidney disease (CKD) is also a risk factor for cardiovascular disease, end-stage renal disease and mortality (5-7). AKI and CKD are known to develop in patients following liver transplantation (8-14). Both types of renal dysfunction have been reported to be associated with the long-term prognosis (8, 12-14). We previously reported that posttransplant AKI led to a deteriorated graft survival after LDLT (15). Although the development of CKD following liver transplantation has been reported, the relationship between AKI and CKD in the posttransplant course remains unclear. The aim of this study was to clarify the relationships among AKI, CKD and the prognosis after LDLT.

Patients and methods

The sources of our data included a chart review of LDLT recipients who had undergone LDLT at Nagasaki University Hospital between April 2005 and December 2012 (n=118). The median follow-up period was 62.5 months (range, 24-115). We reviewed our

experiences concerning patients with AKI and CKD post-LDLT. The database includes information regarding the causes of liver disease, transplant or retransplant status, the Model for End-Stage Liver Disease (MELD) score, and the intraoperative and postoperative clinical data. All patients were included in the study, regardless of their initial serum creatinine level. Patients on dialysis prior to liver transplantation were excluded from the study. The patient characteristics are shown in Table 1.

For this study, we used two definitions to define AKI, as previously reported in our article concerning AKI in liver transplant (LT) recipients, and evaluated the influence of AKI on the patient survival according to these definitions. In addition, the selection of the AKI definitions was made to reflect the changes in the renal function, from mild to more severe, occurring within one week at any time during hospitalization post-LDLT. The two definitions for AKI were as follows: AKI 1 was characterized by an increase in the serum creatinine level of 0.5 mg/dL above the baseline, while AKI 2 was characterized by an increase in the serum creatinine level of 1.0 mg/dL above the baseline (15). These definitions were applied to the serum creatinine levels obtained at regular intervals in the post-LDLT period. The baseline serum creatinine level was the value obtained immediately prior to LDLT.

CKD was diagnosed according to the international classification proposed by Kidney

Disease: Improving Global Outcomes (KDIGO), where grade 1 is characterized by an eGFR ≥ 90 ml/min/1.73m^2, Grade 2 by an eGFR of 60-89, Grade 3a, 45-59; Grade 3b, 30-44; Grade 4, 15-29 and Grade 5, < 15 ml/min/1.73m^2. The eGFR was measured preoperatively and at postoperative years (POY) 1 and 2. Grades 3, 4 and 5 were defined as CKD.

Patients with AKI were compared to a control group without AKI, and patients with CKD were compared to a control group without CKD. We investigated the risk factors for AKI and CKD. The associations among AKI, CKD, patient death, the duration of ICU stay and the hospital stay were investigated.

Immunosuppression and rejection

In patients with an impaired renal function immediately before or after undergoing transplantation, the target trough levels of calcineurin inhibitor (CNI) were decreased (FK506: trough level 5-8 ng/ml, CyA: 100-150 ng/ml) or temporarily withheld until the renal function improved. If CNI was withheld, we generally used basiliximab to provide immunosuppression, in conjunction with MMF and prednisone, until the renal function improved and the CNI treatment could be restarted. Methylprednisolone was injected intravenously during surgery at a dose of 20 mg/kg and given at a dose of 2 mg/kg/day,

tapered for one to six postoperative days to 1 mg/kg/day, followed by oral prednisolone at 0.3 mg/kg/day (days 7 to 28), 0.2 mg/kg/day (after 28 days), and discontinued three months to one year after the procedure. If acute cellular rejection was observed, bolus injections of methylprednisolone were administered in select cases.

Preoperative and postoperative data

The database information from pre-LDLT admission, intraoperative monitoring and post-LDLT care were reviewed. The examined parameters included the patient's age, gender, serum creatinine level, MELD score, graft volume/standard liver volume ratio (GV/SLV ratio), sepsis, CMV and other infections, intraoperative blood loss, regimen of immunosuppressive drugs, causes of liver failure, length of hospital and intensive care unit (ICU) stays and the survival.

Statistical analysis

All categorical data were analyzed by a multivariate logistic analysis. Values of $P < 0.05$ were considered to be statistically significant.

Results

The incidence of AKI varied, depending on the definition applied for AKI (Tables 2, 3). Tables 2 and 3 show the demographics and outcomes of AKI patients compared with the control group.

AKI 1 (an increase in serum creatinine of >0.5 mg/dL in one week)

There was a higher incidence of AKI 1 (78/118 cases, 66.1%) compared to the incidence of AKI 2. The development of AKI 1 was significantly associated with sepsis and a high intraoperative blood loss (>5,000 ml) (p=0.0032, p=0.001, respectively) (Table 2). AKI 1 was not associated with the length of postoperative ICU stay or the hospital stay.

AKI 2 (an increase in serum creatinine of >1.0 mg/dL in one week)

The incidence of AKI 2 was 26.3% (31/118 cases). Sepsis during hospitalization and liver cirrhosis with hepatitis C infection were significantly associated with AKI 2 (p<0.001, p=0.027, respectively) (Table 3).

CKD (Grade 3, 4 or 5 diagnosed by the international classification proposed by KDIGO)

There was a relatively high prevalence of CKD preoperatively, with CKD being diagnosed in 33.9% of all patients (40/118 cases). The percentages of patients with CKD at one and two years after operation were 41.5% (39/94) and 43.7% (38/87), respectively. The ratio of CKD increased annually for the first two years after LDLT.

The development of CKD one year after LDLT (evaluation of grade 1 and 2 patients before LDLT)

We excluded patients whose detailed information was unavailable at one year after LDLT for reasons such as patient death and transferring to another hospital. The number of non-CKD patients (Grades 1 and 2 preoperatively) was 78. Thirty-six patients had grade 1 and 42 had grade 2 CKD. Five of the grade 1 patients developed CKD (15.6%), and 11 of the grade 2 patients developed CKD (34.4%). A preoperative CKD grade of 1 or 2 was not associated with the development of CKD postoperatively (Table 4).

Development of CKD two years after LDLT (evaluation of preoperative grade 1 and 2 patients)

As described above, we excluded some patients and evaluated 58 non-CKD

patients before LDLT. Thirty patients had grade 1 and 28 had grade 2 CKD. Six of the grade 1 patients developed CKD (20.0%) and 15 of the grade 2 patients developed CKD (53.6%) by two years after LDLT. Patients with grade 2 CKD or diabetes were significantly more likely to develop CKD (p=0.018, p=0.002, respectively) (Table 5).

The progression of CKD one and two years after LDLT (evaluation of Grade 3, 4 and 5 patients before LDLT)

We evaluated 31 patients for the progression of CKD after LTLT. A progression of the CKD grade was observed in four of these patients (12.9%). No significant relationship was observed between Grades 3-5 CKD and the progression of CKD at one year. We evaluated 29 patients at two years after LDLT. A progression of the CKD grade was observed in three of these patients (10.3%). No significant relationship was observed between Grades 3-5 CKD and the progression of CKD at two years after LDLT.

Causes of death after LDLT

Within one year after LDLT, 24/118 (20.3%) patients died. The development of AKI 2, sepsis and diabetes were significant risk factors for death (p=0.010, p=0.002 and

p=0.022, respectively) (Table 6).

A total of 29/118 (24.6%) patients died within two years of LDLT. The development of AKI 2, sepsis and no use of FK were significant risk factors for death (p=0.005, p=0.018 and p=0.042, respectively) (Table 7).

Discussion

Although we hypothesized that AKI is a risk factor for CKD in patients following LDLT, there was no association between AKI and CKD in this population. According to the results of the present study, it may be possible to prevent the development of CKD even after the development of AKI with the appropriate management.

The preoperative creatinine level (16), preoperative renal injury (17-20), recipient age, male sex, HCV infection, preoperative hypertension, diabetes (21), red blood cell transfusion (22), use of vasopressors, overexposure to CNI (23-25), hypoalbuminemia (26), intraoperative lower urine output (16), intraoperative hypotension(16) and high MELD score (14) were all previously reported to be risk factors for AKI after orthotopic liver transplantation. With regard to the development of AKI after LDLT, preoperative diabetes, a MELD score > 20, small-for-size syndrome (SFSS; GW/RBW < 0.7%), blood loss/body weight > 55 ml/kg and overexposure to CNI were indicated to be risk

factors (27). LDLT is associated with a disadvantage in terms of the graft volume. SFSS is a well-known complication of LDLT. Although some techniques for preventing SFSS have been proposed, there is currently no proven solution (28). Due to the difficulties associated with managing the fluid balance in cases with SFSS, we hypothesized that SFSS might be a risk factor for renal dysfunction. However, in this study, the GV/SLV ratio was not associated with AKI or CKD. Adequate fluid balance management may prevent renal injury. In support of this, we found that a high intraoperative blood loss (>5,000 ml) was a risk factor for AKI 1. Sepsis and HCV infection were the risk factors for AKI 2 in LDLT patients. Regardless of the type of transplant, renal hypoperfusion was undeniably associated with AKI. Therefore, the maintenance of kidney and whole body perfusion by maintaining a good circulation and the fluid balance can help to prevent kidney injuries. Wong et al. defined AKI in patients with cirrhosis as deterioration of the renal function indicated by a rise in the serum creatinine level of 0.3 mg/dl within 48 hours (29). This criterion includes a small rise in the serum creatinine, comparable to AKI 1 in the criteria we used, although the 48 hours needed for the rise is shorter than that in our criteria. Wong et al. described that the classification has the potential to allow patients with a smaller rise in creatinine to benefit from treatments currently reserved for patients with classical hepatorenal syndrome. Based on the results

of our study, the concept to treat patients with a small rise in creatinine described by Wong et al. is considered applicable in LDLT.

More reports have been published on CKD than AKI after LT. Many risk factors have been reported, including a preoperative low GFR, preoperative high creatinine level, HCV infection, diabetes, AKI, patient age, immunosuppressant use, Child-Pugh score, MELD score, proteinuria, urinary tract infection, and hypercholesterolemia (30-32). In LDLT patients, the recipient age and pretransplant eGFR were considered to be risk factors for CKD (33). In the present study, we found that preoperative CKD grade 2 and diabetes were the risk factors for CKD (higher grades) two years after LDLT.

After LDLT, there are many factors that can lead to the development of renal failure, including the use of CNI, fluid imbalance, and infection. Patients with a poor preoperative renal function are more likely to develop CKD after LDLT. New-onset diabetes was reported in 19.2% of patients within one year after LT (34). Diabetes leads to increases in vascular disease, infections and CKD (35, 36). Because CKD is a major factor that defines the prognosis even in non-transplant patients, close attention should be paid when treating posttransplant patients with diabetes.

A definition for CKD has been proposed by KDIGO. In this study, we simplified

the definition of CKD. The typical CKD definition requires the GFR, laboratory data, imaging and pathological findings for a period of at least three months. For less-invasiveness and simplicity of the evaluation, we measured the eGFR to evaluate CKD. If pathological findings are available, then the mechanism of developing CKD following LDLT might thus be elucidated.

In the analysis concerning the prognosis, AKI 2 and sepsis were significantly associated with mortality within one and two years after LDLT. Even with the exclusion of hospital death cases, the survival of AKI patients after discharge tended to be lower. This indicates that AKI affects the long-term outcome. Although CKD has been reported to be a risk factor for end-stage renal failure and cardiovascular disease, leading to mortality, CKD was not associated with mortality within the 2-year follow-up period in this study. To clarify the influence of CKD on LDLT recipients, an investigation with a longer follow-up period is necessary.

In conclusion, the recognition of the risk factors for AKI and CKD, appropriate treatments for these risks, and meticulous fluid management are considered important to improve the prognosis after LDLT.

References

1. Ponte B, Felipe C, Muriel A, Tenorio MT, Liano F. Long-term functional evolution after an acute kidney injury: a 10-year study. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association. 2008;23(12):3859-66.

2. Parikh CR, Coca SG, Wang Y, Masoudi FA, Krumholz HM. Long-term prognosis of acute kidney injury after acute myocardial infarction. Arch Intern Med. 2008;168(9):987-95.

3. Goldenberg I, Chonchol M, Guetta V. Reversible acute kidney injury following contrast exposure and the risk of long-term mortality. Am J Nephrol. 2009;29(2):136-44.

4. Rifkin DE, Shlipak MG, Katz R, Fried LF, Siscovick D, Chonchol M, et al. Rapid kidney function decline and mortality risk in older adults. Arch Intern Med. 2008;168(20):2212-8.

5. Gansevoort RT, Correa-Rotter R, Hemmelgarn BR, Jafar TH, Heerspink HJ, Mann JF, et al. Chronic kidney disease and cardiovascular risk: epidemiology, mechanisms, and prevention. Lancet. 2013;382(9889):339-52.

6. Levey AS, de Jong PE, Coresh J, El Nahas M, Astor BC, Matsushita K, et al.

The definition, classification, and prognosis of chronic kidney disease: a KDIGO Controversies Conference report. Kidney Int. 2011;80(1):17-28.

7. Norris KC, Greene T, Kopple J, Lea J, Lewis J, Lipkowitz M, et al. Baseline predictors of renal disease progression in the African American Study of Hypertension and Kidney Disease. J Am Soc Nephrol. 2006;17(10):2928-36.

8. Barri YM, Sanchez EQ, Jennings LW, Melton LB, Hays S, Levy MF, et al. Acute kidney injury following liver transplantation: definition and outcome. Liver transplantation : official publication of the American Association for the Study of Liver Diseases and the International Liver Transplantation Society. 2009;15(5):475-83.

9. Fraley DS, Burr R, Bernardini J, Angus D, Kramer DJ, Johnson JP. Impact of acute renal failure on mortality in end-stage liver disease with or without transplantation. Kidney Int. 1998;54(2):518-24.

10. Lima EQ, Zanetta DM, Castro I, Massarollo PC, Mies S, Machado MM, et al. Risk factors for development of acute renal failure after liver transplantation. Ren Fail. 2003;25(4):553-60.

11. Menon S, Kirkendall ES, Nguyen H, Goldstein SL. Acute Kidney Injury Associated with High Nephrotoxic Medication Exposure Leads to Chronic Kidney Disease after 6 Months. J Pediatr. 2014;Sep;165(3):522-7

12. Allen AM, Kim WR, Therneau TM, Larson JJ, Heimbach JK, Rule AD. Chronic kidney disease and associated mortality after liver transplantation - A time-dependent analysis using measured glomerular filtration rate. J Hepatol. 2014;Aug;61(2):286-92

13. Sharma P, Welch K, Eikstadt R, Marrero JA, Fontana RJ, Lok AS. Renal outcomes after liver transplantation in the model for end-stage liver disease era. Liver transplantation : official publication of the American Association for the Study of Liver Diseases and the International Liver Transplantation Society. 2009;15(9):1142-8.

14. Zhu M, Li Y, Xia Q, Wang S, Qiu Y, Che M, et al. Strong impact of acute kidney injury on survival after liver transplantation. Transplantation proceedings. 2010;42(9):3634-8.

15. Inoue Y, Soyama A, Takatsuki M, Hidaka M, Muraoka I, Kanematsu T, et al. Acute kidney injury following living donor liver transplantation. Clin Transplant. 2012;26(5):E530-5.

16. Xu X, Ling Q, Wei Q, Wu J, Gao F, He ZL, et al. An effective model for predicting acute kidney injury after liver transplantation. Hepatobiliary Pancreat Dis Int. 2010;9(3):259-63.

17. Gainza FJ, Valdivieso A, Quintanilla N, Errazti G, Gastaca M, Campo M, et al.

Evaluation of acute renal failure in the liver transplantation perioperative period: incidence and impact. Transplantation proceedings. 2002;34(1):250-1.

18. Bilbao I, Charco R, Balsells J, Lazaro JL, Hidalgo E, Llopart L, et al. Risk factors for acute renal failure requiring dialysis after liver transplantation. Clin Transplant. 1998;12(2):123-9.

19. Cabezuelo JB, Ramirez P, Acosta F, Sanchez Bueno F, Robles R, Pons JA, et al. Prognostic factors of early acute renal failure in liver transplantation. Transplantation proceedings. 2002;34(1):254-5.

20. Lebron Gallardo M, Herrera Gutierrez ME, Seller Perez G, Curiel Balsera E, Fernandez Ortega JF, Quesada Garcia G. Risk factors for renal dysfunction in the postoperative course of liver transplant. Liver transplantation : official publication of the American Association for the Study of Liver Diseases and the International Liver Transplantation Society. 2004;10(11):1379-85.

21. Ojo AO, Held PJ, Port FK, Wolfe RA, Leichtman AB, Young EW, et al. Chronic renal failure after transplantation of a nonrenal organ. N Engl J Med. 2003;349(10):931-40.

22. Chen J, Singhapricha T, Hu KQ, Hong JC, Steadman RH, Busuttil RW, et al. Postliver transplant acute renal injury and failure by the RIFLE criteria in patients with

normal pretransplant serum creatinine concentrations: a matched study. Transplantation. 2011;91(3):348-53.

23. Neuberger JM, Mamelok RD, Neuhaus P, Pirenne J, Samuel D, Isoniemi H, et al. Delayed introduction of reduced-dose tacrolimus, and renal function in liver transplantation: the 'ReSpECT' study. Am J Transplant. 2009;9(2):327-36.

24. Rodriguez-Peralvarez M, Germani G, Darius T, Lerut J, Tsochatzis E, Burroughs AK. Tacrolimus trough levels, rejection and renal impairment in liver transplantation: a systematic review and meta-analysis. Am J Transplant. 2012;12(10):2797-814.

25. Boudjema K, Camus C, Saliba F, Calmus Y, Salame E, Pageaux G, et al. Reduced-dose tacrolimus with mycophenolate mofetil vs. standard-dose tacrolimus in liver transplantation: a randomized study. Am J Transplant. 2011;11(5):965-76.

26. Tinti F, Umbro I, Mecule A, Rossi M, Merli M, Nofroni I, et al. RIFLE criteria and hepatic function in the assessment of acute renal failure in liver transplantation. Transplantation proceedings. 2010;42(4):1233-6.

27. Utsumi M, Umeda Y, Sadamori H, Nagasaka T, Takaki A, Matsuda H, et al. Risk factors for acute renal injury in living donor liver transplantation: evaluation of the RIFLE criteria. Transpl Int. 2013;26(8):842-52.

28. Gruttadauria S, Pagano D, Luca A, Gridelli B. Small-for-size syndrome in adult-to-adult living-related liver transplantation. World J Gastroenterol. 2010;16(40):5011-5.

29. Wong F, Nadim MK, Kellum JA, Salerno F, Bellomo R, Gerbes A, et al. Working Party proposal for a revised classification system of renal dysfunction in patients with cirrhosis. Gut. 2011;60(5):702-9.

30. Lee JP, Heo NJ, Joo KW, Yi NJ, Suh KS, Moon KC, et al. Risk factors for consequent kidney impairment and differential impact of liver transplantation on renal function. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association. 2010;25(8):2772-85.

31. Lamattina JC, Foley DP, Mezrich JD, Fernandez LA, Vidyasagar V, D'Alessandro AM, et al. Chronic kidney disease stage progression in liver transplant recipients. Clinical journal of the American Society of Nephrology : CJASN. 2011;6(8):1851-7.

32. Burra P, Senzolo M, Masier A, Prestele H, Jones R, Samuel D, et al. Factors influencing renal function after liver transplantation. Results from the MOST, an international observational study. Dig Liver Dis. 2009;41(5):350-6.

33. Nishi H, Shibagaki Y, Kido R, Tamura S, Nangaku M, Sugawara Y, et al.

Chronic renal outcome after living donor liver transplantation. Clin Transplant. 2013;27(1):90-7.

34. Karie-Guigues S, Janus N, Saliba F, Dumortier J, Duvoux C, Calmus Y, et al. Long-term renal function in liver transplant recipients and impact of immunosuppressive regimens (calcineurin inhibitors alone or in combination with mycophenolate mofetil): the TRY study. Liver transplantation : official publication of the American Association for the Study of Liver Diseases and the International Liver Transplantation Society. 2009;15(9):1083-91.

35. Thuluvath PJ. When is diabetes mellitus a relative or absolute contraindication to liver transplantation? Liver transplantation : official publication of the American Association for the Study of Liver Diseases and the International Liver Transplantation Society. 2005(11 Suppl 2):S25-9.

36. Trail KC, Stratta RJ, Larsen JL, Ruby EI, Patil KD, Langnas AN, et al. Results of liver transplantation in diabetic recipients. Surgery. 1993;114(4):650-6; discussion 6-8.

Table1 Patients' characterestics

	Category	n=118
Follow-up period (months)		62.5 (24-115)
Gender, n (%)	male female	69 (58.5%) 49 (41.5%)
Recipients' age (yr)		57 (16-72)
Donors' age (yr)		37 (27-65)
MELD score		15 (7-40)
Median GV/SLV ratio		40.3 (23.6-85.3)
Preoperative CKD Stage, n (%)	1 2 3	36 (30.5%) 42 (35.6%) 40 (33.9%)
LC-B, n (%)		30 (25.4%)
LC-C, n (%)		46 (39.0%)
LC-Alcoholic, n (%)		9 (7.6%)
Diabetes, n (%)		35 (29.7%)
Hypertension, n (%)		15 (12.7%)
Hyperlipidemia, n (%)		3 (2.5%)
Intraoperative bleeding (ml)		5,375 (520-47,530)
Immunosuppression (except CNI), n (%)		89 (75.4%)
Immunosuppresion (except CNI from POD1), n (%)		34 (28.8%)
Use of FK506, n (%)		110 (93.2%)
Postoperative sepsis, n (%)		39 (33.1%)
Postoperative CMV infection , n (%)		47 (40.0%)

Table 2 Description of patients with AKI 1 (increase in serum creatinine of >0.5 mg/dL)

Criteria	Category	n	AKI 1	Univariate logistic regression OR	Univariate logistic regression p Value	Multivariate logistic regression OR	Multivariate logistic regression p Value
Number		118	78 (66.1%)	—	—		
Pre-operative CKD Stage	1	36	22 (61.1%)	Reference	[0.650]		
	2	42	30 (71.4%)	1.581	0.470		
	3, 4, 5	40	26 (65.0%)	1.179	0.909		
Gender	male	69	44 (63.8%)	Reference	—		
	female	49	34 (69.4%)	1.285	0.664		
Age of donor	<55	98	66 (67.3%)	Reference	—		
	55≦	20	12 (60.0%)	0.729	0.698		
Age of recipient	<55	52	33 (63.5%)	Reference	—		
	55≦	66	45 (68.2%)	1.232	0.731		
MELD score	<15	51	33 (64.7%)	Reference	—		
	15≦	67	45 (67.2%)	1.115	0.931		
GV/SLV ratio	<38	46	29 (63.0%)	Reference	—		
	38≦	72	49 (68.1%)	1.247	0.715		
Sepsis	(−)	79	46 (58.2%)	Reference	—	Reference	—
	(+)	39	32 (82.1%)	3.248	0.016 *	2.903	0.032 *
CMV infection	(−)	71	48 (67.6%)	Reference	—		
	(+)	47	30 (63.8%)	0.847	0.818		
Intra-operative bleeding	<5000	55	27 (49.1%)	Reference	—	Reference	—
	5000≦	63	51 (81.0%)	4.348	<0.001 ***	4.083	0.001 **
Use of immunosuppressant (except CNI)	(−)	29	21 (72.4%)	Reference	—		
	(+)	89	57 (64.0%)	0.681	0.554		
Use of immunosuppressant (except CNI from POD1)	(−)	84	55 (65.5%)	Reference	—		
	(+)	34	23 (67.6%)	1.102	0.999		
Use of FK506	(−)	8	6 (75.0%)	Reference	—		
	(+)	110	72 (65.5%)	0.634	0.901		
LC-B	(−)	88	58 (65.9%)	Reference	—		
	(+)	30	20 (66.7%)	1.034	1.000		
LC-C	(−)	72	48 (66.7%)	Reference	—		
	(+)	46	30 (65.2%)	0.938	1.000		
LC-Alcholic	(−)	109	72 (66.1%)	Reference	—		
	(+)	9	6 (66.7%)	1.028	1.000		
Diabetes	(−)	83	50 (60.2%)	Reference	—		
	(+)	35	28 (80.0%)	2.620	0.059		
Hypertension	(−)	103	67 (65.0%)	Reference	—		
	(+)	15	11 (73.3%)	1.473	0.750		
Hyperlipidemia	(−)	115	77 (67.0%)	Reference	—		
	(+)	3	1 (33.3%)	0.250	0.530		

Table 3 Description of patients with AKI 2 (increase in serum creatinine of >1.0 mg/dL)

Criteria	Category	n	AKI 1	Univariate logistic regression OR	Univariate logistic regression p Value	Multivariate logistic regression OR	Multivariate logistic regression p Value
Number		118	31 (26.3%)	—	—		
Pre-operative CKD Stage	1	36	8 (22.2%)	Reference	[0.676]		
	2	42	13 (31.0%)	1.560	0.544		
	3, 4, 5	40	10 (25.0%)	1.164	0.991		
Gender	male	69	17 (24.6%)	Reference	—		
	female	49	14 (28.6%)	1.221	0.786		
Age of donor	<55	98	27 (27.6%)	Reference	—		
	55≦	20	4 (20.0%)	0.660	0.694		
Age of recipient	<55	28	5 (17.9%)	Reference	[0.666]		
	55≦	29	8 (27.6%)	1.735	0.578		
MELD score	<15	31	10 (32.3%)	2.162	0.333		
	15≦	30	8 (26.7%)	1.658	0.627		
GV/SLV ratio	<38	52	13 (25.0%)	Reference	—		
	38≦	66	18 (27.3%)	1.124	0.949		
Sepsis	(−)	28	6 (21.4%)	Reference	[0.908]	Reference	—
	(+)	30	9 (30.0%)	1.559	0.658	4.672	<0.001 ***
CMV infection	(−)	27	7 (25.9%)	1.278	0.940		
	(+)	33	9 (27.3%)	1.368	0.822		
Intra-operative bleeding	<5000	51	13 (25.5%)	Reference	—		
	5000≦	67	18 (26.9%)	1.073	1.000		
Use of immunosuppressant	(−)	25	5 (20.0%)	Reference	[0.719]		
(except CNI)	(+)	26	8 (30.8%)	1.758	0.577		
Use of immunosuppressant	(−)	35	8 (22.9%)	1.182	1.000		
(except CNI from POD1)	(+)	32	10 (31.3%)	1.799	0.516		
Use of FK506	(−)	46	11 (23.9%)	Reference	—		
	(+)	72	20 (27.8%)	1.222	0.808		
LC-B	(−)	29	8 (27.6%)	Reference	[0.895]		
	(+)	30	7 (23.3%)	0.802	0.939		
LC-C	(−)	29	9 (31.0%)	1.178	1.000	Reference	—
	(+)	30	7 (23.3%)	0.802	0.939	0.324	0.027 *
LC-Alcholic	(−)	29	4 (13.8%)	Reference	[0.058]		
	(+)	26	5 (19.2%)	1.477	0.855		
Diabetes	(−)	33	9 (27.3%)	2.312	0.323		
	(+)	30	13 (43.3%)	4.651	0.025 *		
Hypertension	(−)	26	3 (11.5%)	Reference	[0.104]		
	(+)	25	5 (20.0%)	1.892	0.657		
Hyperlipidemia	(−)	27	8 (29.6%)	3.159	0.198		
	(+)	40	15 (37.5%)	4.502	0.037 *		

Table 4　Description of patients with CKD one year after LDLT

Criteria	Category	n	Development of CKD	Univariate logistic regression OR	p Value
Number		64	16 (25.0%)	—	—
Pre-operative CKD Stage	1	32	5 (15.6%)	Reference	—
	2	32	11 (34.4%)	2.783	0.148
Gender	male	44	9 (20.5%)	Reference	—
	female	20	7 (35.0%)	2.068	0.349
AKI1	(−)	25	4 (16.0%)	Reference	—
	(+)	39	12 (30.8%)	2.304	0.300
AKI2	(−)	52	13 (25.0%)	Reference	—
	(+)	12	3 (25.0%)	1.000	1.000
Age of donor	<55	55	13 (23.6%)	Reference	—
	55≦	9	3 (33.3%)	1.602	0.798
Age of recipient	<55	33	6 (18.2%)	Reference	—
	55≦	31	10 (32.3%)	2.117	0.312
MELD score	<15	31	11 (35.5%)	Reference	—
	15≦	33	5 (15.2%)	0.331	0.111
GV/SLV ratio	<38	22	5 (22.7%)	Reference	—
	38≦	42	11 (26.2%)	1.203	1.000
sepsis	(−)	50	14 (28.0%)	Reference	—
	(+)	14	2 (14.3%)	0.434	0.499
CMV infection	(−)	40	11 (27.5%)	Reference	—
	(+)	24	5 (20.8%)	0.698	0.775
Intra-operative bleeding	<5000	36	10 (27.8%)	Reference	—
	5000≦	28	6 (21.4%)	0.713	0.776
Use of immunosuppressan	(−)	18	3 (16.7%)	Reference	—
(except CNI)	(+)	46	13 (28.3%)	1.951	0.532
Use of immunosuppressan	(−)	51	13 (25.5%)	Reference	—
(except CNI from POD1)	(+)	13	3 (23.1%)	0.879	1.000
Use of FK506	(−)	0	—	Reference	—
	(+)	64	16 (25.0%)	—	
LC-B	(−)	44	12 (27.3%)	Reference	—
	(+)	20	4 (20.0%)	0.671	0.771
LC-C	(−)	43	9 (20.9%)	Reference	—
	(+)	21	7 (33.3%)	1.869	0.438
LC-Alcholic	(−)	58	15 (25.9%)	Reference	—
	(+)	6	1 (16.7%)	0.578	1.000
Diabetes	(−)	49	10 (20.4%)	Reference	—
	(+)	15	6 (40.0%)	2.556	0.236
Hypertension	(−)	57	12 (21.1%)	Reference	—
	(+)	7	4 (57.1%)	4.841	0.118
Hyperlipidemia	(−)	64	16 (25.0%)	Reference	—
	(+)	0	—	—	

Table 5 Description of patients with CKD two years after LDLT

Criteria	Category	n	Development of CKD	Univariate logistic regression OR	Univariate logistic regression p Value	Multivariate logistic regression OR	Multivariate logistic regression p Value
Number		58	21 (36.2%)	—	—		
Pre-operative CKD Stage	1	30	6 (20.0%)	Reference	—	Reference	—
	2	28	15 (53.6%)	4.486	0.016 *	4.9	0.018 *
Gender	male	42	12 (28.6%)	Reference	—		
	female	16	9 (56.3%)	3.144	0.101		
AKI1	(−)	23	5 (21.7%)	Reference	—		
	(+)	35	16 (45.7%)	2.975	0.111		
AKI2	(−)	47	16 (34.0%)	Reference	—		
	(+)	11	5 (45.5%)	1.601	0.706		
Age of donor	<55	50	19 (38.0%)	Reference	—		
	55≦	8	2 (25.0%)	0.549	0.775		
Age of recipient	<55	31	7 (22.6%)	Reference	—		
	55≦	27	14 (51.9%)	3.605	0.041 *		
MELD score	<15	29	13 (44.8%)	Reference	—		
	15≦	29	8 (27.6%)	0.475	0.274		
GV/SLV ratio	<38	19	5 (26.3%)	Reference	—		
	38≦	39	16 (41.0%)	1.926	0.425		
sepsis	(−)	45	16 (35.6%)	Reference	—		
	(+)	13	5 (38.5%)	1.130	1.000		
CMV infection	(−)	36	14 (38.9%)	Reference	—		
	(+)	22	7 (31.8%)	0.737	0.798		
Intra-operative bleeding	<5000	33	12 (36.4%)	Reference	—		
	5000≦	25	9 (36.0%)	0.985	1.000		
Use of immunosuppressan	(−)	17	7 (41.2%)	Reference	—		
(except CNI)	(+)	41	14 (34.1%)	0.745	0.828		
Use of immunosuppressan	(−)	46	17 (37.0%)	Reference	—		
(except CNI from POD1)	(+)	12	4 (33.3%)	0.855	1.000		
Use of FK506	(−)	0	—	Reference	—		
	(+)	58	21 (36.2%)	—			
LC-B	(−)	39	14 (35.9%)	Reference	—		
	(+)	19	7 (36.8%)	1.041	1.000		
LC-C	(−)	40	11 (27.5%)	Reference	—		
	(+)	18	10 (55.6%)	3.222	0.080		
LC-Alcholic	(−)	52	19 (36.5%)	Reference	—		
	(+)	6	2 (33.3%)	0.871	1.000		
Diabetes	(−)	43	10 (23.3%)	Reference	—	Reference	—
	(+)	15	11 (73.3%)	8.657	0.002 **	9.568	0.002 **
Hypertension	(−)	51	16 (31.4%)	Reference	—		
	(+)	7	5 (71.4%)	5.296	0.104		
Hyperlipidemia	(−)	58	21 (36.2%)	Reference	—		
	(+)	0	—	—			

Table 6 Risk factors for patient's death within one year after LDLT

Criteria	Category	n	death within one year	Univariate logistic regression OR	Univariate logistic regression p Value	Multivariate logistic regression OR	Multivariate logistic regression p Value
Number		118	24 (20.3%)	—	—		
Pre-operative CKD Stage	1	36	5 (13.9%)	Reference	[0.552]		
	2	42	10 (23.8%)	1.921	0.414		
	3, 4, 5	40	9 (22.5%)	1.786	0.505		
Gender	male	69	14 (20.3%)	Reference	—		
	female	49	10 (20.4%)	1.007	1.000		
AKI1	(−)	40	3 (7.5%)	Reference	—		
	(+)	78	21 (26.9%)	4.496	0.019 *		
AKI2	(−)	87	10 (11.5%)	Reference	—	Reference	—
	(+)	31	14 (45.2%)	6.213	<0.001 ***	4.112	0.010 *
Age of donor	<55	98	17 (17.3%)	Reference	—		
	55≦	20	7 (35.0%)	2.541	0.147		
Age of recipient	<55	52	8 (15.4%)	Reference	—		
	55≦	66	16 (24.2%)	1.752	0.339		
MELD score	<15	51	10 (19.6%)	Reference	—		
	15≦	67	14 (20.9%)	1.082	1.000		
GV/SLV ratio	<38	46	11 (23.9%)	Reference	—		
	38≦	72	13 (18.1%)	0.703	0.587		
sepsis	(−)	79	7 (8.9%)	Reference	—	Reference	—
	(+)	39	17 (43.6%)	7.777	<0.001 ***	5.564	0.002 **
CMV infection	(−)	71	14 (19.7%)	Reference	—		
	(+)	47	10 (21.3%)	1.099	1.000		
Intra-operative bleeding	<5000	55	9 (16.4%)	Reference	—		
	5000≦	63	15 (23.8%)	1.591	0.441		
Use of immunosuppressan	(−)	29	9 (31.0%)	Reference	—		
(except CNI)	(+)	89	15 (16.9%)	0.454	0.173		
Use of immunosuppressan	(−)	84	16 (19.0%)	Reference	—		
(except CNI from POD1)	(+)	34	8 (23.5%)	1.305	0.753		
Use of FK506	(−)	8	3 (37.5%)	Reference	—		
	(+)	110	21 (19.1%)	0.397	0.410		
LC-B	(−)	88	19 (21.6%)	Reference	—		
	(+)	30	5 (16.7%)	0.728	0.771		
LC-C	(−)	72	14 (19.4%)	Reference	—		
	(+)	46	10 (21.7%)	1.149	0.938		
LC-Alcholic	(−)	109	24 (22.0%)	Reference	—		
	(+)	9	0 (0.0%)	0.291	0.238		
Diabetes	(−)	83	11 (13.3%)	Reference	—	Reference	—
	(+)	35	13 (37.1%)	3.816	0.009 **	3.527	0.022 *
Hypertension	(−)	103	20 (19.4%)	Reference	—		
	(+)	15	4 (26.7%)	1.503	0.723		
Hyperlipidemia	(−)	115	22 (19.1%)	Reference	—		
	(+)	3	2 (66.7%)	8.240	0.210		

Table 7 Risk factors for patient's death within two years after LDLT

Criteria	Category	n	death within two years	Univariate logistic regression OR	Univariate logistic regression p Value	Multivariate logistic regression OR	Multivariate logistic regression p Value
Number		118	29 (24.6%)	—	—		
Pre-operative CKD Stage	1	36	5 (13.9%)	Reference	[0.199]		
	2	42	13 (31.0%)	2.744	0.128		
	3, 4, 5	40	11 (27.5%)	2.326	0.241		
Gender	male	69	16 (23.2%)	Reference	—		
	female	49	13 (26.5%)	1.194	0.838		
AKI1	(−)	40	5 (12.5%)	Reference	—		
	(+)	78	24 (30.8%)	3.084	0.045 *		
AKI2	(−)	87	13 (14.9%)	Reference	—	Reference	—
	(+)	31	16 (51.6%)	5.954	<0.001 ***	4.142	0.005 **
Age of donor	<55	98	21 (21.4%)	Reference	—		
	55≦	20	8 (40.0%)	2.423	0.148		
Age of recipient	<55	52	10 (19.2%)	Reference	—		
	55≦	66	19 (28.8%)	1.690	0.326		
MELD score	<15	51	11 (21.6%)	Reference	—		
	15≦	67	18 (26.9%)	1.333	0.659		
GV/SLV ratio	<38	46	13 (28.3%)	Reference	—		
	38≦	72	16 (22.2%)	0.727	0.597		
sepsis	(−)	79	12 (15.2%)	Reference	—	Reference	—
	(+)	39	17 (43.6%)	4.253	0.002 **	3.241	0.018 *
CMV infection	(−)	71	17 (23.9%)	Reference	—		
	(+)	47	12 (25.5%)	1.088	1.000		
Intra-operative bleeding	<5000	55	12 (21.8%)	Reference	—		
	5000≦	63	17 (27.0%)	1.321	0.665		
Use of immunosuppressan	(−)	29	9 (31.0%)	Reference	—		
(except CNI)	(+)	89	20 (22.5%)	0.647	0.488		
Use of immunosuppressan	(−)	84	19 (22.6%)	Reference	—		
(except CNI from POD1)	(+)	34	10 (29.4%)	1.421	0.581		
Use of FK506	(−)	8	5 (62.5%)	Reference	—	Reference	—
	(+)	110	24 (21.8%)	0.171	0.042 *	0.177	0.042 *
LC-B	(−)	88	23 (26.1%)	Reference	—		
	(+)	30	6 (20.0%)	0.709	0.682		
LC-C	(−)	72	17 (23.6%)	Reference	—		
	(+)	46	12 (26.1%)	1.141	0.925		
LC-Alcholic	(−)	109	29 (26.6%)	Reference	—		
	(+)	9	0 (0.0%)	0.227	0.142		
Diabetes	(−)	83	16 (19.3%)	Reference	—		
	(+)	35	13 (37.1%)	2.454	0.072		
Hypertension	(−)	103	24 (23.3%)	Reference	—		
	(+)	15	5 (33.3%)	1.638	0.582		
Hyperlipidemia	(−)	115	27 (23.5%)	Reference	—		
	(+)	3	2 (66.7%)	6.388	0.298		