ELSEVIER

Long-term Complications After Liver Transplantation

K. Kuramitsu, T. Fukumoto, T. Iwasaki, M. Tominaga, I. Matsumoto, T. Ajiki, and Y. Ku

ABSTRACT

Background. Along with an increased number of cases of liver transplantation (LT), perioperative mortality has decreased and short-term survival has improved. However, long-term complications have not been fully elucidated today.

Purpose. Chronic complications were analyzed individually to find risk factors and to improve long-term outcomes after LT.

Subjects. There were 63 cases of LT from our outpatient clinic that were included in this study. Among them, 58 were performed using living donor LT and 5 were performed using deceased donor LT. Original diseases mainly consisted of hepatitis C virus (HCV; 45.9%) and hepatitis B virus (23.0%).

Findings. The median follow-up was 5.4 ± 3.3 years (range, 0.1∼17 years). Overall survival at 2, 3, 5, and 10 years was 89.3%, 83.4%, 81.3%, and 81.3%, respectively. Long-term complications mainly consisted of renal dysfunction (62.7%), dyslipidemia (29.4%), diabetes mellitus (21.6%), and arterial hypertension (21.6%). In univariate analysis, HCV ($P = .03$) and elapsed years after LT ($P = .02$) were identified as predictive factors for arterial hypertension and recipient age >50 ($P = .03$), and elapsed years after LT for renal dysfunction ($P = .03$), respectively. In multivariate Cox regression analysis, HCV (odds ratio [OR] 5.25, 95% confidence interval [CI] 1.05–34.06, $P = .04$) was identified as a predictive factor for arterial hypertension, and recipient age older than 50 years for renal dysfunction (OR 5.67, 95% CI 1.34–28.88, $P = .02$). The number of elapsed years after transplantation was also identified as a predictive factor for arterial hypertension/dyslipidemia/renal dysfunction (OR 13.88/14.15/4.10, 95% CI 1.91–298.26/2.18–290.78/1.09–18.03, $P = .01/.003/.04$). Fifty percent of the recipients developed renal dysfunction within 8 years after LT, and fluctuation of estimated glomerular filtration rate (eGFR) within 3 months after LT was successfully associated with an annual decrease of eGFR (r^2 value = 0.574, $P < .0001$).

Conclusion. Renal dysfunction is the most frequent chronic complication after LT. As chronic individual eGFR can be now accurately predicted with deterioration speed, recipient strata for renal protection strategies should be precisely targeted.

SINCE the first liver transplantation (LT) was performed in 1963 [1], short-term survival has improved rapidly [2]. Along with an improvement in surgical techniques, an immunosuppression regimen that is highly effective for antirejection, and management of infections, long-term survival after LT has significantly improved in recent years. Currently, median survival is reported to be 90% at 1 year and long-term survival to be 60% at 10 years [3]. In Japan, more than 6000 cases of both living (LDLTs) and deceased donor transplantations (DDLTs) were performed until 2012, and patient survival after DDLT was reported to be 80.5% at 1 year and 68.5% at 10 years, whereas that

From the Division of Hepato-Biliary-Pancreatic Surgery, Department of Surgery, Kobe University Graduate School of Medicine, Japan.

Address reprint requests to Takumi Fukumoto, MD, PhD, Division of Hepato-Biliary-Pancreatic Surgery, Department of Surgery, Kobe University Graduate School of Medicine, 7-5-2, Kusunoki-cho, Chuo-ku, Kobe City, Hyogo, Japan. E-mail: fukumoto@med.kobe-u.ac.jp

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after LDLT was reported to be 83.4% at 1 year and 72.4% at 10 years [4]. As both DDLT and LDLT is now established as a treatment option for end-stage liver disease all over the world, the number of the long-term survivor recipients continues to increase year after year. Longer lengths of follow-up inevitably require subsequent increased exposure to immunosuppression. As patients who require long-term immunosuppression are at higher risk of developing cardiovascular disease [2,5–8], de novo malignancy [7,9], infections, and renal dysfunction [10,11], several studies have already performed analysis focusing on these complications. However, there are few studies which focused on the incidence of overall chronic complications, the risk factors, and predictive factors to decrease patient mortality from these complications.

In this study, we first analyzed the incidence of chronic complications after LT. Second, we sought risk factors to develop each of the chronic complications. As renal dysfunction was the most frequent chronic complication among all patients in our study, we finally tracked individual estimated glomerular filtration rate (eGFR) over time and identified a predictive factor to assess chronic renal function with deterioration speed. Within our knowledge, this is the first study to assess individual deterioration speed of renal function and its predictor. We believe the study can target recipient strata where modulatory treatment works most beneficially, resulting in superior outcomes after LT.

METHODS

All the liver transplant recipients who were included in our study survived more than 1 year and were followed up at our outpatient.

Liver Transplantation

For LDLT, donors were selected from parents, grandparents, siblings, offspring, and spouses of their recipients. Preoperative evaluation for estimating graft and remnant liver volume in the donor were performed using three-dimensional reconstructed images of the hepatic vascular anatomy, which was produced using a software package based on the reconstructed images from a multidetector computed tomography (CT) scan of the liver. Resection lines were selected according to this estimated CT volumetry, aiming to obtain 0.6% or more graft weight compared to the recipient body weight. We rejected a donor if the remnant liver volume was less than 30%. All LDLT and DDLT procedures for both donors and the recipients were performed according to methods reported elsewhere [12,13]. The immunosuppressant regimen consisted of tacrolimus and low-dose steroid administration. The dosage of tacrolimus was changed according to the trough level: 10–15 ng/mL for the first month, 5–10 ng/mL for the first year, and approximately 5 ng/mL thereafter. Steroid was withdrawn within 6 months after LDLT as a protocol.

Long-term Complications

After discharge, recipients received follow-up examinations at our outpatient clinic based on their conditions between once per week and once every 2 months. Each time, blood chemistries and the trough level of immunosuppressant were measured. Abdominal CT scans were performed every year to detect abdominal malignant tumors. Magnetic resonance cholangiopancreatography was performed ever year to detect bile duct complications. For recipients with hepatitis C virus (HCV), combined pegylated interferon (PEG-IFN) and ribavirin treatment was introduced 1 to 3 months after LT. A protocol biopsy was performed to confirm the pathological graft fibrosis status and the recurrence of original disease annually for recipients with HCV and primary biliary cirrhosis. Patient survival, causes of mortality, and complications were analyzed in the study. The date of the most recent hospital visit was considered the last follow-up among surviving recipients to a maximum set in June 2013. Long-term complications, arterial hypertension, diabetes mellitus, dyslipidemia, and renal dysfunction were evaluated. Among the characteristics of the recipients, gender, etiology of original disease, recipient age, and the number of years elapsed after transplantation were evaluated as predictive factors for long-term complications.

Definitions

The following definitions were used in the study:

1. Arterial hypertension: systolic blood pressure $\geq$140 mm Hg and/or diastolic blood pressure of $\geq$90 mm Hg, in at least three consecutive evaluations or the need for antihypertensive treatment [14].
2. Diabetes mellitus: fasting glycemia $\geq$126 mg/dL or $\geq$200 mg/dL at any time during the day, in at least three consecutive tests, or the need for anti-diabetic agents [15].
3. Dyslipidemia: fasting cholesterol and/or triglyceride levels higher than 240 mg/dL and 150 mg/dL, respectively, in at least three consecutive blood tests or the need for anti-lipidemic agents [16].
4. Renal dysfunction: Renal function was accessed by measuring glomerular filtration rate (GFR). GFRs are expressed as mL/min/1.73 m^2, and estimated GFR (eGFR) was calculated using the Schwartz formula [17]. Renal dysfunction was diagnosed either by eGFR of $<$60 mL/min/1.73 m^2 corresponding to stage 3 or greater chronic kidney disease as defined by the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) [18].

Assessment of Annual Decrease of eGFR

The annual decrease of eGFR was calculated as follows for a patient n years after transplantation; $\Sigma(eGFR_n - eGFR_1)/n-1$. For example, for a recipient who has 7 years follow-up, the annual decrease of eGFR was calculated as follows: $(eGFR_7 - eGFR_1)/6$. Three parameters were determined to be potential predictors to assess annual decrease of eGFR after LDLT: preoperative eGFR levels [19,20], eGFR level at month 3 [21], and ΔeGFR. Associations with these three parameters and deterioration speed of eGFR were assessed using the linear regression analysis. ΔeGFR is defined as the fluctuation of eGFR during the perioperative phase and was calculated by subtracting the lowest from highest eGFR during the first 3 months after LDLT.

Statistical Analysis

Continuous data were expressed as median and range. Differences between patients' characteristics were compared using the chi-square or Fischer exact test. The univariate and multivariate Cox proportional-hazard regression model was calculated to identify the independent prognostic factors. Multivariate logistic regression analysis was used to identify the independent risk factors. In this study, all factors analyzed in univariate analysis were included in the subsequent multivariate analysis. Recipient survival was estimated using the Kaplan-Meier method. Statistical significance was