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Risk factors and criteria predicting early graft loss after adult-to-adult living donor liver transplantation

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ABSTRACT

Background: Because deceased liver donors are scarce, adult-to-adult living donor liver transplantation (LDLT) is considered a suitable alterative. However, LDLT grafts are usually partial, resulting in a higher risk of early graft loss (EGL). The aim of the present study was to identify the risk factors and criteria predicting EGL after LDLT.

Methods: We retrospectively analyzed 178 consecutive adults who underwent LDLT. The recipients were divided into two groups as follows: group I, wherein patients showed graft survival longer than 3 mo after LDLT ($n = 164$), and group II, wherein graft loss occurred within 3 mo after transplantation ($n = 14$).

Results: Univariate analysis showed various risk factors; however, only the preoperative model for end-stage liver disease score, the presence of obvious pretransplant portal hypertension, and intraoperative blood loss were identified as independent predictors of EGL by multivariate analysis. After LDLT, significant differences were observed between the groups in the fold change in total bilirubin levels over postoperative day (POD) 1 (TBIL-f1) and in the international normalized ratio over POD 1 (INR-f1). The combination of TBIL-f1 and INR-f1 on POD 10 was found to be a strong EGL predictor. Furthermore, a minimum indocyanine green (ICG) clearance rate constant K (m-K_{ICG}) <0.100/min after POD 3 was found to be the strongest predictor of EGL (sensitivity, 100%; specificity, 97.2%).

Conclusions: The postoperative m-K_{ICG} and combination of TBIL-f1 and INR-f1 on POD 10 were useful predictors of EGL; moreover, m-K_{ICG} was superior and is expected to be especially useful for ensuring timely retransplantation.

1. Introduction

Liver transplantation is a widely accepted treatment method for patients with end-stage liver diseases or fulminant hepatic failure [1,2]. Several studies have shown that advances in surgical technology, anesthesia management, and the detection and treatment of complications made over the last decade or so have significantly improved the 1-, 5-, and 10-y survival rates by 85%, 70%, and 60%, respectively [3,4]. However, these encouraging outcomes are greatly limited by the lack of deceased donations, and many patients die during the long waiting period [5]. In response to the organ donor shortage, adult-to-adult living donor liver transplantation (LDLT) has emerged as an effective alternative to deceased donor liver

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transplantation (DDLT), and its use has rapidly spread worldwide since the first reported case in 1998 [6]. Compared with DDLT, LDLT offers a reduced waiting time and more optimal timing of surgery, but it is also associated with a high surgical risk and complications for the recipient because of the differences in graft quality, size, and preservation time [7,8]. Previous studies have reported some risk factors that affect recipient survival and graft loss after DDLT [9,10], but it is not clear whether the same risk factors pertain to LDLT. Furthermore, unlike DDLT, LDLT involves partial liver grafts, which may not be adequate for meeting the recipients' requirements [11,12] and may therefore entail other risk factors. Therefore, the aims of this study were to characterize early graft loss (EGL) occurring in the first 3 mo after LDLT as well as to propose and assess the exact prediction criteria for EGL after LDLT.

2. Patients and methods

2.1. Patients

From June 2007 to May 2012, 180 consecutive adult patients (≥18 y) underwent adult-to-adult LDLT at the Liver Transplantation Centre, West China Hospital, Sichuan University. Among these patients, one recipient who died during surgery and one patient with dual grafts were excluded from the study. Thus, 178 recipients were finally analyzed in the present study.

In all cases, graft implantation was performed using right lobe grafts without the middle hepatic vein, and major middle hepatic vein tributaries >5 mm were maximally reconstructed to prevent congestion. The LDLT surgical technique has been described in detail elsewhere [13–15]. EGL was defined as death or retransplantation because of graft failure within 3 mo after transplantation. The clinical course in each case was followed up for a minimum of 3 mo after LDLT.

To identify the predictors of EGL, we investigated the pretransplant and intratransplant characteristics of 27 parameters for both recipients and donors. Importantly, the presence of obvious pretransplant portal hypertension (OPPH) was reviewed because previous studies reported that the recipients with OPPH may be at high risk of early death [16,17]. OPPH was defined to fulfill one of the following criteria: (1) upper digestive hemorrhage caused by portal hypertension at least once before transplantation; (2) persistent ascites of at least moderate severity despite diuretic treatment and confirmed by the present imaging studies or recent paracentesis; (3) and hypersplenism, indicated by an enlarged spleen and excessive destruction of one or more kinds of blood cells in the spleen.

We also reviewed and compared the dynamic changes in blood parameters between recipients with and without EGL on postoperative days (PODs) 1–5, 7, 10, 14, 21, and 28. We found two abnormalities in the values of total bilirubin (TBIL) and international normalized ratio (INR) in the recipients after LDLT: (1) stabilization at high levels in the first few days after transplantation with no reduction afterward or only very slight decrease; and (2) a gradual and stable increase after POD 1. These two trends were collectively classified into two parameters, namely, TBIL-f1 and INR-f1, calculated as the fold change in TBIL and INR, respectively, on POD X over their values on POD 1. TBIL-f1 and INR-f1 reflected the dynamic changes in TBIL and INR values, and we considered these to indicate the function of the graft more precisely than TBIL and INR values.

In addition, we also used the indocyanine green (ICG) clearance rate constant K (K_{ICG}) to predict EGL. ICG is a synthetic dye that is eliminated by the liver without extrahepatic metabolism and excretion, and its blood clearance has been applied to reflect hepatic function. The rate of elimination of ICG from the blood is delayed when the effective hepatic blood flow is lowered or the dye uptake of hepatocytes is reduced because of cirrhosis or other diseases. The ICG test has been described in detail elsewhere [18,19].

2.2. Donors

The primary selection criterion for the living liver donors was that the individual had to volunteer and provide informed consent clearly knowing that living liver donation may be associated with donor morbidity or mortality. Furthermore, the donors had to fulfill the following criteria: (1) they had to be healthy adult relatives of the recipients and have normal results in clinical laboratory examinations, such as biochemical, viral serology, and tumor marker tests; electrocardiography; and chest radiography. (2) The right liver lobe without the middle hepatic vein had to weigh >40% of the estimated standard liver weight of the recipient and the remaining liver volume had to be ≥30% of the total liver volume of the donor. To ensure fulfillment of the latter criterion, the donors were examined using computed tomography and volumetry to evaluate graft size, remnant donor liver volume, and hepatic vascular anatomy. In each case, our institutional LDLT indication committee was the final approver of the candidate.

2.3. Immunosuppression and anti-hepatitis B therapy

The basic post-LDLT immunosuppression protocol included calcineurin inhibitors (tacrolimus or cyclosporine), mycophenolate mofetil, and low-dose corticosteroids. The latter two were tapered and discontinued by 3 mo after transplantation. Steroid pulse therapy was administered to patients with acute rejection. The postoperative anti-hepatitis B protocols consisted of lamivudine combined with a low dose of intramuscular hepatitis B virus immunoglobulin therapy. For patients with HBV recurrence and lamivudine resistance, potential therapeutic choices included the addition of adefovir or switching to entecavir.

2.4. Statistical analysis

Descriptive statistics included means, ranges, standard deviations, and proportions. Categorical data are presented as percentages, and differences between proportions were compared using the χ^2 test or Fisher exact test. Continuous variables were compared using the unpaired Student t-test. Multivariate analysis was performed to identify independent determinants for the occurrence of EGL (logistic regression stepwise backward procedure). Post-transplant graft survival curves were computed using the Kaplan–Meier method and compared using the log-rank test. All statistical evaluations were performed using SPSS for Windows (SPSS 18.0 for Windows, Chicago, IL). For receiver operating characteristic (ROC)