Role of the postoperative cholesterol in early allograft dysfunction and survival after living donor liver transplantation

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BACKGROUND: Many studies have confirmed that serum total cholesterol (sTC) concentrations were associated with underlying liver damage and the synthesis capacity of liver. However, the role of postoperative sTC level on evaluating graft function and predicting survival of recipients who underwent liver transplantation has not been discussed.

METHODS: Clinical data of 231 living donor liver transplantation recipients from May 2003 to January 2015 were retrospectively collected. Patients were stratified into the low sTC group (sTC <1.42 mmol/L, 57 recipients) and high sTC group (sTC ≥1.42 mmol/L, 174 recipients) according the sTC level on postoperative day 3 based on receiver-operating characteristic curve analysis. The clinical characteristics and postoperative short- and long-term outcomes were compared between the two groups.

RESULTS: Recipients with sTC <1.42 mmol/L experienced more severe preoperative disease conditions, a higher incidence of postoperative early allograft dysfunction (38.6% vs 10.3%, *P*<0.001), 90-day mortality (28.1% vs 10.9%, *P*=0.002) and severe complications (29.8% vs 17.2%, *P*=0.041) compared to recipients with sTC ≥1.42 mmol/L. The multivariate analysis demonstrated that sTC <1.42 mmol/L had a 4.08-fold (95% CI: 1.83-9.11, *P*=0.001) and 2.72-fold (95% CI: 1.23-6.00, *P*=0.013) greater risk of developing allograft dysfunction and 90-day mortality, and patients with sTC <1.42 mmol/L had poorer overall recipient and graft survival rates at 1-, 3-, and 5-year than those with sTC ≥1.42 mmol/L (67%, 61% and 61% vs 83%, 71% and 69%, *P*=0.025; 65%, 59% and 59% vs 81%, 68% and 66%, *P*=0.026, respectively). Cox multivariate analysis showed that sTC <1.42 mmol/L was an independent predicting factor for total recipient survival (HR=2.043; 95% CI: 1.173-3.560; *P*=0.012) and graft survival (HR=1.905; 95% CI: 1.115-3.255; *P*=0.018).

CONCLUSIONS: sTC <1.42 mmol/L on postoperative day 3 was an independent risk factor of postoperative early allograft dysfunction, 90-day mortality, recipient and graft survival, which can be used as a marker for predicting postoperative short- and long-term outcomes.

(*Hepatobiliary Pancreat Dis Int 2017;16:610-616*)

KEY WORDS: lipid metabolism; graft survival; early allograft dysfunction; morbidity; mortality

Introduction

Liver transplantation (LT) has been accepted as the effective and standard therapeutic modality for patients with end-stage liver disease.[1] With the refinement of surgical techniques and perioperative management in LT during the past decades, outcomes after LT have improved substantially in recent years. However, the postoperative morbidity and mortality remain high, which obviously affect the short- and long-term outcomes. Early allograft dysfunction (EAD) is a frequently adopted clinical endpoint and frequent postoperative complication, with the incidence ranging from 6.6% to 25%, which may ultimately progress to graft loss and death.[2-4] Therefore, rapid and accurate assessment or prediction of allograft function in the early postoperative period is critical for identifying patients at risk for graft loss so as to take measures to improve graft and patient survival.[5] Many models and index, such as laboratory values, model for end-stage liver disease (MELD) score,[3] Olthoff criteria and low bile output or production of thin bile through a T tube, have been used to evaluate

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doi: 10.1016/S1499-3872(17)60008-0
Published online April 24, 2017.

or predict graft function during the early postoperative period.[2, 5] However, few studies have reported the role of postoperative serum total cholesterol (sTC) level on predicting graft function. sTC which is predominantly synthesized in the liver can reflect the synthesis function of liver. An alteration in liver functions resulting from cellular injury can lead to changes in the level of sTC.[6] Many studies have confirmed that sTC was associated with underlying liver damage deriving from hepatitis B virus (HBV) infection, cirrhosis or fulminant hepatic failure and low sTC level was an independent predictor for liver failure.[6-10] In addition, study on LT also showed that low sTC was related to unsuccessful LT cases.[11] But, the role of postoperative sTC on evaluating graft function and predicting graft survival has not been discussed. The present study was to evaluate whether the postoperative sTC can predict postoperative EAD and whether it is associated with short- and long-term postoperative survival.

Methods

Study population

Clinical data of 320 living donor LT (LDLT) recipients and donors from May 2003 to January 2015 at West China Hospital were retrospectively collected. Family members were the living donors for each transplant recipient. Serum samples for all recipients were collected before breakfast with 12 hours' fasting. sTC test was performed preoperatively, once a day from postoperative day 1 to day 7, once a week from week 2 to week 4. Patients with age less than 18 years (67 recipients) and patients without sTC results on appropriate time (22 recipients) were excluded in our study. This resulted in a total of 231 remaining patients included in our study. These patients were divided into the low sTC group (sTC <1.42 mmol/L, 57 recipients) and the high sTC group (≥1.42 mmol/L, 174 recipients) according to their sTC level based on receiver-operating characteristic (ROC) curve analysis. Clinical and demographic data of donors and recipients were collected from the records of the Chinese Liver Transplant Registry (CLTR: http://cltr.cotr.cn). The protocol was approved by the West China Hospital Ethical Committee. Follow-up information was collected at least 3 months after transplantation. The donor selection, surgical procedures (for donors and recipients) and post-transplant management were as previous described.[12]

Outcome parameters

The primary outcome measure was EAD, defined as the presence of one or more of the following postoperative laboratory: bilirubin ≥10 mg/dL on day 7, international normalized ratio ≥1.6 on day 7, and alanine or aspartate aminotransferases >2000 IU/L within the first 7 days.[2] The secondary outcome included 90-day mortality, severe complications, graft survival and recipient survival. The 90-day mortality was defined as any death occurring from the time of surgery up to 90 days after transplantation.[13] Primary graft nonfunction was defined as death or re-transplantation within the first postoperative week after the exclusion of technical, immunological, and infectious causes.[13-15] The Clavien-Dindo complication classification system was used for postoperative complication grading and grade III-IV complications were defined as severe complications.[16]

Statistical analysis

All statistical analyses were performed using SPSS version 17 statistical software (Chicago, IL, USA), and statistical significance was set at $P<0.05$. Continuous variables were reported as mean or median (range), and were compared using the Student's t test for continuous variables with parametric distribution, Mann-Whitney U test or Kruskal-Wallis H test for those with nonparametric distribution. Categorical variables were reported as numbers and percentages, and compared using Pearson's Chi-square analysis or Fisher's exact test. The predictive ability of sTC for EAD was assessed by the ROC curve and corresponding area under the ROC (AUROC) curve. The optimal cut-off value was set as the value maximizing the sum of sensitivity and specificity, namely Youden's index.[13] To identify risk factors for EAD, 90-day mortality and severe complications, only significant factors in the univariate analysis were entered into the forward stepwise logistic regression analysis. Kaplan-Meier analysis was used to compute overall recipient and graft survival. Cox proportional-hazards analysis was adopted to identify factors independently associated with recipient and graft survival.

Results

sTC changes and patient characteristics

A total of 231 adult-to-adult LDLT were included in our cohort. Pre-transplant diagnosis included 103 hepatocellular carcinoma (82 patients accompanying with cirrhosis), 45 fulminant hepatic failure, 40 hepatitis B cirrhosis, 7 hepatocholangiocarcinoma, 5 Budd-Chiari syndrome, 4 re-transplantation, 6 biliary cirrhosis, 5 alcoholic cirrhosis, 6 cirrhosis with hepatitis C virus and 10 others. Most of the patients (212, 91.8%) received right lobe of liver without middle hepatic vein and the others were as follows: 13 (5.6%) recipients received right lobe of liver with middle hepatic vein and 2 (0.9%) received left lobe of liver and 4 (1.7%) received dual donors LT. sTC lev-