Severe Sepsis After Living Donor Liver Transplantation: Risk Factors and Outcomes

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ABSTRACT

Background. The post-operative mortality and morbidity rates associated with living-donor liver transplantation (LDLT) are still relatively high. Several papers have reported the risk factors associated with post-operative infectious complications, but few have analyzed the risk factors with respect to the severity of sepsis. The aim of this study was to clarify the risk factors that affect severe sepsis after LDLT.

Methods. For 63 LDLT patients at our institute, we compared peri-operative characteristics in 29 patients who developed sepsis after surgery and 34 patients who did not. The sepsis group was further divided into severe sepsis (n = 16) and sepsis (n = 13) subgroups to identify significant peri-operative risk factors.

Results. Multivariate analysis identified 3 significant risk factors for post-operative sepsis after LDLT: ABO incompatibility ($P = .015$), low estimated glomerular filtration rates (<90 mL/min/1.73 m^2; $P = .074$), and low peripheral lymphocyte counts (<850/μL; $P = .008$). Multivariate analysis showed that the only significant risk factor for severe sepsis was a low pre-operative lymphocyte count (<850/μL; $P = .01$). In the 2 sepsis subgroups, the 5- and 10-year survival rates for the severe sepsis subgroup (37.5% and 37.5%) were significantly lower than for the sepsis subgroup (83.3% and 62.5%; $P = .05$). The lung was the most common site of severe sepsis (n = 8; 50.0%).

Conclusions. Patients who developed severe sepsis after LDLT had poor long-term survival, with pre-operative lymphocyte counts <850/μL being the significant risk factor. Pre-operative nutritional intervention and rehabilitation should be considered to improve LDLT outcomes.

LIVER transplantation (LT) is now accepted as a reliable treatment for patients with end-stage liver disease [1]. In recent years, surgical techniques and post-operative management have advanced significantly [2,3]. However, the post-operative mortality and morbidity rates associated with living-donor liver transplantation (LDLT) are still relatively high. For these patients, infectious complications are the most frequent causes of death in-hospital [4]. LT recipients have always been a high-risk group for peri-operative infections for many reasons, including their pre-operative poor nutritional status, often associated with end-stage cirrhosis, the long surgery times involved, the need for blood transfusions to compensate for massive intra-operative bleeding, the administration of immuno-suppressants, and long-term catheterization. [4]. One of the most important issues that could improve survival rates in LDLT recipients is reducing or effectively treating peri-operative infectious complication. Several papers have reported the risk factors associated with post-operative infectious complications [4–8], but few have analyzed the risk factors with respect to the severity of sepsis. Therefore, the aim of this study was to clarify the risk factors that affect post-operative sepsis, and especially severe sepsis, after LDLT.

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METHODS

Sixty-three patients, including 1 case of re-transplantation, underwent LDLT at the Yokohama City University School of Medicine, Yokohama, Japan, between 1992 and 2015. Retrospective examination of these medical records was approved by the institution's Ethics Committee (UMIN ID; UMIN000020375) and carried out in accordance with the ethical standards set out in the Declaration of Helsinki. Peri-operative factors were compared between patients who developed sepsis within 90 days of undergoing LDLT and patients who remained sepsis-free. We defined sepsis in this study, with reference to the Surviving Sepsis Campaign Guidelines [9] and the Japanese Guidelines for the management of Sepsis [10], as an infection accompanying systemic inflammatory response syndrome (SIRS). Infections were defined using the criteria proposed by the Centers for Disease Control and Prevention [11] and previous reports of infections in LT recipients [6]. We further divided patients with sepsis into 2 subgroups according to its severity, based on the guidelines on sepsis mentioned above. Patients were categorized in the severe sepsis subgroup rather than the sepsis subgroup if sepsis-induced organ dysfunction or tissue hypoperfusion was present [9]; that is, they had lactate levels >1.78 mmol/L, acute lung damage with ratio between arterial oxygen tension and fractional inspired oxygen (PaO_2/FiO_2) <250, creatinine levels >2.0 mg/dL, total bilirubin >2.0 mg/dL, platelet counts <100,000/μL, prothrombin times >1.5 INR, or a circulatory disorder requiring a systemic agonist despite fluid replacement. Peri-operative factors were also compared between these 2 subgroups to evaluate the risk factors.

Peri-Operative Treatment of Transplant Recipients

Peri-operative treatment of LDLT recipients in our institution has been described previously [12]. All LT procedures were performed with the use of the piggyback technique. A splenectomy was performed in patients who were ABO-incompatible with the transplant, who had pancytopenia caused by splenomegaly, whose primary diagnosis was HCV, or whose hepatic portal vein pressure was >20 mm Hg after liver graft reperfusion. A Witzel tube jejunostomy was carried out to insert an 8F enteral feeding tube in the proximal jejunum. All patients received the same immunosuppressant regimen of tacrolimus and steroids. Mycophenolate mofetil was frequently added to this regimen to reduce the risk of renal dysfunction induced by tacrolimus. The minimum level of tacrolimus in whole blood was adjusted to 10 to 12 ng/mL during the first week after surgery, and thereafter the dose was tapered. Methylprednisolone was administered twice during surgery at 10 mg/kg, and the dose was then tapered. If the liver function had stabilized 2 months after LDLT, steroids were discontinued. Steroid pulse therapy was administered if severe or moderate acute cellular rejection was diagnosed by means of liver biopsy.

Surveillance cultures were collected once per week and included tests for cytomegalovirus pp65 antigen (C10) and β-D-glucan. The administration of antiviral drugs was considered when C10 values were >10. Prophylactic antibiotics were given after surgery, which included flomoxef sodium for 5 days and micafungin sodium for 1 week. The patients were started on an enteral diet when contrast medium that had been administered intra-operatively reached the ileocecum. The central vein and arterial catheters that were used during LDLT were diverted post-operatively. If any infections of the catheters were suspected, they were removed and submitted for laboratory culture.

The protocol used for ABO-incompatible LDLT patients has also been reported in detail previously [12]. Oral mycophenolate mofetil at 1000 to 2000 mg/day was given for 14 days before LDLT to inhibit B-cell proliferation, and the anti-CD20 monoclonal antibody, rituximab, was administered to deplete B cells. Plasma exchange was performed 2 or 3 times before surgery to reduce ABO antibody titers. Direct hepatic infusion was started during surgery, with prostaglandin E1 and methylprednisone administered via the hepatic artery or portal vein for 2 to 3 weeks.

Statistical Analysis

Quantitative variables were expressed as mean ± standard deviation (SD) and categorical variables as values and percentages. Continuous data were analyzed by use of the Mann-Whitney test and categorical data were analyzed by use of the χ^2 test. Overall survival was calculated by use of the Kaplan-Meier method and compared by use of the log-rank test. Stepwise logistic regression analysis was used for multivariate analysis. The cut-off levels for continuous variables were determined by use of receiver operating characteristic (ROC) curves. Any variable identified as significant in univariate analysis was considered as a candidate for multivariate analysis. Values of $P < .1$ were considered significant. All statistical calculations were carried out with the use of the SPSS V10.0 program (SPSS, Chicago, Ill, United States).

RESULTS

Characteristics of LDLT Patients

The characteristics of the LDLT patients who developed sepsis after surgery (n = 29, 46.1%) and those who did not (n = 34, 53.9%) are compared in Table 1. Among the pre-operative factors, 3 showed significant differences between the 2 groups. The number of ABO-incompatible cases in the sepsis group (n = 12, 41.2%) was significantly higher than in the sepsis-free group (n = 3, 8.8%; $P = .002$). The mean estimated glomerular filtration rate (e-GFR) was significantly lower in the sepsis group (84.0 ± 50.3 mL/min/1.73 m^2) than in the sepsis-free group (97.2 ± 46.7 mL/min/1.73 m^2; $P = .08$). The mean lymphocyte count in peripheral blood was also significantly lower in the sepsis group (709.9 ± 516.8/μL) than the in sepsis-free group (1190.3 ± 693.6/μL; $P = .002$).

Among the intra-operative factors, splenectomy had been performed significantly more frequently in the sepsis group (n = 19; 65.5%) than in the sepsis-free group (n = 15; 44.1%; $P = .08$). Two post-operative factors were significantly different between the 2 groups. Cytomegalovirus infections occurred more frequently in the sepsis group (n = 17; 58.6%) than in the sepsis-free group (n = 10; 29.4%; $P = .02$), and hospital deaths were more frequent in the sepsis group (n = 6; 20.6%) than in the sepsis-free group (n = 2; 5.8%; $P = .07$).

Risk Factors for Post-Operative Sepsis After LDLT

To identify predictive risk factors for post-operative sepsis, we further analyzed the pre-operative and intra-operative patient characteristics that had shown significant differences. Table 2 shows the univariate analysis for ABO incompatibility, a low e-GFR (<90 mL/min/1.73 m^2), a low lymphocyte count in peripheral blood (<850/μL), and whether surgery had included a splenectomy. Multivariate