Risk Factors of Mortality After Liver Transplantation in Uruguay

D. Olivari[a,b], V. Mainardi[a,b,*], K. Rando[a,b], G. Rey[a], J. Menendez[a,b], J. Prieto[a,b], J. Medina[a,b], M. Valverde[a,b], J. Castelli[b], G. Grecco[b], A. Leites[a,b], G. Zunini[a,b], S. Gozalez[a,b], M. Harguindeguy[a,b], and S. Gerona[a,b]

[a]Hepatic Biliary and Pancreatic National Center–Teaching and Assistance Unit (UDA) from Uruguay University (UDELAR), Montevideo, Uruguay; and [b]National Liver Transplant Program, Hospital Central de las Fuerzas Armadas, Montevideo, Uruguay

ABSTRACT

Introduction. Identification of predictive factors of mortality in a liver transplant (LT) program optimizes patient selection and allocation of organs.

Objective. To determine survival rates and predictive factors of mortality after LT in the National Liver Transplant Program of Uruguay.

Methods. A retrospective study was conducted analyzing data prospectively collected into a multidisciplinary database. All patients transplanted since the beginning of the program on July 2009 to April 2017 were included (n = 148). Twenty-nine factors were analyzed through the univariate Kaplan-Meier model. A Cox regression model was used in the multivariate analysis to identify the independent prognostic factors for survival.

Results. Overall survival was 92%, 87%, and 78% at discharge, 1 year, and 3 years, respectively. The Kaplan-Meier survival curves were significantly lower in: recipients aged >60 years, Model for End-Stage Liver Disease score >21, LT due to hepatocellular carcinoma (HCC) and acute liver failure (ALF), donors with comorbidities, intraoperative blood loss beyond the median (>2350 mL), red blood cell transfusion requirement beyond the median (>1254 mL), intraoperative complications, delay of extubation, invasive bacterial, and fungal infection after LT and stay in critical care unit >4 days. The Cox regression model (likelihood ratio test, $P = 1.976\ e^{-06}$) identified the following independent prognostic factors for survival: LT for HCC (hazard ratio [HR] 4.511; $P = .001$) and ALF (HR 6.346; $P = .004$), donors with comorbidities (HR 2.354; $P = .041$), intraoperative complications (HR 2.707; $P = .027$), and invasive fungal infections (HR 3.281; $P = .025$).

Conclusion. The survival rates of LT patients as well as the mortality-associated factors are similar to those reported in the international literature.

LIVER TRANSPLANTATION (LT) has become the standard of care for patients with end-stage liver disease, acute liver failure (ALF), and hepatocellular carcinoma (HCC). Despite the improvements in the survival after LT in the last decades, early mortality still occurs in the modern era [1,2]. Identifying the predictors of mortality after LT is an important issue that might improve the management of such potential events and help to minimize mortality [1].

Approximately 6000 LTs are performed each year in the United State and Europe, with survival of 70% at 5 years at most centers [3]. However, the organ shortage is a global phenomenon, with the possibility of the patient worsening and being removed from the list or dying [4]. The Model for End-Stage Liver Disease (MELD) is an allocation organ system based on the urgency and hierarchy of the sickest patients that has proven to reduce mortality in waiting list. Although the MELD score accurately predicts pretransplant

*Address correspondence to Victoria Mainardi, MD, José Felix Zubillaga 1133/1, CP11300, Montevideo, Uruguay. Tel: +598 99 59 74 86. E-mail: victoria_mainardi@hotmail.com or olivari.daniela@gmail.com

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mortality, recent studies showed no direct correlation with post-transplant mortality [5,6].

Four major dynamic inter-related factors ultimately determine the outcome after LT: organ availability and timing of LT, recipient characteristics, operative factors, and organ donor characteristics and graft type [4]. Multiple objective parameters such as recipient age, renal impairment, coagulation parameters, mechanical ventilation, liver function, vascular intraoperative complications, intraoperative blood loss, and blood transfusion requirement have been associated with diminished outcomes after LT [4].

Diagnosis of hepatitis C virus (HCV) cirrhosis and preoperative diagnosis of HCC correlate inversely with long-term survival [3,7]. Also, the LTs due to ALF are related to higher 30-day and 1-year mortality [2]. Retransplantation of the liver (ReLT) has been associated with lower survival rates than first transplantation. Most of the deaths in ReLT occur in the first month, and among those who died of sepsis, 50% died from fungal infection [8].

The determination of predictive risk factors in a transplantation program optimizes the selection of patients and organs to decrease the mortality after LT and avoids the futile transplant. The aim of this study is to determine the survival rates and identifying predictive factors of mortality after LT in the National Liver Transplant Program of Uruguay.

METHODS

A retrospective study of prospectively collected data from the Multidisciplinary National Liver Transplantation Database was performed. All the patients transplanted since the beginning of the program on July 2009 to April 2017 were included in the study. Twenty-nine factors were analyzed. Recipient factors included gender; age >60 years; MELD score >21; LT due to HCV, HCC, and ALF; and ReLT. Donor factors included age >60 years, serum sodium >150 mEq/L, cerebrovascular accident as cause of death, and the presence of comorbidities (mellitus diabetes, hypertension, obesity, addiction). Operative factors included intraoperative blood loss beyond the median (>2350 mL); red cells blood transfusion and plasma requirements beyond the median (>1354 and 1475 mL, respectively); use of platelet, colloids, and albumin; use of vasoactive drugs; cold ischemia time >360 minutes; warm ischemia time beyond the median (39 minutes), surgical total time beyond the median >444 minutes; intraoperative complications (hypotension, vascular and cardiac complications), and early extubation in surgical block. Post-LT variables also were analyzed: days in critical care unit and total hospital stay beyond the median (4 and 17 days, respectively), bacterial and fungal invasive infection, the presence of pulmonary edema, and acute kidney injury.

Univariate Kaplan-Meier model was used to investigate the factors' possible associations with survival. A Cox regression model was used in the multivariate analysis to identify the independent prognostic factors for survival. The institutional review board of our program approved the study.

RESULTS

In all, 148 LTs were performed, with combined liver and kidney transplant in 7 of them, and 62% of the patients were men. The mean age was 45 years and the mean MELD score at LT was 22. The etiologies were (1) cirrhosis in 91 patients (61%): 28 alcoholic, 21 autoimmune, 18 cholestasis (10 primary sclerosing cholangitis, 7 primary biliary cholangitis, and 1 secondary biliary cirrhosis), 8 nonalcoholic steatohepatitis, 7 cryptogenic, 6 HCV, 2 hepatitis B virus (HBV) and 1 alpha-1-antitrypsin deficiency; (2) HCC in 28 (19%): 9 alcoholic, 8 HCV, 4 autoimmune, 2 HBV, 2 hemochromatosis, 1 primary biliary cholangitis, 1 nonalcoholic steatohepatitis, and 1 Wilson disease; (3) ReLT in 12 (8%): 2 due to primary nonfunction and 10 due to delayed graft dysfunction; (4) ALF in 7 (5%): 2 autoimmune, 2 Wilson disease, 1 HBV, 1 Budd-Chiari, and 1 cryptogenic; and (5) others in 10 (7%): 4 non-HCC tumors (2 neuroendocrine and 2 hemangioendothelioma), 3 polycystic disease, 2 vascular (1 Budd-Chiari and 1 portal cavernoma with biliopathy hypertension), and 1 metabolic (primary hyperoxalosis).

The survival rates of patients were 92%, 87%, and 78% at discharge, 1 year, and 3 years, respectively.

The Kaplan-Meier survival curves were significantly inferior in recipients aged >60 years, MELD score >21, LT due to HCC and ALF, donors with comorbidities, intraoperative blood loss beyond the median (>2350 mL), red cells blood transfusion requirement beyond the median (>1254 mL), intraoperative complications, non–early extubation, bacterial and fungal invasive infection after LT, and critical care unit stay >4 days.

The Cox regression model (likelihood ratio test; $P = 1.976e^{-06}$) used in multivariate analysis identified the followings as independent prognostic factors for survival: LT due to HCC and ALF, donors with comorbidities, intraoperative complications, and fungal invasive infection. The Kaplan-Meier curves of these variables are shown in Fig 1 and the hazard ratios in Table 1.

DISCUSSION

The survival rates of the LT program of Uruguay met the quality international criteria for LT [9,10]. Knowing the risk factors associated with mortality is important to create strategies that adjust to the reality and level of expertise of each LT program.

MELD score, age of the recipient, and blood transfusion requirements were associated with mortality in the Kaplan-Meier curves but they had no association when the Cox regression model was used. Although some studies showed that recipient age >60 is an independent risk factor of post-LT death [11], others did not demonstrate this association [12]. The lack of association between age and mortality can reflect an adequate selection of the LT candidates in our center. Studies have also identified intraoperative blood transfusions as a significant risk factor for mortality after LT [13]; nevertheless, others like ours did not demonstrated this association in the multivariate analyses [14], probably because transfusion is a substitute for intraoperative complications.