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Early mortality after liver transplantation: Defining the course and the cause ☆,☆☆

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ABSTRACT

Background: The objective of the current study was to define the incidence, as well as time course of mortality within the first year after liver transplantation.

Methods: Data on adult, first-time liver transplant recipients transplanted between February 2002 and June 2016 were obtained from the United Network for Organ Sharing.

Results: Among 64,977 who underwent liver transplantation, the incidence of 90-day and 1-year mortality was 5% and 10%, respectively. Although death associated with cardiovascular/cerebrovascular/pulmonary/hemorrhage was the most cause of death within the first 21 days (7-day: 53%), only 20% of liver transplantation patients died from these causes after 180 days. Infections were the most frequent cause of death during 30–180 days after liver transplantation. In contrast, after roughly 200 days from the time of liver transplantation, other causes of death were the most frequent cause of death. Although patients with autoimmune hepatitis, nonalcoholic steatohepatitis, and alcoholic cirrhosis had a similar risk of 1-year mortality, patients undergoing liver transplantation for viral hepatitis and hepatocellular carcinoma had an increased risk of 1-year mortality (viral: OR 1.56; hepatocellular carcinoma: OR 1.57; $P < .001$).

Conclusion: Roughly, 1 in 10 patients died within the first year after liver transplantation. The cause of death had a notable, time-specific variation over the first year after liver transplantation.

Introduction

In 2016, a total of 7,841 liver transplants (LT) were performed in the United States, with the majority ($n = 7,496$, 95.6%) being deceased donor transplants.[1] Despite the trend for LT recipients in the United States being globally sicker, advances in operative techniques and medical management have resulted in incremental improvements in posttransplant survival.[2–4] In fact, patients who underwent LT between 2008 and 2011 experienced a 5-year patient survival of 80%–85%.[1] Survival after LT can vary among centers, with greater volume centers having better posttransplant patient survival.[5,6] In addition to center-specific characteristics, some authors have proposed certain predictive models to estimate risk of survival after LT.[7–9] For example, the survival outcomes after LT transplantation score and the balance of risk score seek to assess survival 3 months posttransplant.[7] In contrast, the risk models of the Scientific Registry of Transplant Recipients (SRTR) are largely used to assess post-LT outcomes at 1-year.[10] In fact, after LT, the United Network for Organ Sharing (UNOS) uses 1-year mortality as the standard quality metric to assess program performance.[11–13]

Although 1-year mortality has become the metric to assess the performance of the LT program, understanding the timing and etiology-specific causes of death within the first year post-LT may

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be important. Despite this, most previous studies have not explicitly examined the causes of death after LT within the first year.[14–16] In addition, reports on early post-LT death have only focused on perioperative risk factors, as well as on donor and recipient factors.[17,18] In contrast, there have been very few reports on the specific causes of death after LT within the first year. Rana et al[10] reported an analysis of early death after adult LT. In this study, the authors noted that mortality was greatest within the first few days after LT, with the predominant cause of death being technical or operative.[10] Other causes of early death after LT can be attributed to a variety of reasons, including operative complications, graft failure, cardiovascular disease, hemorrhage, infections, as well as to other factors. Timing of post-LT death within the first year may vary relative to a specific etiology. In turn, knowledge about the timing and specific causes of mortality within the first post-LT year may facilitate quality improvement.

Therefore, the objective of the current study was to define the mortality incidence, as well as time course of post-LT mortality within the first year after LT. In addition, we sought to characterize the specific causes of death and examine the cumulative incidence of cause-specific mortality relative to post-LT time of death within the first year after LT.

Methods

Population

A retrospective analysis was performed using the Standard Transplant Analysis and Research (STAR) files obtained from UNOS.[19] The STAR file contained patient-level data collected by the Organ Procurement and Transplantation Network (OPTN). Data were collected at the time of LT, at 6-months post-LT, and then annually. Data on adult, first-time LT recipients transplanted between February 1, 2002, and June 30, 2016, were included to have 1-year outcomes for all patients. The September 2017 STAR file includes data on patients who received transplants through June 30, 2017. Patients who received live-donor or multiple organ LTs were excluded. Additionally, patients with cause of death reported as “unknown” or “not reported” were excluded. Specifically, among the 273,052 entries in the September 2017 STAR file, patients who did not undergo LT ($n = 120,834$), received split-liver transplant ($n = 9,404$), were younger than 18 years of age ($n = 12,666$), received a previous LT ($n = 11,344$), received a multi-organ transplant ($n = 7,322$), and underwent LT before January 1, 2002, or after June 30, 2016, ($n = 42,463$) were excluded. In addition, 951 patients were excluded who experienced mortality within 1 year, because the cause of death was not recorded; 3,091 patients were also excluded, because the cause of death was reported as “unknown.” After exclusion, 64,977 patients remained in the final analytic cohort.

Causes of death

Cause of death was categorized using an established coded entry in the STAR file (Supplemental Table I).[19] Causes of death were classified as graft failure, cardiovascular, cerebrovascular, pulmonary, hemorrhage, infection, and other cause. Graft failure included graft failure attributable to a range of causes, including primary graft failure, vascular thrombosis, biliary tract complications, hepatitis, non-hepatitis recurrent disease, rejection, non-hepatitis infection, and other causes of graft failure. Cardiovascular causes included arterial or pulmonary embolism, arrhythmia, congestive heart failure, myocardial infarction, cardiac arrest, and other cardiovascular causes. Pulmonary insufficiency or edema and respiratory failure were included as pulmonary causes of death. Infectious causes included bacterial peritonitis, Legionella pneumonia, generalized sepsis, fungal infection, opportunistic infections, viral infections, and other types of infection. Other causes of death included trauma, diabetes, suicide, fluid or electrolyte disorders, acid or base disorders, acute pancreatitis, cancer recurrence, and acquired immunodeficiency syndrome.

Statistical analysis

Continuous variables were summarized, using the median and interquartile range (IQR), and categorical variables were reported as frequencies and percentages. The Wilcoxon rank sum test and Student t test were used to compare continuous data, as appropriate. Categorical variables were compared using χ^2 tests. Univariate comparisons were made, and statistically significant variables ($P < .05$) were tested in a multivariable logistic regression model to assess for the independence of the association between the variables and 90-day and 1-year mortality. The locally weighted, scatterplot smoother (LOWESS) curve fitting method was used to examine incidence patterns of cause of death over time. A P value of $< .05$ (two-tailed) was considered statistically significant. All analyses were performed using STATA v 12.0 (StataCorp LP, College Station, TX, USA) or R software for statistical computing, v 3.0.2 34, with the additional packages: survival, ggplot2, and Hmisc.[20,21]

Results

Among the 64,977 patients who underwent LT, median (IQR) age of recipient patients was 55 years (49–61), and the median age of donors was 43 years (27–55) (Table 1). The majority of recipient and donor patients were male (recipient: $n = 43,998$, 67.7%; donor: $n = 38,324$, 59.5%) and white (recipient: $n = 46,774$, 72.0%; donor: $n = 43,567$, 67.0%). The most common indications for LT included viral hepatitis cirrhosis ($n = 16,292$, 25.1%), hepatocellular carcinoma (HCC) ($n = 14,464$, 22.3%), and alcoholic cirrhosis ($n = 11,316$, 17.4%). The median albumin, bilirubin, and international normalized ratio (INR) pretransplant levels for recipient patients were 3.0 g/dL (2.5–3.5), 3.8 mg/dL (2.5–3.5), and 1.6 (1.3–2.2), respectively. The median model for end-stage liver disease (MELD) increased form 16 (12–23) at listing to 19 (13–28) at transplantation. Pretransplant, 34,609 (53.9%) and 7,315 (11.4%) patients had grade 1–2 and 3–4 encephalopathy, respectively, and 31,053 (48.3%) and 18,139 (28.3%) patients had slight and moderate ascites, respectively. Most donors died from cerebrovascular disease/stroke ($n = 24,751$, 40.2%), and 21,452 (34.9%) and 13,775 (22.4%) donors died from head trauma and anoxia, respectively. Median donor risk index (DRI) was 1.88 (IQR, 1.63–2.23).

90-day and 1-year mortality: Timing and cause of death after LT

The incidence of 90-day and 1-year mortality was 5.1% ($n = 3,320$) and 9.9% ($n = 6,459$), respectively. Among the patients who were alive 90-days after LT, the 1-year mortality was 5.1% ($n = 3,139$; Table 2; Fig. 1).

Among the 6,459 recipient patients who died within 1 year after LT, 1,111 (17.2%) patients died during the first week post-LT, with peak mortality on the day of the LT ($n = 505$, 7.8%), followed by postoperative day 1 ($n = 243$, 3.7%; Fig. 1). Although the incidence of mortality decreased over the time, 13.4% ($n = 866$) and 20.7% ($n = 1,343$) of patients died during 8–30 and 31–90 days after LT, respectively. Furthermore, roughly half of patients (48.6%) who died within the first year after LT died after 90-days from the time of LT (91–120 days, $n = 440$, 6.8%; 121–180 days, $n = 825$, 12.7%; 181–365 days, $n = 1,886$, 29.1%).

Interestingly, the relative incidence related to the cause of death (cardiovascular/cerebrovascular/pulmonary/hemorrhage, in-

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