Improving Long-Term Outcomes After Liver Transplantation

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KEYWORDS

• Liver transplantation • Metabolic syndrome • Immunosuppression • Graft rejection

KEY POINTS

- About two-thirds of deaths after the first year following liver transplantation are unrelated to graft dysfunction.
- Although chronic rejection is an unusual cause of graft loss and mortality, treated acute cellular rejection is associated with attenuated patient and graft survival for patients with hepatitis C virus infection.
- Obesity and components of the metabolic syndrome are important risk factors for many of the most common causes of mortality following liver transplantation.
- The frequency of malignancies is greatly increased among liver transplant recipients, who are at risk of a distinct spectrum of neoplasia.
- Liver transplant recipients should undergo specific screening and management protocols to screen and treat features of the metabolic syndrome and neoplasia.
- Because of the central role of immunosuppression in common causes of morbidity and mortality following liver transplantation, the minimum degree of immunosuppression needed to achieve excellent allograft function should be sought for recipients.

INTRODUCTION

Professor Thomas Starzl performed 5 human liver transplants (LTs) between March and October of 1963. The longest patient survival was 21 days. Shortly after Starzl's initial procedures, surgeons in Boston and Paris made single, failed attempts at LT. In the wake of these poor results, the medical community agreed to a moratorium on LTs that lasted for 3 years. The subsequent evolution of LT from an experimental procedure to a nearly routine operation, limited only by the number of available donor organs, has been one of the most remarkable achievements in medicine. The Scientific Registry of Transplant Recipients reports that more than 60,000 LT recipients are

Disclosure: None.
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Clin Liver Dis 18 (2014) 717–730
http://dx.doi.org/10.1016/j.cld.2014.05.011 **liver.theclinics.com**
1089-3261/14/$ – see front matter

alive with a functioning graft in the United States alone. Currently, overall 3-year patient survival following LT in the United States is 80%, with a 10-year survival rate of approximately 50% (http://www.unos.org). Patient and graft survival rates continue to improve year to year (**Fig. 1**) despite steady increases in the severity of illness (as measured by model for end-stage liver disease [MELD] score) and increasing recipient and donor age at time of transplantation. The sequential improvement in patient and graft survival following LT have been contributed to by many factors. They also have been inversely related to the frequency of steroid-resistant rejection, which now accounts for less than 4% of long-term graft loss.[1] Specific disease etiologies with recurrence of original liver diseases, such as primary sclerosing cholangitis (PSC) and hepatitis C virus (HCV), are the basis of one-third of late posttransplant deaths.[2] As LT recipients live longer, the impact of long-term side effects of highly effective calcineurin inhibitor (CNI)-based immunosuppression has become more important. Understanding graft and nongraft-related causes of long-term mortality is critical to enhancing long-term outcomes.

CAUSES OF DEATH AFTER LT

The most robust data regarding medium and long-term causes of mortality after LT were generated by the National Institute of Diabetes and Digestive and Kidney Diseases prospective multicenter study.[2] Causes of death beyond the first postoperative year were 28% hepatic, 22% malignancy, 11% cardiovascular, 9% infection, and 6% renal failure (**Fig. 2**).[2] Renal-related death increased dramatically over time. Recurrence of hepatitis C is, by far, the most common cause of late hepatic-related mortality. Risk factors for overall mortality beyond the first postoperative year include male gender, age, pretransplant and posttransplant diabetes, posttransplant hypertension, posttransplant renal insufficiency, retransplantation, pretransplant malignancy, and metabolic liver disease. Optimal management of cardiovascular disease, diabetes, hypertension, malignancy, and renal insufficiency are thus all necessary to reduce long-term mortality for LT recipients. Although considerable attention has been given to center-specific variability in 1-year posttransplant survival, there is much greater center-to-center variation in long-term outcomes, for example, 3 years

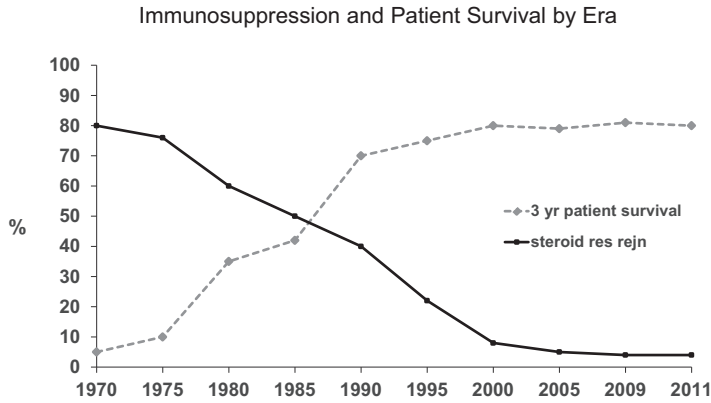

Fig. 1. Changes in 3-year patient survival after LT in the United States are shown. Increased 3-year survival has been mirrored by fall in steroid-resistant rejection, reflecting increasing efficacy of immunosuppression. (*Data from* Scientific Registry of Transplant Recipients. Available at: www.SRTR.org.)