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Review Articles

Risk Factors for Alcohol Relapse Following Orthotopic Liver Transplantation: A Systematic Review

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Background: *Each year, 5000–6000 individuals undergo orthotopic liver transplantation (OLT) in the United States, and of these, nearly 18% have alcoholic liver disease. Relapse to alcohol occurs in more than 40% of patients with OLT for alcoholic liver disease.* **Objectives:** *We sought to identify factors that predict relapse to alcohol or medication nonadherence following OLT in patients with alcoholic liver disease and to review what randomized clinical interventions have addressed these factors following OLT. Our hypothesis was that there would be factors before and after OLT that predict relapse to alcohol following OLT, and that these, if targeted, might improve sobriety and associated outcomes of adherence with medications and appointments.* **Methods:** *We performed a review (focusing on articles published since 2004) with PubMed and MEDLINE searches using the following search terms: liver transplantation, recidivism, alcohol relapse, and predictors of alcohol relapse. We supplemented the online searches with manual reviews of article reference lists and selected relevant articles for further review by author consensus.* **Results:** *In largely white populations, prospective studies document that shorter length of pretransplantation sobriety is a significant predictor of time to first drink and time to binge use. Presence of psychiatric comorbidity, high score on standardized High-risk Alcoholism Relapse Scale, and diagnosis of Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition) alcohol dependence are predictive of posttransplantation alcohol relapse. Pretransplantation alcohol use history variables (e.g., family history of alcoholism) reliably discriminate between complete abstainers and those who drink, while medical and psychosocial characteristics at early post–liver transplantation period (e.g., more bodily pain) maximally discriminate patterns of alcohol use. Alcoholic individuals with early-onset, rapidly accelerating moderate use and early-onset, continuously increasing heavy use have more than double the prevalence of steatohepatitis or rejection on biopsy and graft failure and more frequent mortality resulting from recurrent alcoholic liver disease than late-onset (i.e., peak of heaviest drinking at 6 y posttransplantation) alcohol users do. Fortunately, pretransplantation screening combined with a structured pretransplantation management program and a 12-step program attendance reduced recidivism. No randomized clinical trials have been performed that target pretransplantation risk factors in individuals with alcoholic liver disease before or after OLT to improve post-OLT outcomes.* **Conclusions:** *Recent research findings suggest that screening can reveal individuals who are vulnerable to alcohol relapse*

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and targeted intervention can prevent their relapse to alcohol. Based on existing addiction treatments (e.g., relapse prevention plan construction), randomized clinical trials tailored to post-OLT patients should be conducted to improve their survival and quality of life.
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INTRODUCTION

Results from the National Epidemiologic Survey on Alcohol and Related Conditions showed that, of the US population, lifetime alcohol abuse and dependence occurs in nearly one-third (30.3%) and 12-month alcohol abuse and dependence occurs in 8.5%.[1] These disorders are widely acknowledged to be associated with significant disability; they present a costly and deadly public health problem.[1]

Orthotopic liver transplantation (OLT), a procedure being performed since 1963[2,3] in which the native liver is removed and a new liver is placed in the same anatomic location, is the definitive therapy for liver failure in patients with end-stage liver disease (ESLD).[4] More than 40,000 patients with chronic liver disease annually show progression to ESLD which without transplantation often leads to liver failure and death.[5]

Each year, approximately 5000–6000 people in the United States with ESLD receive new livers with 1-, 3-, and 5-year patient survival rates of 87%, 78%, and 73%, respectively.[6] A total of 5805 people underwent OLT in 2011, 1024 (17.6%) of whom had alcoholic liver disease (ALD) as their primary cause of liver disease.[7]

However, with the current shortage of donor organs, approximately 5%–10% of patients currently listed for liver transplantation (LTX) will die without receiving an organ.[8] Given the imbalance between donor availability and demand, an early controversy existed whether OLT should be carried out for patients with alcohol-induced cirrhosis.[9] As summarized by DiMartini et al.,[9] there were concerns over survival,[10,11] morbidity and mortality,[12,13] patient compliance,[14,15] alcohol recidivism,[16] and ethical issues.[17]

The demonstration of similar survival rates at 1, 3, and 5 years following LTX for alcoholic ESLD (e.g., 77.1%, 68.9%, and 60.8%, respectively) and nonalcoholic ESLD (e.g., 77.3%, 67.5%, and 61.0% for patients infected with hepatitis C virus [HCV], respectively) led to the consideration of ALD as an indication for transplantation.[18] Another study of 497 OLT recipients even documented that survival was significantly *longer* in patients undergoing transplantation for alcoholic cirrhosis or mixed cirrhosis (related to alcohol *and* HCV) cirrhosis than in patients with HCV-related cirrhosis alone.[19] Specifically, patient survival at 1, 5, and 7 years in the alcohol group (90%, 76%, and 67%, respectively) was higher than that in the mixed group (86%, 73%, and 63%, respectively), and both groups had survival rates higher than that of the HCV group (72%, 49%, and 43%, respectively). The greater survival of the patients with alcoholic cirrhosis may have been partly because of the prevalence of hepatocellular carcinoma in the 2 groups of patients in whom there was HCV infection in comparison with those in the alcohol group owing to the oncogenicity of the virus. Potential explanations for the greater survival of patients in the mixed group relative to those in the HCV group were younger age and greater use of antiviral treatment in these patients; however, the authors noted that further studies with follow-up including repeated measurements of viral titers are needed to verify these results.[19] Interestingly, ALD is the second most common reason for OLT after HCV infection in the United States and Europe.[7,20] Yet, there is no uniformly accepted, standardized addiction protocol or therapy for patients with alcohol dependence either before or after transplantation.[21]

According to many, alcohol relapse is defined as any form of drinking or as more than 50% of the patient's pretreatment quantity.[22] Another definition suggests that relapse is a more sustained resumption of drinking characterized as "abusive," "addictive," or "harmful drinking."

We sought to determine if pretransplantation or posttransplantation variables could predict alcohol relapse. Such predictors, once identified, might help health professionals and patients prevent relapse following OLT, given the scarce resource of donor liver organs. We wondered if modifiable predictors (e.g., patterns of addiction, mood, cognitive dysfunction, and social support) might respond to structured interventions, such that optimal adherence and abstinence by the OLT patient might be maintained.