Outcomes after liver transplantation for combined alcohol and hepatitis C virus infection

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Abstract
Alcohol abuse and chronic hepatitis C virus (HCV) infection are two major causes of chronic liver disease in the United States. About 10%-15% of liver transplants performed in the United States are for patients with cirrhosis due to combined alcohol and HCV infection. Data on outcomes on graft and patient survival, HCV recurrence, and relapse of alcohol use comparing transplants in hepatitis C positive drinkers compared to alcohol abuse or hepatitis C alone are conflicting in the literature. Some studies report a slightly better overall outcome in patients who were transplanted for alcoholic cirrhosis vs those transplanted for HCV alone or for combined HCV and alcohol related cirrhosis. However, some other studies do not support these observations. However, most studies are limited to a retrospective design or small sample size. Larger prospective multicenter studies are needed to better define the outcomes in hepatitis C drinkers.

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Key words: Alcoholic liver disease; Hepatitis C virus; Liver transplantation; Graft survival; Mortality

Core tip: This article deals with prevalence and impact of hepatitis C virus (HCV) on progression and severity of alcoholic cirrhosis. We searched the literature on graft and patient survival among patients receiving liver transplantation for combined alcohol and HCV infection comparing to transplants received for either disease alone.

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INTRODUCTION
Hepatitis C virus (HCV) infection and alcohol abuse represent the two most common causes of cirrhosis and indications for liver transplantation (LT) in the West[1-3]. The prevalence of HCV infection peaked in 2001 at 3.6 million people infected. Cirrhosis accounted for 20% of all cases of HCV in 2006 and based upon mathematical modeling, the proportion of HCV with cirrhosis is projected to reach 45% by 2030[4]. It is now well recognized that HCV-infected patients have worse patient and graft survival than those transplanted for other etiologies[5-9]. Liver disease in patients with HCV recurrence post-LT takes an aggressive course and cirrhosis can occur within 5 years[6,7]. In contrast, outcomes after LT for alcoholic liver disease (ALD) are as good as for other etiologies[8-10].
About 8%-10% of all LT in the United States are performed in patients with cirrhosis due to combined HCV and alcohol or mixed etiology.[11] It has been shown that about 30% of patients with HCV-related cirrhosis, listed for LT have a significant history of alcohol consumption.[11] These conflicting data may be due to physicians not carefully eliciting the drinking patterns in HCV patients. Several studies have shown a synergistic interaction between HCV and alcohol resulting in more severe disease with rapid progression of fibrosis[12][13]. However, little is known about the interaction between HCV and alcohol consumption in the post-transplant setting. In this article, we will review the current literature on the outcome of patients receiving LT for liver disease due to mixed etiology.

**BASELINE CHARACTERISTICS**

Patients undergoing LT for cirrhosis due to mixed etiology are younger than those transplanted for HCV or alcohol abuse alone, with a median age of 49.5 years vs 59 years vs 53 years respectively, *P < 0.001*. Similar findings were reported in another study on the mean age of HCV transplants, alcoholic cirrhosis transplants, and patients transplanted for combined alcohol and HCV (53 ± 9 years vs 52 ± 8 years vs 49 ± 8 years respectively, *P < 0.001*)[14]. In one study, the duration of liver disease before LT was reported to be shorter in patients with mixed etiology by about 10 years as compared to alcohol alone, with a median age of 49 ± 8 years respectively, *P < 0.001*. Even though alcoholic cirrhosis patients were older, they were sicker at the time of transplantation than those with cirrhosis secondary to HCV or mixed etiology; the proportion of patients with Child-Pugh-Turcotte stage C were 47% vs 50% vs 43% respectively, *P = 0.01*.[15] In this study, the prevalence of hepatocellular carcinoma (HCC) was higher in patients with HCV-induced cirrhosis and patients with cirrhosis due to mixed etiology as compared to alcoholic cirrhosis (44% vs 35% vs 18% respectively, alcohol vs mixed, *P = 0.01*, HCV vs alcohol *P < 0.001*).[16] Similar findings were observed in another study on the prevalence of HCC in the three groups.[17] Further, the tumors in the mixed group were found to be larger compared to those in patients with alcoholic cirrhosis (mean diameter 4.25 cm vs 0.85 cm).[17] It may be inferred that patients transplanted for mixed etiology tend to have a more aggressive and faster progression to end-stage liver disease requiring transplantation.

**WAIT LIST MORTALITY**

Patients with cirrhosis due to mixed etiology are more likely to die while they are waiting for LT. Lucey et al.[16] showed that patients with cirrhosis due to alcohol differed from patients with cirrhosis due to causes other than alcohol for wait list mortality only with respect to HCV positive cases, with 14% higher risk of death in patients with liver disease due to mixed etiology, *P = 0.006*. In this study, the survival benefit from LT was dependent upon the MELD score in patients with HCV, with a transplant benefit seen with a MELD score > 29. However, the survival benefit from LT was independent of MELD score for alcohol-related cirrhosis.[17] This finding is probably due to the apparent low rate of post-transplantation heavy drinking. Further, it takes up to 5-10 years of alcohol use to have a negative impact on the graft.[18][19]

**GRAFT AND PATIENT SURVIVAL**

Several studies have reported the outcomes after LT in patients with cirrhosis due to mixed etiology and compared the findings with patients transplanted for HCV and for alcoholic cirrhosis alone (Table 1). However, these studies have provided conflicting results.[17][20][21][22] A database looking at the experience of multiple European transplant centers found the survival rates following LT to be lower in patients transplanted for viral or mixed etiology compared to patients transplanted for alcoholic cirrhosis[14]. The authors further found that *de novo* tumors were a major cause of death in patients receiving LT for alcoholic cirrhosis. Patient mortality due to social issues including non-compliance to medications and non-adherence to medical instructions was more frequent in alcoholic cirrhosis and mixed etiology groups compared to HCV cirrhosis. In a more recent study based on the UNOS database, the five year graft and patient survival were similar in patients transplanted for mixed etiology and HCV cirrhosis but were lower compared to those transplanted patients for alcoholic cirrhosis (76% vs 6% vs 79% respectively; HCV vs mixed etiology *P = 0.87* and HCV vs alcohol, *P < 0.0001*).[19] However, a retrospective study at a single center in Europe obtained different results. In this study, the outcome of 60 patients with LT for cirrhosis due to mixed etiology was compared with

| Study design | 1 yr survival (sample size) | 5 yr survival (sample size) |
|--------------|----------------------------|-----------------------------|
| Dhar et al.[16] Retrospective | 31 (80) | 11 (72) |
| Aguilera et al.[16] Retrospective | 122 (72) | 51 (86) |
| Burra et al.[16] Population | 4166 (81) | 714 (84) |
| Singal et al.[16] Population | 15595 (88) | 6003 (88) |

ALD: Alcoholic liver disease; HCV: Hepatitis C virus.
patients with HCV cirrhosis and alcoholic cirrhosis\textsuperscript{[18]}. The authors found that patient survival at 5 years after LT was lower in patients with HCV cirrhosis compared to mixed etiology and alcoholic cirrhosis (49% vs 73%, and 76% respectively, HCV vs mixed group, \( P = 0.0001 \))\textsuperscript{[18]}. Factors such as variations in the study design, data source, study population, and sample size may account for the differences in the findings among various studies. Further, in the study reported from the single European center showed increased rates of anti-HCV treatment and of re-transplantation in patients with cirrhosis due to mixed etiology as compared to the other two groups which may explain the conflicting results\textsuperscript{[18]}. These data on HCV treatment are not available in studies reporting data using UNOS or European LT databases.

**ALCOHOL RELAPSE**

Recidivism (relapse of alcohol consumption) rates after LT vary widely, ranging from 7% to 95\%\textsuperscript{[28-31]}. These variations are due to differences in the definitions used for recidivism, methods used for diagnosing alcohol abuse, the follow-up period, and the study population across different studies\textsuperscript{[18]}. In a pooled analysis of 50 studies evaluating recidivism after LT, the rates of any alcohol use after LT were 5.7\% per 100 person years, and 2.5\% per 100 person years risk for harmful drinking\textsuperscript{[27]}. The data on the negative impact of recidivism on the graft are conflicting\textsuperscript{[28-31]}. Conjevaram et al\textsuperscript{[28]} observed that the incidence of heavy drinking post OLT was uncommon, but fatal in terms mortality and graft loss. They further observed that the presence of steatosis and Mallory bodies in the explanted liver predicted recidivism\textsuperscript{[19]}. In one study, the recidivism rates were similar in transplants performed for alcoholic cirrhosis and for mixed etiology (5 out of 56 vs 3 out of 32 patients). Further, the return to excessive drinking was not common\textsuperscript{[17]}. All the five patients in the ALD group were alive at 5 to 8.8 years after LT. Of the three patients that returned to drinking in patients transplanted for mixed etiology, one patient died of continued alcohol abuse\textsuperscript{[17]}. Another study examined the impact of recidivism on the liver graft in patients transplanted for alcoholic cirrhosis with or without concomitant HCV. No significant differences in the graft histology were observed between HCV positive heavy drinkers (> 200 g/wk), occasional drinkers (< 200 g/wk), and abstainers\textsuperscript{[17]}. Aguilera et al\textsuperscript{[19]} noted that patients undergoing transplantation for ALD had a higher rate of relapse compared to patients receiving LT for HCV cirrhosis and for cirrhosis due to mixed HCV and alcohol (18\%, 3\%, and 8\% respectively, HCV vs alcohol \( P < 0.001 \)). However, the duration of alcohol consumption was shorter, with a relatively small quantity of alcohol use. Further, no significant differences were noted in the liver tests in the three groups\textsuperscript{[18]}. Based upon the current literature, recidivism after LT in patients with cirrhosis due to both alcohol and HCV does not seem to affect the liver function adversely. However, long-term outcome of patients with recidivism is less favorable compared to occasional drinkers and abstainers\textsuperscript{[13]}. Hence, these patients should be advised to maintain complete abstinence after LT.

**HCV RECURRENCE**

Perhaps, one of the major concerns in patients transplanted for HCV cirrhosis is the risk for HCV recurrence and its impact on the liver graft. Alcohol may potentiate this damage by transiently increasing the circulating levels of HCV RNA\textsuperscript{[19]}. However, the current literature does not provide convincing evidence that HCV recurrence in patients transplanted for liver disease secondary to mixed etiology is more aggressive than that in patients with HCV cirrhosis alone\textsuperscript{[17,18]}. The results of a study from a single center on patients transplanted for alcoholic cirrhosis, HCV cirrhosis, or cirrhosis secondary to mixed etiology showed that the only variable associated with a better outcome after LT was the use of anti-HCV therapy after LT\textsuperscript{[18]}. There was no difference after one year in patients transplanted for HCV-related cirrhosis compared to LT in patients with mixed etiology with respect to the development of severe recurrent HCV infection (45\% vs 45\%, \( P = 0.66 \)), acute hepatitis (26\% vs 28\%, \( P = 0.85 \)), or fibrosis stage > 1 (34\% vs 35\%, \( P = 0.88 \))\textsuperscript{[18]}. Patients transplanted for mixed etiology received anti-HCV treatment more often compared to patients transplanted for HCV cirrhosis. With regard to alcohol relapse, the data was limited by the small sample size, and needs further validation.

**CONCLUSION**

The current literature supports the notion that cirrhosis secondary to mixed etiology (combined alcohol and HCV) is an acceptable indication for LT, with graft and patient survival comparable to patients receiving LT for HCV cirrhosis or for ALD. The synergistic interaction between alcohol and HCV leads to more aggressive disease prior to LT including higher wait-list mortality. However, the impact of mixed disease after LT remains unclear, with conflicting findings, suggesting the need for more prospective multicenter studies on a larger sample size to better examine this question and devise strategies to improve the management of these patients.

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