

# Liver Transplantation for Alcohol-Related Liver Disease

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**Alcoholic liver disease (ALD) is a common indication for liver transplantation. It is a much debated indication for deceased donor liver transplantation due to organ shortage and potential of alcohol relapse after liver transplantation. A six-month abstinence before liver transplantation is required at most centers to decrease chances of alcohol relapse after liver transplantation. However, this rule is not relevant for patients with severe alcoholic hepatitis or severely decompensated patients who are unlikely to survive till 6 months. Long-term care of these patients after liver transplantation includes assessment of relapse, smoking, and surveillance of de novo malignancies. Current review discusses role of abstinence, factors affecting alcohol relapse, liver transplantation for alcoholic hepatitis, role of living donor liver transplantation, and long-term care of ALD patients who undergo liver transplantation. (J CLIN EXP HEPATOL 2016;6:47-53)**

**A**lcoholic liver disease (ALD) is common indication for liver transplantation worldwide,<sup>1,2</sup> and is a common cause of decompensated cirrhosis and acute-on-chronic liver failure in India as well.<sup>3,4</sup> ALD has good outcome after liver transplantation that is comparable or better than other etiologies of liver transplantation. Recent European liver transplant registry data showed 73% 5-year and a 59% 10-year survival rate for ALD.<sup>2</sup> However, survival is lower in recipients who relapse to harmful pattern of drinking as noted in a systemic review of 13 studies by Rustad et al.<sup>5</sup> Liver transplantation for ALD leads to improvement in quality of life and employment rates.<sup>6,7</sup> During selection of these patients for liver transplantation, it is important to identify other alcohol-related problems like cardiomyopathy, chronic pancreatitis, skeletal muscle wasting, and neurotoxicities that may preclude or impair outcome of liver transplantation.<sup>8</sup> Patients who have lack of social support, are active smokers, and have psychiatric disorders or alcohol dependence should be listed only with reservations.<sup>9</sup> Smoking worsens the outcome of alcohol-related liver disease<sup>10</sup> and active smoking at the time of liver transplantation has been shown to be associated with post-transplant recidivism also.<sup>11</sup>

## PREDICTORS OF RELAPSE

While liver transplantation improves functions of liver and cures complications of portal hypertension, it does not affect alcoholism and recipients may relapse again, sometimes to harmful levels of drinking, and pretransplant sobriety does not confirm sobriety after liver transplant.<sup>12-14</sup> Relapse may be in the form of occasional slips or harmful drinking pattern for a prolonged period; the later affects graft and patient survival.<sup>5,11</sup> Initially, 6-month abstinence was considered as a requirement before allocating organ to patients with ALD; however, it was based on poor quality small data.<sup>15</sup> The 6-month rule serves 2 purposes; it provides patient time to demonstrate a certain period of abstinence and patient may recover on medical management, and thus preemptive liver transplantation may be avoided.<sup>16</sup> However, patients who are very sick may not survive for a period of 6 months. The authors of Lille model (6 variables: age, renal impairment, albumin, prothrombin time, bilirubin at baseline, and at day 7 of treatment with steroids) showed that survival was only 25% in nonresponder to steroid group.<sup>17</sup> Mathurin et al. showed a cumulative 6-month survival rate of 77 ± 8% in patients with severe nonresponding alcoholic hepatitis who had early liver transplant versus 23 ± 8% for controls,  $P < 0.001$ .<sup>18</sup> Prevalence of alcohol relapse after liver transplantation varies widely.<sup>19-21</sup> This wide range of relapse after liver transplantation reflects several methodological differences among studies, variable follow-up, and difference in definition of relapse (any alcohol intake versus harmful drinking).<sup>21</sup> Mackie et al.<sup>22</sup> compared alcohol intake in alcoholics with other etiologies of liver transplantation and found similar rates. Several larger studies evaluating rate of relapse and factors predicting relapse after liver transplantation are shown in Table 1, the relapse rate varies from 16% to 42% and harmful relapse rate varies from 10% to 18%.<sup>11,23-33</sup> Various factors found to predictive of post-transplant alcohol relapse are shown in

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*Abbreviations:* ALD: alcoholic liver disease; CDT: carbohydrate-deficient transferrin; GGT: gamma-glutamyltranspeptidase; HRAR: High Risk Alcoholism Relapse score; LDLT: living donor liver transplantation; MELD: Model for End-Stage Liver Disease score  
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**Table 1 Rate of Alcohol Relapse in Various Studies.**

Author, year	N	Follow-up	Relapse rate %
Björnsson, <sup>23</sup> 2005	103	31 months (median)	33%, 18% heavy drinking
DiMartini, <sup>24</sup> 2006	167	5 years (mean)	42%
Pfizzmann, <sup>25</sup> 2007	300	89 months (median)	19%
De Gottardi, <sup>26</sup> 2007	387	61.2 months (mean)	11.9% harmful alcohol consumption
Gedaly, <sup>27</sup> 2008	142	41.2 months (median)	19%
Tandon, <sup>28</sup> 2009	171	64.8 months (mean)	24%, 13% problem drinking
Karim, <sup>29</sup> 2010	80	Not mentioned	10% harmful relapse
Hartl, <sup>30</sup> 2011	120	31 months (mean)	16%
Rodrigue, <sup>31</sup> 2013	118	55 months (mean)	33.8%
Deruytter, <sup>32</sup> 2013	108	55 months (mean)	29%, 16% problem drinking
Egawa, <sup>33</sup> 2014	140	1319 days (median)	22.9%, living donor liver transplantation
Satapathy, <sup>11</sup> 2015	128	1354 days (mean)	16 (10.8%) harmful alcohol consumption

**Table 2.** Following variables have been shown to be associated with risk of post-transplant alcohol relapse: absence of structured management program pretransplant, length of pretransplant sobriety, alcohol or other substance dependence, prior alcohol rehabilitation, poor social support/lack of partner, poor psychosomatic prognosis or psychiatric comorbidity, female sex, patients' nonacceptance of having an alcohol problem before LT, continued alcohol use after liver disease diagnosis, low motivation for alcohol treatment, and presence of a first-degree relative with alcohol abuse in family.<sup>11,23-33</sup> Pretransplant sobriety predicting absence of alcohol relapse after liver transplant is not a universal finding.<sup>11,15,23-33</sup> Scoring systems also have been proposed to predict post-transplant alcohol relapse. In a study of 118 patients by Rodrigue et al.,<sup>31</sup> the authors advised a scoring system (Alcohol Relapse Risk Assessment) to predict risk of relapse. They studied 25 hypothesized risk factors and found 9 as significantly predictive of relapse after transplant. These factors were absence of hepatocellular carcinoma, dependence on tobacco, ongoing alcohol use after diagnosis of liver disease, poor skills of stress management, absence of rehabilitation relationship, low motivation for alcohol treatment, limited social support, lack of non-medical behavioral consequences, and continued engagement in social activities with presence of alcohol. Each predictor was given a score of 1 and patients were classified into 1 of 4 groups by ARRA score. Patients in groups ARRA III (score 4-6) and ARRA IV (score 7-9) had significantly higher rates of alcohol relapse and were more likely to return to pretransplant levels of drinking. Another score found to be useful to predict post-transplant alcohol relapse is High Risk Alcoholism Relapse (HRAR) score;<sup>26</sup> it consists of the following three variables: duration of heavy drinking, number of daily drinks, and number of prior alcoholism inpatient treatment experiences. Each item is scored as 0-2 and total possible score ranges from 0 to 6. The authors have

shown a HRAR score higher than 3 as associated with high risk of alcohol relapse after liver transplantation.<sup>26</sup>

Dew et al.<sup>13</sup> found alcohol relapse rate of 5.6 cases (any alcohol use) and 2.5 cases (heavy alcohol use) per 100 liver transplant recipients per year in a meta-analysis including 50 liver transplantation studies conducted between 1986 and 2005 in North America or Europe. These studies were mainly cross-sectional or retrospective ( $n = 44$ ) and included a total of 3551 recipients with median follow-up of 3.4 (range 0.9-12.3 years). The authors studied 12 psychosocial variables and found small (effect size 0.17-0.21) but significant association of post-transplant relapse with poorer social support, pretransplant sobriety <6 months, and alcohol abuse/dependence history in family, thus having some predictability but not high degree of accuracy to predict post-transplant relapse. The factors not found to be significant were male sex, higher age, higher education, unmarried status, unemployment, poorer social support, presence of psychiatric history before transplant, use of illicit drugs, history of alcohol abuse or dependence on family, and no alcohol rehabilitation before liver transplantation.<sup>13</sup>

In a systemic review of 13 studies published since 2004, Rustad et al. found shorter sobriety before transplantation as a significant predictor of time to first and binge alcohol use. Other factors predicting alcohol relapse included presence of alcohol dependence/psychiatric comorbidity and higher score on High-risk Alcoholism Relapse scale. Recipients with early-onset accelerating moderate/increasing heavy use had more than twice prevalence of steatohepatitis or rejection and graft failure/mortality than late-onset (peak of drinking at 6 years after transplantation) alcohol users.<sup>5</sup>

Active involvement of a psychiatrist may decrease relapse after liver transplant.<sup>23,34</sup> In a study of structured management program including a psychiatrist, Björnsson et al. demonstrated relapse rate of 48% (19/40) compared

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