PREDICTORS OF RELAPSE TO HARMFUL ALCOHOL AFTER ORTHOTOPIC LIVER TRANSPLANTATION

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Abstract — Background: End-stage alcoholic liver disease (ALD) is a common indication for liver transplantation. Outcomes may be limited by return to harmful drinking. Previous studies have identified few predictors of drinking relapse. Aim: This study examined novel postulated predictors of relapse to drinking. Method: The case notes of all patients transplanted for ALD at the Royal Prince Alfred Hospital from 1987–2004 were reviewed. Pre-transplant characteristics were rated by a psychiatrist independent of the transplant team, blind to the outcome. Outcomes were rated by a second independent alcohol treatment specialist also blind to the pre-transplant ratings. Results: Of 100 patients, 6 died before discharge from hospital, 4 had <6 months follow-up, 18 relapsed to harmful drinking, 10 drank below harmful levels, and 62 remained abstinent after a mean of 5.6 years follow-up. Univariate analyses identified six potential pre-transplant predictors of return to harmful drinking. These were a diagnosis of mental illness (of which all cases were of depression), the lack of a stable partner, grams per day consumed in the years before assessment for transplant, reliance on ‘family or friends’ for post-transplant support, tobacco consumption at time of assessment, and lack of insight into the alcohol aetiology. Duration of pre-transplant abstinence and social class by occupation did not predict relapse. A multivariate model based on the above characteristics correctly predicted 89% of the outcomes. Conclusion: A model based on readily defined behaviours and psychosocial factors predicted relapse to harmful drinking after transplant for ALD. This model may improve assessment and post-transplant management of patients with advanced ALD.

Alcoholic liver disease (ALD) is a common cause of cirrhosis of the liver and is also a common indication for liver transplantation. Following early uncertainty, it is now widely accepted that the overall clinical outcomes of liver transplantation for carefully selected patients with ALD are similar to those of other forms of liver disease (Lucey et al., 1992; Haber et al., 1999; Bjornsson et al., 2005). However, relapse after transplant to harmful use of alcohol remains a concern and can lead to significant problems. Up to 40% of those receiving a liver transplant will return to consuming alcohol (Bird et al., 1990; Lucey et al., 1997; Gish et al., 2001; Pageaux et al., 2003; Lim and Keeffe, 2004). Up to 20% drink heavily (Pageaux et al., 2003; Lim and Keeffe, 2004), which can lead to recurrent ALD (Pageaux et al., 2003), graft failure due to non-compliance with immunosuppression treatment and other serious alcohol-related harms including death (Cuadrado et al., 2005).

Orthotopic liver transplantation is a highly resource intensive treatment with access typically limited by availability of suitable donor livers. The identification of those patients likely to experience the maximum sustained benefit is very important. Specific and objective selection criteria have been sought without success to date. A minimal period of 6 months pre-transplant abstinence from alcohol is an objective measure widely adopted as it provides adequate time to demonstrate cessation of alcohol use and also provides the opportunity for many patients to recover adequately so as to no longer require transplantation. However, this ‘six month rule’ has been criticized as being arbitrary and the pre-transplantation duration of abstinence is a poor predictor of outcome (Weinrieb et al., 2000; Neuberger et al., 2002; Lim and Keeffe, 2004). Lucey et al. (1992) proposed that four factors defined risk of post-transplant relapse to heavy drinking (insight, stable partner, stable housing, stable employment). Subsequent research from several groups has shown that pre-transplant assessment does not predict the minority who return to heavy drinking after successful transplantation (Lucey et al., 1997; Mackie et al., 2001; Bjornsson et al., 2005). However, DiMartini et al. (2001) reports predictive data in a study of 36 patients surviving transplantation for ALD. Post-transplant use of any alcohol was significantly associated with prior non-alcohol substance use, presence of a first-degree relative with alcoholism, prior alcohol rehabilitation but not with prior psychiatric history. Diagnosis of alcohol dependence by an addiction psychiatrist was the only pre-transplant factor assessed, which predicted return to harmful drinking (Smyth et al., personal communication).

The relevance of factors associated with relapse in addictions outside the transplant context remains unclear. Prognostic factors of interest include insight, presence of psychiatric comorbidity, stability of relationships, housing and employment, maintenance of abstinence while physically well enough to drink, and expansion of social role with abstinence. Rather than any consumption of any alcohol, the outcome variable of interest was harmful alcohol consumption as the latter is of greater clinical significance. The aim of this study was to test the value of these parameters as predictors of relapse to harmful drinking after liver transplantation for ALD.

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METHODS

The study protocol was approved by the Ethics Review Committee of Central Sydney Area Health Service (RPA Zone). The Australian National Liver Transplant Unit is based at Royal Prince Alfred Hospital and maintains a prospective database of all liver transplants, which includes the underlying aetiology for liver disease. The standardized pre-operative checklist did not include the specific questions we wished to look at, covering medical and demographic items. Accordingly, the notes of all patients who received a liver transplant with a record of alcoholic cirrhosis as either the primary or secondary diagnosis were reviewed.

From study of the literature, consultation with the transplant team, including the liaison psychiatrist and the substance misuse specialist who had interviewed a proportion of the patients, a list was prepared of candidate predictors of post-transplant drug and alcohol misuse, which was refined to include only the items for which the pre-transplant assessment and medical records would provide data. Some pre-transplant variables of possible interest were not included because data were not consistently recorded, e.g. alcohol rehabilitation experience and family history of alcoholism.

A psychiatrist (M.K.) who was blind to the post-transplant outcome examined the pre-transplant hospital notes for all information recorded of relevance to the candidate predictors of outcome (Table 1). All patients had had a discussion with the transplant team about their alcohol use, and the need for life-long abstinence from that point was routinely stressed. Only when it was noted specifically that motivation or insight was a concern was that patient given a negative score for that binary variable. Where there had been no mention of concern, the patient was rated by M.K. as ‘positive’. A senior alcohol specialist (J.C.), who was blind to the pre-transplant ratings, examined the post-transplant notes to rate outcome. Neither had met the patients or had any role in the treatment of the patient was rated by M.K. as ‘positive’. A senior alcohol specialist (J.C.), who was blind to the post-transplant assessment may not have included consultation with addictions or psychiatry specialist

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As a measure of inter-rater reliability, the assessments made on eight patients by a third rater (M.H.) were compared with the ratings made by M.K. and J.C.

Outcome variables

Our primary outcome variable was the incidence of return to harmful drinking. The definition of harmful drinking was drinking with recorded medical or social harm, or drinking above 140 g ethanol/week. ‘Harm’ included evidence of ongoing abnormal liver tests consistent with alcohol, which could not be accounted for by other factors despite investigations and careful consideration of organ rejection and medication.

None of the case records includes results of breathalyser tests, or blood or urine ethanol. In our analysis, those who drank below harmful limits are included with the abstainers. Any record or evidence of post-transplant drinking was noted.

Statistical analysis

Univariate tests of significance between the two outcome groups were conducted using cross-tabulations and Chi-squared tests for categorical variables (continuity corrected), with appropriate attention to small cell sizes. Mann-Whitney U-tests were used for continuous variables. Stepwise logistic regression analysis (forward conditional) was conducted to identify significant predictors to harmful drinking. The Statistical Package for the Social Sciences (SPSS Version 13 for Windows, Chicago, IL) was used for all analyses.

RESULTS

There were 100 patients between 1987 and 2004 who received liver transplants for ALD alone or with a diagnosis of chronic viral hepatitis. Three patients were transplanted twice, owing to complications unrelated to substance misuse, making a total of 103 such transplants. The numbers of patients transplanted for ALD increased as the years went by. Between 1987 and 1990, there were only 3; from 1991 to 1994, 14; from 1995 to 1998, 26; from 1999 to 2002, 30; and from 2003 to 2004, 30.

Six died at or soon after the transplant, and four had less than 6 months of follow-up at the time of the ratings and were not included in the study. Of the remaining 90, 18 (20%) relapsed to harmful drinking and another 10 drank below harmful levels up to the date of the study (total drinkers 28, 31%; Fig. 1). Of the 26 patients who had ever used illicit drugs prior to transplant, 22 of whom had injected, 10 (38%) resumed illicit drug use post-transplant, and 2 (9.1%) resumed injecting. Of those who consumed illicit drugs post-transplant four were also harmful drinkers and six were abstainers from alcohol. Of the abstainers and non-harmful drinkers, 67 were male (81%); of the 18 harmful drinkers, 15 were male (83%).
The time to a record in the casenotes of harmful drinking post-transplant varied from 60 days to over 10 years (Fig. 2). Fifty percent of relapses were recorded within the first 2 years. The mean duration of follow-up was 5.6 years, suggesting the duration of follow-up was sufficient to detect most relapse events. Relapse to harmful drinking emerged as very serious for several patients. One patient had a drink drive offence, another’s drinking led to his partner leaving, one patient developed life-threatening alcoholic pancreatitis, and one man died on the waiting list for a second transplant liver having once again developed ALD.

Inter-rater reliability
In all eight cases there was complete agreement between raters on all pre-transplant and outcome variables.

Univariate analysis
The characteristics of interest as possible predictors of relapse among these 90 patients are shown in Table 2. A series of univariate tests, showed that tobacco consumption at the time of assessment, the presence of mental illness diagnosis prior to transplant, lack of a stable partnership, and tobacco consumption were significantly associated with post-transplant harmful drinking. In addition, there were a number of variables approaching significance. These were a lack of insight into alcohol as the main aetiology of liver failure, lack of a meaningful abstinent lifestyle, unstable housing, grams per day of alcohol consumed when drinking in the years before the assessment for transplant, late referral for transplant assessment, and a lack of consensus concerning suitability amongst the transplant team. The presence of stated family or friend...
support correlated with harmful drinking outcome (see Discussion).

Multivariate analysis

A stepwise logistic regression analysis showed that a model based on six pre-operative predictor variables accounted for 52% of the variance in outcome ($P < 0.0001$). All the hypothesized predictor variables were significant and were included in the following order (Table 3):

1. grams per day alcohol before assessment for transplant;
2. mental illness diagnosis;
3. stable relationship;
4. family or friends support;
5. tobacco use per day;
6. insight into alcohol aetiology.

The multivariate model correctly classified the outcome of 89% of patients (Table 4). Ten of the twelve who the model predicted would return to harmful drinking did so, indicating that the positive predictive value was 83%. Two were incorrectly predicted to return to harmful drinking. Of the 77 cases where the model predicted no return to heavy drinking, 8 cases relapsed indicating that the negative predictive value was 90%.

### Table 2. Univariate analysis of pre-transplant risk factors for harmful alcohol consumption post-transplant

<table>
<thead>
<tr>
<th>Pre transplant variable</th>
<th>None/not harmful drinking</th>
<th>Harmful drinkers</th>
<th>Significance $P$-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcoholic cirrhosis—primary diagnosis n (%)</td>
<td>44 (61%)</td>
<td>7 (40%)</td>
<td>0.089</td>
</tr>
<tr>
<td>Age at transplant mean (SD) (median)</td>
<td>50.8 (7.2) (50.5)</td>
<td>47.5 (5.8) (48.5)</td>
<td>0.101</td>
</tr>
<tr>
<td>Days from transplant to outcome assessment mean (SD) (range)</td>
<td>2022 (1689) (143–6302)</td>
<td>2195 (963) (635–4175)</td>
<td>0.246</td>
</tr>
</tbody>
</table>

### Table 3. Final regression model

<table>
<thead>
<tr>
<th>Variables entered in final model</th>
<th>Coefficient $\beta$</th>
<th>Standard error</th>
<th>$P$-value for use in model</th>
<th>Odds ratio</th>
<th>Lower</th>
<th>Upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grams per day alcohol</td>
<td>0.009</td>
<td>0.005</td>
<td>0.059</td>
<td>1.009</td>
<td>1.000</td>
<td>1.018</td>
</tr>
<tr>
<td>Mental illness</td>
<td>2.005</td>
<td>1.026</td>
<td>0.051</td>
<td>7.424</td>
<td>0.993</td>
<td>55.485</td>
</tr>
<tr>
<td>Partner</td>
<td>-2.611</td>
<td>0.823</td>
<td>0.002</td>
<td>0.073</td>
<td>0.015</td>
<td>0.368</td>
</tr>
<tr>
<td>Family/friends</td>
<td>3.669</td>
<td>1.444</td>
<td>0.011</td>
<td>39.16</td>
<td>2.314</td>
<td>663.792</td>
</tr>
<tr>
<td>Cigarettes/day</td>
<td>0.061</td>
<td>0.025</td>
<td>0.016</td>
<td>1.065</td>
<td>1.012</td>
<td>1.116</td>
</tr>
<tr>
<td>Insight</td>
<td>-1.770</td>
<td>0.754</td>
<td>0.019</td>
<td>0.170</td>
<td>0.039</td>
<td>0.748</td>
</tr>
<tr>
<td>Constant</td>
<td>-4.079</td>
<td>1.681</td>
<td>0.015</td>
<td>0.017</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Continuity correction used for $2 \times 2$ tables.

### Table 4. Classification of outcome by model at step 7

<table>
<thead>
<tr>
<th>Predicted Drinking status</th>
<th>Observed</th>
<th>Abstinent/not harmful drinking</th>
<th>Harmful drinking</th>
<th>% correct</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abstinent/not harmful drinking</td>
<td>69</td>
<td>2</td>
<td>97.2</td>
<td></td>
</tr>
<tr>
<td>Harmful drinking</td>
<td>8</td>
<td>10</td>
<td>55.6</td>
<td></td>
</tr>
<tr>
<td>Overall percentage</td>
<td></td>
<td></td>
<td>88.8</td>
<td></td>
</tr>
</tbody>
</table>
DISCUSSION

This study has demonstrated that pre-transplant assessment of patients with ALD is able to identify patients at particular risk of returning to harmful consumption of alcohol post-transplant. The predictors of outcome were those that could be defined by the transplant hepatologist without specialist skills in addiction medicine, or psychiatry. A comprehensive structured assessment battery was not in place in the service studied; a role for routine use of such batteries is not yet established. The model predicted the presence or absence of relapse in 89% of cases. There is evidence that relapse to alcohol use adversely impacts on survival. The findings of this study should be replicated in a different transplant population before being incorporated into transplant assessment protocols. Additionally, prospective identification of the group at greatest risk of post-transplant substance use problems creates the opportunity for additional intervention to prevent relapse and its associated adverse clinical events.

Strengths and limitations

The strengths of the study design are that we had independent blind raters who assessed clinically relevant outcomes with a relatively large sample size for a single centre study. The study looked strictly at recorded material and was not influenced by any knowledge or personal involvement in any clinical care. The outcome ratings were done by an expert in alcohol problems with experience in detecting alcohol abuse using all clinical indicators. Harmful drinking, not ‘any drinking’ was used as the outcome of interest; this is a more clinically relevant outcome measure. It avoids making assumptions of whether low-level drinking may or may not lead to later harm, although it may be noted that only one-third of post-transplant drinking was rated as ‘non-harmful’. The focus for this study was the clinical records made by clinicians performing routine care, yielding a measure of clinically significant relapse. This may have been less sensitive than any self-reported alcohol consumption, but was likely to be more specific by focussing on clinically important use of alcohol. It did not include sub-clinical alcohol consumption and thus reduced ‘noise’ in the data. Self-reports of consumption, unreliable in many contexts, may be especially unreliable when, as in a transplant unit, the patient had given a vow to abstain. However it is possible that relying only on case records will miss some cases of return to heavy drinking, which have not aroused clinical suspicion, despite frequent close monitoring by the transplant and community teams of both clinical and laboratory parameters, and regular communication between transplant clinicians and the patients carers.

Similarly, the date of recording of harmful drinking does not necessarily indicate the date harmful drinking commenced, because it may have been hidden for some time. Nonetheless, it is striking that the majority of relapses occurred early, and therefore interventions even only in the first post-transplant year would be likely to help reduce the total relapse rate. However, as almost half the relapses occurred after the first 2 years, close monitoring of an at risk group should be sustained long term.

The model

Our findings indicate that if each patient is assessed and given a score according to these variables it is possible to predict with a fair reliability the patients who are vulnerable to a return to harmful drinking. It is important to validate these findings in a different transplant population before applying the model more widely. This study has also shown that no single predictor, when used on its own, predicted relapse with any reliability. The diagnosis of mental illness, the lack of a stable partner, and tobacco use were individually significant; however, the increase in relapse risk was modest. The illnesses recorded were, in the event, all cases of depression of varying severity, all with previous treatment. However, depression is a condition that can respond to psychiatric treatment, and relapses can be prevented, if treatment is available and accepted. These findings do not suggest that a history of depressive illness should be an exclusion from transplant, but an indication for specific assessment and outpatient monitoring.

Entry to the transplant waiting list is based on consensus decision from a weekly meeting of transplant clinicians. The clinical opinion of transplant psychiatrist and substance misuse physician is included in this process. The present statistically significant findings have emerged despite the possibility that the more extreme scorers on these parameters would already have been excluded from transplantation, thus biasing the study against identifying predictive factors. This helps to support the validity of the identified factors. Even though these findings are statistically impressive, it is important to place them in the appropriate clinical context. The transplant team would not wish to refuse transplantation on the basis of a wrong prediction that the candidate will return to harmful drinking. This would have occurred on 2 of 12 occasions based on a model using these predictors. Indeed, 8 of 18 relapses occurred in those predicted to be at low risk according to our model. Moreover, many relapses were not life threatening. Once identified, most patients responded to further interventions and reduced their drinking.

Comments on individual predictors

The finding that average consumption in grams per day during heavy drinking periods during the years before the assessment for transplant correlates positively with the risk of relapse may say something important about the recording of alcohol consumption data. Studies that have found that pre-transplant consumption was not a predictor of relapse may have used weekly consumption or some other averaging method, which blurred the importance of heavy session drinking as a predictor of harm (Miller et al., 2005).

Unlike in the Edinburgh follow-up study (Smyth et al., personal communication), the presence or absence of a diagnosis of previous alcohol dependence was not often stated in the notes. The reason may be that relatively few patients receive assessment by an addictions specialist so more of those who relapsed may have met the criteria for dependence than we have shown. Previous studies have found that a significant number of patients transplanted for ALD never met criteria for dependence (Lucey et al., 1992).

Looking further at the factors that contributed to our predictor model, we suggest that the evaluation of insight into cause
of illness and motivation to change may be valuable for every candidate during the pre-transplant assessment. The level of insight described in this study is relatively modest and future research might evaluate this in greater detail to include insight into personal limitations and treatment needs. This should also, ideally, be a time for planning long-term support and an illness-free and addiction-free lifestyle.

The stated presence of family and friend support correlated with return to drinking, which seems counter-intuitive. One explanation is as follows. The pre-transplant patient is asked to name a support network and if he/she does not have a cohabiting partner, may identify ‘family or friend support’. A number of patients named former spouses who agreed to give specific support for a limited time period—for example, the acute post-operative period. The same applied to parental or other family support where a patient planned to move temporarily into a family or friends’ home during the early recovery period. However, this is also the time that they are least likely to resume drinking. The years after the acute illness has passed are likely to be more risky (Fig. 2) and in some of the cases where ‘family and friends’ support’ had been named, perhaps the least supported.

It was noteworthy that pre-transplant tobacco use was a predictor of post-transplant alcohol use. This association might reflect the presence of a greater tendency to substance misuse in general. In our centre, transplant candidates are strongly encouraged to stop smoking in view of the association with a range of adverse events post-transplant including post-operative respiratory complications, vascular complications (Pungpapong et al., 2002), and osteoporosis (McCaughan and Feller, 1994). It is not surprising that those who continue to smoke against advice may be at risk of other therapeutic non-adherence. Post-transplant smoking has recently been shown to adversely impact on clinical outcomes (DiMartini et al., 2005). Thus, smoking is both a marker of the risk of returning to alcohol consumption and a significant clinical problem per se.

The duration of abstinence prior to transplantation was not a predictor. Our transplant centre generally adopts the six-month rule and accordingly only six cases were transplanted with less than 6 months abstinence. Nonetheless, the finding is consistent with other studies that have found that other factors are more important predictors of outcome than the duration of abstinence taken in isolation (Weinrieb et al., 2000). Finally, we wish to underline that, in this sample, social class measured by occupation did not predict outcome, either in univariate analysis or after adjustment for other variables.

In conclusion, we have found that a multivariate model based on four adverse factors (presence of documented mental illness, level of alcohol consumption, continuing tobacco use, and the need to rely on friends or family for support) and two protective factors (presence of a cohabiting partner and insight into the aetiological role of alcohol) was able to predict the likelihood of relapse to harmful alcohol consumption after liver transplantation for ALD in 89% of cases. Similar factors are known to influence the prognosis of alcohol dependence outside the transplant context (Neuberger et al., 2002), but this is the first study to identify pre-transplant factors that can predict return to harmful alcohol consumption after successful transplantation. The detailed psychosocial assessment plays a role in predicting outcome after liver transplant for ALD in terms of harmful drinking. The factors highlighted in this report can be assessed by non-specialist staff, but assessment by an addictions specialist may also be valuable because several of these factors may be amenable to change. Additional research should be directed towards validating these findings in other transplant populations, applying them prospectively to enhance pre-transplant assessment and case selection, and in designing pre-transplant and post-transplant monitoring and intervention programmes to minimize the relapse rates and attending harms to transplant patients and the community.

REFERENCES


