LIVER TRANSPLANTATION FOR ALCOHOLIC LIVER DISEASE: A SYSTEMATIC REVIEW OF PSYCHOSOCIAL SELECTION CRITERIA

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Abstract — **Aims:** To examine the evidence base for psychosocial selection criteria for liver transplant candidates with alcoholic liver disease. **Method:** Systematic review using three electronic databases supplemented by hand searches. **Results:** Out of 96 published studies, 22 were included. All but one were cohort design, most were retrospective, single centre, and small sample. Methodology varied considerably, such that meta-analysis was not feasible. **Conclusions:** Social stability, no close relatives with an alcohol problem, older age, no repeated alcohol-treatment failures, good compliance with medical care, no current polydrug misuse, and no co-existing severe mental disorder have all been associated with future abstinence in more studies than not, in those that examined these variables. Duration of preoperative abstinence was a poor predictor. We recommend that, if predicting future abstinence is considered necessary by transplant teams, a standardized approach is agreed and deployed amongst transplant units, then audited and reviewed.

Alcoholic liver disease (ALD) is one of the commonest indications for elective liver transplantation in Europe and USA. Survival rates following liver transplant for ALD are at least as good as for other liver diseases (Neuberger and Tang, 1997; Lim and Keeffe, 2004). The main additional risk to the graft is damage by a resumption of harmful drinking, which is also a major concern for maintaining public confidence in the system and, hence, optimizing organ donation. In spite of developments such as split grafts and living related donor transplants, demand for liver transplant continues to outstrip supply and the transplant community has to select among potential recipients. The philosophical basis for selection is utilitarian, i.e. dependent on an evaluation of likely outcome, rather than based on a right to an organ or personal responsibility for the disease (Masterton, 2000). For patients who have ALD, virtually all transplant centres have adopted additional criteria to select candidates. These are aimed at predicting abstinence from alcohol following the transplant. This paper provides a systematic literature review to establish the evidence base for these criteria.

METHOD

Data sources

The search covered the Cochrane Database, Medline, and Psychlit using the keywords: psychol*, psychiatr*, liver transplant*, alcohol*, selection, and treatment. This was supplemented by following up references from papers identified by the search. Then the following journals were hand searched from 1995–2004: *Alcohol and Alcoholism*, *Alcoholism, Clinical and Experimental Research*, *British Journal of Psychiatry*, *Gut*, *Hepatology*, *Journal of Psychosomatic Research*, *Liver Transplantation and Surgery*, and *Psychosomatic Medicine*.

Inclusion criteria

Good quality [as assessed according to standard techniques of the Scottish Intercollegiate Guidelines Network (2001)] randomized controlled trials (RCTs), cohort, case–control studies and systematic reviews were included if the subjects were adults, had a diagnosis of ALD, and had been assessed for liver transplantation. Psychosocial selection criteria had to be clearly defined, outcome measured as alcohol relapse (definition stated), and the means for assessing alcohol relapse given. The studies were each critically appraised and data extracted independently by both authors.

RESULTS

A total of 96 studies were originally identified. Nine disagreements between the authors about allocation were resolved by discussion. A total of 22 studies were included (Table 1) while 74 were excluded. Of the excluded studies, 32 were narrative reviews or editorials, 21 studies were found not to be directly relevant, and 21 had significant design faults (references and further information available from authors). No RCTs had been undertaken: 21 studies employed a cohort outcome design, the exception being a case–control design, 14 were retrospective, 8 prospective. Sample size was invariably small (range 14–118, median = 46 patients) and follow-up duration was inconsistently reported. The alcohol-relapse prevalence was a median 21% (range 7–49%), which compares with 60% (range 20–90%) (Neuberger and Tang, 1997), 20% (range 7–95%) (Lim and Keefe, 2004), and summary proportion 32 ± 8% (Bravata *et al.*, 2001) in previous meta-analyses.

After considering four core aspects—whether specialist assessment should occur, the diagnosis of the alcohol problem, the definition of relapse drinking and then its establishment—the following subheadings cover the different selection criteria, with a brief appraisal.

Assessment

First, it is worth commenting that selection has already occurred prior to assessment by the liver transplant unit given the small proportion of ALD patients who are referred in the

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†*Declaration of interest.* G.M. has clinical sessions funded by the Scottish Liver Transplant Unit.

Table 1. Summary of studies included

Authors	Type of study	Number	% relapsed	Follow-up duration in months: median or mean* (range)
Anand et al. (1997)	Retrospective	39	13	25 (7–63)
Berlakovich et al. (1994)	Prospective	44	32	33 (not stated)
Berlakovich et al. (2000)	Retrospective	118	13	53* (9–179)
Bharadhwaj et al. (1996)	Retrospective	34	15	Not stated (0–84)
Campbell et al. (1998)	Prospective	38	32	84* (not stated)
Coffman et al. (1997)	Prospective	91	20	Not stated (12–72)
DiMartini et al. (2001)	Prospective	34	38	Not stated (3–12)
Fabrega et al. (1998)	Prospective	44	18	39* (4–77)
Foster et al. (1997)	Prospective	63	21	49* (not stated)
Gerhadt et al. (1996)	Retrospective	41	49	47* (36–96)
Gish et al. (1993)	Prospective	29	21	24* (12–41)
Gish et al. (2001)	Prospective	89	18	83 (30–112)
Hillebrand et al. (1997)	Retrospective	52	10	26 (24–51)
Jauhar et al. (2004)	Retrospective	111	15	44* (not stated)
Lucey et al. (1992)	Retrospective	45	11	15 (12–24)
Mackie et al. (2001)	Retrospective	46	54	25 (5–47)
Pageaux et al. (1999)	Retrospective	47	32	42* (1–100)
Raakow et al. (1995)	Retrospective	78	22	25* (0–64)
Stefanini et al. (1997)	Retrospective	14	21	Not stated (4–60)
Tang et al. (1998)	Retrospective	56	50	Not stated (0–108)
Tripp et al. (1996)	Retrospective	68	13	Not stated (0–84)
Zibari et al. (1996)	Retrospective	29	7	Not stated (0–36)

*All cohort studies apart from Tang et al. (1998) which was case–control.
Mean, otherwise figure is median.

first place. This is not quantified in literature, but we have calculated this figure for the Scottish population and it is ∼4% based on 139 referrals to our unit from Scottish centres between 1999 and 2002 and 3167 deaths from ALD recorded by the Registrar General for Scotland during this period.

There was a unanimous view that a candidate with suspected or confirmed ALD has a comprehensive alcohol assessment by a specialist as part of evaluating suitability for a liver transplant. A psychiatrist assessed patients in 20 of the 22 studies: the two centres that had no specialist assessment commented that they wanted it but no one was available (Stefanini et al., 1997; Pageaux et al., 1999).

Diagnosis

ALD is complicated by comorbidity in 30–50% of cases but in all included studies ALD had been diagnosed. Only 14 studies provided a formal psychiatric diagnosis of the alcohol problem, of which 11 used the DSM system (American Psychiatric Association, 1987, 1994). Where psychiatric diagnoses were given, all studies reported a mixture of patients with alcohol dependence and harmful alcohol use.

Definition of relapse drinking

All studies defined relapse as any alcohol use at all. It is an easy cut-off and an apparently hard endpoint, but unlike the general alcohol literature, this does not distinguish between a slip (an isolated drinking event) and a relapse (a more prolonged and harmful drinking episode). While some of the studies (Berlakovich et al., 1994; Raakow et al., 1995; Gerhardt et al., 1996; Tripp et al., 1996; Stefanini et al., 1997; Campbell et al., 1998; Tang et al., 1998; Jauhar et al., 2004) did distinguish between slips and relapses in reporting their results, most did not. Clarifying this issue has been identified as crucial in that the current definition will include patients whose drinking lapse(s) will have no implications for their

outcome. Proposals have been made for introducing standardized definitions (Weinrieb et al., 2000).

Establishing relapse drinking

All 22 studies established relapse by admission of drinking by the patient. Two studies also routinely asked the family, nine employed biochemical tests (on blood and urine samples) and a further five did all three. There was general agreement that diagnosing relapse was difficult. Fabrega et al. (1998) picked up only three relapsed patients using history but five others had ethanol detected in their urine by gas chromatography. DiMartini et al. (2001) used all three methods but concluded clinical interview the best way to identify relapse.

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Duration of abstinence pre-assessment

This is the main selection criterion employed by transplant units for allowing assessment in the first place, understandably so, in that the measure is a numerical value that can often be established with reasonable confidence and it also enables some patients to recover medically such that assessment for transplant becomes unnecessary. A 'six months' abstinence rule' has evolved in many centres, but not infrequently this has become the minimum duration before transplant is allowed.

Of the twenty-two studies, 11 examined duration of preoperative abstinence: nine did not find this a useful predictor of ongoing sobriety (Table 2). Hillebrand et al. (1997) and Raakow et al. (1995) did find that relapse was associated with shorter periods of pretransplant abstinence. Stefanini et al. (1997) used 6 months preoperative abstinence as the only selection criterion and found a relapse rate of 21%.

However, none of the studies took into account that the circumstances of the patient's abstinence might have a major

Table 2. Predictive Variables

Factor	Associated	Not associated
Less than 6 months abstinence	Hillebrand *et al*. (1997) Raakow *et al*. (1995)	Anand *et al*. (1997) Coffman *et al*. (1997) DiMartini *et al*. (2001) Foster *et al*. (1997) Gerhardt *et al*. (1996) Gish *et al*. (1993, 2001) Jauhar *et al*. (2004) Mackie *et al*. (2001) Tang *et al*. (1998)
Polysubstance abuse	DiMartini *et al*. (2001) Foster *et al*. (1997) Hillebrand *et al*. (1997)	Coffman *et al*. (1997) Jauhar *et al*. (2004)
Social instability	Coffman *et al*. (1997) Foster *et al*. (1997) Gish *et al*. (1993, 2001) Lucey *et al*. (1992) Zibari *et al*. (1996) Pageaux *et al*. (1999)	Mackie *et al*. (2001)
Family history of alcoholism in 1st degree relative	DiMartini *et al*. (2001) Foster *et al*. (1997) Jauhar *et al*. (2004)	Mackie *et al*. (2001)
Younger age	Foster *et al*. (1997) Pageaux *et al*. (1999)	Mackie *et al*. (2001)
Poor previous treatment responses	DiMartini *et al*. (2001) Gish *et al*. (1993, 2001)	Jauhar *et al*. (2004)
Lack of insight		Berlakovich *et al*. (1994) Campbell *et al*. (1998) Foster *et al*. (1997) Lucey *et al*. (1992) Pageaux *et al*. (1999) Raakow *et al*. (1995) Zibari *et al*. (1996)
Contract	Gish *et al*. (1993, 2001)	Gerhardt *et al*. (1996)
Non-compliance	Gish *et al*. (1993, 2001) Zibari *et al*. (1996)	
Co-existing mental disorders	Coffman *et al*. (1997) Gish *et al*. (1993 and 2001) Tripp *et al*. (1996)	DiMartini *et al*. (2001) Jauhar *et al*. (2004)
MAPS		Coffman *et al*. (1997) Lucey *et al*. (1992)

bearing on outcome. It seems plausible that patients who had obligatory abstinence as a result of spending most or all of the abstinence period in hospital because of severe illness might react differently post-transplant compared with patients whose abstinence had been established during a period when their health and social circumstances would have enabled them to have drunk alcohol if they had wanted.

Psychiatric diagnosis of the alcohol problem

Only one study (Tripp *et al*., 1996) looked at the psychiatric diagnosis of the alcohol problem and abstinence. They observed that the severity of the alcohol problem did not necessarily correlate with the severity of ALD at presentation. They teased out the different groups of those who were dependent and those who were harmful users. They found no association between abstinence and any particular alcohol diagnosis but only 13% of their sample relapsed.

Polysubstance abuse

Alcohol can be an element in a more general abuse of substances, either as a preferred or alternative drug of abuse.

Five of the studies looked at this (Table 2). Hillebrand *et al*. (1997) found that the use of preoperative illicit drugs was associated with an increase in alcohol relapse in those patients who had other liver diseases (notably HCV) complicated by alcohol. However the numbers who relapsed were still a minority. Foster *et al*. (1997) found that the absence of illicit drug use at any point was a statistically significant predictor of post-transplant abstinence. However Coffman *et al*. (1997) did not find any difference in relapse rates between polysubstance abusers and those with only alcohol abuse—but many had stopped using illicit drugs many years earlier rather than being current polysubstance users.

There is a distinction to be made between patients who switched to alcohol from illicit drugs many years earlier and those who continue to use illicit drugs in conjunction with or instead of alcohol, which again has rarely been teased out.

Social stability/support

Seven centres have used this as a selection criterion but the definition has varied, which made it difficult to assess: it tended to be a general assessment of social support. Social stability with other favourable prognostic factors was associated with a good prognosis in six studies (Table 2). Pageaux *et al*. (1999) found that in those who relapsed, the divorce/separation rate was significantly higher. Foster *et al*. (1997) noted an active life insurance policy (suggesting dependents) at the time of transplant predicted post-transplantation abstinence. Coffman *et al*. (1997) found that poor relationships with immediate family and poor sexual relationship with spouse were associated with relapse. Mackie *et al*. (2001), however, did not find any association between social support and return to drinking. Jauhar *et al*. (2004) had a mixed result. They found that education or employment factors did not predict abstinence but that lack of spouse or partner tended towards predicting relapse without reaching significance.

Although studies cite family support as being a factor, and it does appear to be a consistent predictor of outcome, little is known about the details of this—for instance does having no partner lead to a worse outcome than having one who condones the patient's drinking or has an alcohol problem too? This needs to be explored—probably using a qualitative methodology.

Family history

Both DiMartini *et al*. (2001) and Jauhar *et al*. (2004) found relapse was significantly associated with a family history of alcohol problems in a first-degree relative. Mackie *et al*. (2001) again bucked the trend, finding no association between any family history of alcohol problems and relapse.

Age

Foster *et al*. (1997) in a prospective study found that those patients who remained abstinent following liver transplant were more likely to be over 50 years of age, which was nearly 10 years older than those who relapsed. Pageaux *et al*. (2000) also found that the mean age of those who relapsed was younger (44 years) compared with those who did not (50 years). This was statistically significant. With this variable too Mackie *et al*. (2001) were alone in reporting no association.

Previous treatment responses

The history of what advice patients had been given by their doctors, how they had responded to this, whether they accepted alcohol rehabilitation, and how they responded to this treatment are relevant. Gish *et al*. (1993, 2001) used this as one of the factors for categorizing patients into risk groups and found that no previous failure at alcohol rehabilitation was a good prognostic indicator when used in conjunction with other factors. Di Martini *et al*. (2001) in a short prospective study found that any prior experience of alcohol rehabilitation was significantly associated with post-transplant relapse. Jauhar *et al*. (2004) found that it was not predictive in a retrospective case review.

This variable also has problems in definition. A patient may not have had previous treatment because they, their family, and GP were not aware they had been drinking harmfully until ALD emerged; on the other hand no previous treatment might reflect denial of a severe alcohol problem, which would be as bad if not worse than patients who had sought help but had failed to abstain.

Insight

Insight, acceptance, and responsibility that alcohol was the cause of the patient's liver disease is widely regarded as being essential for maintenance of abstinence but, perhaps surprisingly, this has not been found to predict abstinence in any of the studies that examined this aspect. The explanation may be that patients who denied responsibility or would not accept that their drinking had caused their liver disease were not listed in the first place. Another explanation may be that insight is not defined in the papers—one clinician's idea of insight may not be another's.

Denial is another complex variable. Patients may deny their liver disease was caused by alcohol abuse (and occasionally be proved right about this!), or they may accept this but deny they ever drank excessively or had an alcohol problem. They may deny drinking when there is evidence that they were; they may deny being told to abstain, they may deny agreeing to abstain; they may deny they require to remain abstinent or that they would have a problem maintaining abstinence. None of this complexity has been addressed in literature.

Contract

Gish *et al*. (2001) found that a contract was associated with decreased risk of relapse when other favourable factors were present. In their earlier paper they argued that a contract clarifies for patients what is expected of them and can be used as a point of reference if the patient relapses (Gish *et al*., 1993).

Gerhardt *et al*. (1996) found no correlation between relapse and use of a contract. Although Tripp *et al*. (1996) and Campbell *et al*. (1998) used a treatment contract, it was not analysed individually as a risk factor.

A problem with a contract approach is that many patients are cognitively impaired at the time of signing and may not remember giving this assurance. Mackie *et al*. (2001) found that one-third of the patients studied had no recollection of being advised to remain abstinent despite it being standard practice in their centre, and Tang *et al*. (1998) found an even higher proportion (59%) could not recall pretransplant advice regarding alcohol use post-transplantation.

Compliance

A history of repeated non-compliance with medical care was considered to be an absolute contraindication to transplantation by Gish *et al*. (1993, 2001), given it emerged as a highly significant predictor of alcohol relapse. Zibari *et al*. (1996) also used compliance as one of the selection criteria in a small study ($n = 29$) that had a very low relapse rate of 7%; however, it was not analysed independently as risk factor but in conjunction with insight and social stability.

Co-existing mental disorders

There is consensus that certain medical diseases are acknowledged to be absolute contraindications to liver transplant usually because of reduced life expectancy or perioperative risk. In the case of mental disorders a persistent incapacity, which is so severe that the patient cannot understand and agree to the procedures required, or will be unable to cope with the graft, or will be unable to comply adequately with treatment requirements, is generally regarded as a psychiatric contraindication.

Mental disorders are almost invariably associated with higher than expected mortality (Harris and Barraclough, 1998), while their nature and severity may affect the patient's ability to care for and cope with a graft. In transplant selection these factors can amount to absolute contraindications. Those conditions that have been studied specifically in ALD are substance misuse disorders and personality disorders (Table 2) but organic brain disorders (notably dementia or amnesic syndrome) and chronic psychotic illnesses have also been reviewed (Tripp *et al*., 1996).

Coffman *et al*. (1997) specifically excluded those with treatment resistant psychosis and those with non-epileptic seizures. They also found that antisocial behaviour and eating disorders increased the risk of relapse. Gish *et al*. (1993, 2001) excluded those with severe mental retardation, acute severe psychiatric disease, chronic psychosis, and severe personality disorders. They included those with moderate personality disorders but found that it was a highly significant predictor of relapse post-transplantation. Tripp *et al*. (1996) found that four out of nine patients who relapsed had a comorbid psychiatric disorder.

Michigan alcohol prognosis scale

This is a summation of selection criteria based on good prognostic factors in the general alcohol literature (insight, hope, substitute activities, and social stability) from which a numeric total is generated (Lucey *et al*., 1992). It was developed by the Michigan group in an early attempt to standardize a reliable selection procedure for ALD. Campbell *et al*. (1998) used the Michigan alcohol prognosis scale (MAPS) as part of their assessment and found a 30% relapse rate. Coffman *et al*. (1997) found MAPS score was not a significant predictor of post-transplantation abstinence. Lucey *et al*. (1992) found that MAPS did not distinguish between patients who abstained and those who relapsed.

DISCUSSION

This review confirms there is no single, reliable, well-defined predictor of abstinence or relapse that can be applied usefully to inform liver transplant selection decisions in this clinical presentation. This should come as no surprise given the obvious weaknesses in the evidence base. All studies are based on follow-up of those who were selected and transplanted: almost nothing is known about those who were not.

ALD transplant candidates are already a highly selected population: what the transplant team is trying to establish are the best candidates among a cohort of better prognosis patients. Other factors that complicate the picture are different transplant systems among countries, the effects of public opinion and graft availability, variations in service configuration between units, and shifts in their selection criteria stemming from experience.

It might be argued that ALD patients should not be subjected to additional selection criteria given all this uncertainty and the fact that among the minority of patients who do relapse, few will experience recurrent alcohol misuse sufficiently severe to compromise the graft and, thereby, affect outcome—which, after all, is the basis of selection. However public attitudes to transplanting ALD patients have been highly unfavourable (Neuberger *et al*., 1998; Everhart and Beresford, 1997), evident too in the Oregon Health Service Commission finding that of 714 medical procedures to be prioritized by the public, liver transplant for non-ALD ranked 314th but for ALD was 695th (Dixon and Welch, 1991). Ignoring the alcohol component in determining transplant suitability may undermine public confidence and so adversely affect organ donation.

However, is the usual reflex reaction of advocating more, bigger, and better-designed studies when the evidence base is poor likely to help here? This solution of prospective, multicentre studies with better data collecting and sharper endpoints has already been proposed (Beresford and Everson, 2000). Whether reliable, definitive, and practically useful answers would result is debatable given the fundamental design limitations that will inevitably exist but it would, nevertheless, remain valuable to sharpen up clinical procedures. To achieve this, standardization among centres of definitions of selection criteria such as insight, social stability, and in methods for detecting alcohol relapse would be required.

In the meantime there are two strategies that might be considered. The first is to make no attempt to select ALD patients on the basis of their likelihood of relapse. Every ALD patient is entitled to as expert an assessment of his or her drinking problem as any other medical consideration but instead of this work being primarily to assist selection it would be focussed on enabling the patient to receive the correct post-transplant management of their drinking problem so that the graft outcome is optimized. This might simply involve monitoring or might include active treatment. The transplant team's decision about suitability with regard to drinking would then depend on specialist advice about whether treatment, if necessary, would be feasible, and confirmation that the patient was willing to accept alcohol monitoring and/or treatment as recommended by the specialist.

The other approach is to deploy the available evidence as best we can on the basis that this is preferable to relying on whim, guesswork, or prejudice and that some attempt to select patients who are less likely to resume harmful drinking post-transplant is necessary, if for no other reason than to maintain public confidence in the system. Ideally predictors of relapse should be objective, just, and reliably measured. Fundamentally, they must be agreed upon by consensus among the units so that there is fairness across the system.

Some factors were found more often than not to be associated with abstinence: social stability, no alcohol problems among first-degree relatives, older age, no repeated alcohol-treatment failures, good compliance with medical care, no current polydrug misuse, and no co-existing severe mental disorder. Duration of preoperative abstinence was a poor predictor of abstinence despite extensive research and wide usage. We recommend that, if predicting future abstinence is to be taken into account in selecting candidates, a standardized approach using variables that may include some of these predictors is agreed and deployed amongst transplant units, then audited and reviewed.

However this strategy must recognize two fundamental realities. First, in practice, relapse into harmful use or dependence on alcohol occurs among a minority of patients after a liver transplant, and graft failure in these circumstances is rare. Second, there will inevitably be some ALD patients who will relapse no matter how strict the selection criteria and how assiduous the follow-up and treatment.

The role of the psychiatrist or other alcohol specialist is to help the transplant team make best use of the limited supply of organ donations. This means first and foremost ensuring the individual patient has as expert an assessment of their drinking problem as they receive for their liver disease, followed-up by appropriate help to maintain their health after the transplant. However, there is another dimension to transplantation medicine, which is a wider responsibility to all patients who require liver transplantation to enable best outcomes to be achieved for as many patients as possible—and it is in this context that selection policies have to be implemented. Whether this should include assessing the likelihood of relapse drinking in patients with ALD is for transplant units and authorities—and ultimately society at large—to determine.

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