Long-term follow-up of patients with alcoholic liver disease after liver transplantation in Sweden: Impact of structured management on recidivism

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Abstract

Objective. No systematic evaluation has been performed previously in the Scandinavian countries on patients transplanted for alcoholic liver disease (ALD). Data are limited on the impact of structured management of the alcohol problem on the risk of recidivism following transplantation in ALD. Material and methods. A total of 103 ALD patients were compared with a control group of patients with non-alcoholic liver disease (NALD). The recidivism rates for ALD patients transplanted between 1988 and 1997 as well as after 1998 (institution of structured management) were compared.

Results. The median follow-up was 31 (6–60) months in the ALD group and 37 (12–63) months in the control group (NS). The overall survival rates at 1- and 5 years were, respectively, 81% and 69% for the ALD group and 87% and 83% for the non-alcoholic group. The proportion of patients with Child-Pugh C (75%) was higher in ALD patients than in NALD patients (44%) (p < 0.01). Thirty-two (33%) ALD patients resumed taking some alcohol after transplantation; 17 patients (18%) were heavy drinkers. A multivariate analysis showed that: sex, age, marital and employment status, benzodiazepine use and a history of illicit drug abuse did not predict the risk of alcohol relapse post-Tx. Nineteen out of 40 (48%) patients transplanted before the start of structured management had resumed alcohol but 13 (22%) out of 58 after this intervention (p = 0.002). Conclusions. ALD is a good indication for liver transplantation, with similar results in the ALD patients. Structured management of the alcohol problem before and after transplantation is important in minimizing the risk of recidivism.

Key Words: Alcoholic liver disease, alcohol recidivism, liver transplantation, malignancy

Introduction

During the past decade, indications for liver transplantation have changed and, along with hepatitis C, alcoholic liver disease (ALD) is the most common indication for liver transplantation in both Europe and the USA nowadays [1,2]. According to the Nordic Liver Transplantation Registry [3], alcoholic cirrhosis has also become one of the most common indications for liver transplantation in the Scandinavian countries in recent years. No systematic evaluation has been performed previously in Scandinavia on the results of long-term follow-up of patients undergoing liver transplantation for alcoholic cirrhosis.

In most early studies, both patient and graft survival were reported to be similar for those transplanted for alcoholic liver disease and for patients transplanted for other indications [4–11]. However, Jain et al. recently reported significantly lower graft and patient survival rates during the past 5 years of follow-up in ALD compared with controls with a variety of other indications for transplantation, probably owing to an increased frequency of upper airway malignancies in the ALD group [12]. De novo malignancies have been reported after liver transplantation [13,14] but no particular risk in patients with ALD has been...
recognized, although Kelly et al. observed a higher incidence of malignancies in ALD than in patients undergoing liver transplantation for other indications [15].

Unfortunately, a small proportion of patients return to a damaging pattern of drinking after liver transplantation although the consequences for graft and patient survival seem surprisingly low [12,16–19]. There are limited data on the impact of structured management of these patients on the risk of recidivism following liver transplantation. Although most liver transplantation centers in the US have a psychiatric and/or addiction medicine specialist as part of their program, a detailed case history or an addiction diagnosis was obtained at only 68% of the centers [20,21].

Since 1998, all patients with ALD referred to our center have been evaluated by a consultant specialized in alcohol and other substance abuse disorders. We sought to assess the impact of this structured management on recidivism by comparing those transplanted before 1998 with those who were transplanted after this intervention. An important objective was also to study the effects of recidivism on outcome in the ALD group.

Material and methods

Patients

The liver transplantation program at Sahlgrenska University Hospital, Gothenburg, Sweden, started in 1985. Alcoholic liver disease was a contraindication during the first three years but in 1988 the first patient was transplanted on this indication. All patients who were accepted for liver transplantation for alcoholic liver disease between February 1988 and May 2003 were identified. During this period a total of 613 liver transplantations were performed on 555 patients at Sahlgrenska University Hospital. Of these 555 first-time liver transplantations, 103 (19%) patients had ALD. Of these 103 patients, 36 also had hepatitis C (35%) and 8 of these patients also had concomitant hepatitis B. Six patients had ALD and concomitant hepatitis B (but not hepatitis C). The proportion of patients with ALD out of all the patients transplanted during this period is shown in Figure 1.

The control group consisted of patients matched for sex, age ± 5 years and year of transplantation ± 1 year. The diagnoses of the control patients are presented in Table I. Patients transplanted for malignancy, acute liver failure, familial amyloid polyneuropathy as well as cryptogenic cirrhosis were excluded. Patients with cryptogenic cirrhosis were excluded due to the difficulty of sometimes excluding alcoholic etiology in this group of patients. The reason for not including malignancy in our control group is the following. Although there were a number of patients with known hepatocellular carcinoma (HCC) in the ALD population, there were also a number of incidental and known HCC cases in the hepatitis C population in the control group. However, the indication for liver transplantation in these patients with hepatitis C was mainly decompensated liver disease and not the HCC. If we were to match the number, we would have had to include the patients primarily accepted for liver transplantation with an HCC mainly from the first decade of transplantation. These patients often had large tumors with an expected poorer prognosis, so we chose not to include them in our control group.

Patient and graft survival rates were compared between patients with ALD and the control group. All patients were included in this analysis, not only those who survived 3 months. All patients were also included in the analysis of age and sex at transplantation, the age of the donor, cold-ischemia time of the graft and liver biochemistry tests. Certain variables (see below), i.e. employment status, marital status and alcohol and other drug recidivism were only examined in those who survived 3 months. A retrospective analysis of the case notes was made and information was obtained about alcohol and other substance use, and psychosocial parameters and medical factors of potential prognostic interest were analyzed.

Structured management

No formal psychiatric evaluation was carried out on the ALD patients before 1998, although, several psychiatrists were involved in the evaluation of most of these patients. During the period before 1998 some psychosocial evaluations were made with the aim of identifying those patients who were considered to be at risk of recidivism. However, no formal routines existed and there was no follow-up plan.

At the beginning of 1998, structured management of patients referred for liver transplantation with alcoholic liver disease was initiated. A team was led by a psychiatrist with long-standing experience in addiction medicine, and who was also the head of a clinic taking care of patients with alcohol abuse and other addiction problems. This team collaborated with our team, which included a social worker and a patient coordinator. At the work-up before transplantation, there was an obligatory interview and evaluation and evaluation of the specialist and his team. This also included an interview with close relatives of the patient and, if necessary, the doctors in charge of the patient’s previous treatment were
An evaluation was thus performed of patients' current and previous abuse problems and, if needed, the patients were asked to participate in a motivation program to assure total abstinence from alcohol. No exact time limit of abstinence was introduced, however. The patients also had to sign a formal contract on abstinence and follow-up. Treatment for alcoholism was initiated in most of those individuals who had not already received treatment for alcoholism at the time of referral for transplantation. The type of treatment was the 12-step method widely used in the treatment of alcoholism. After transplantation, the transplant unit's social worker and transplant coordinator kept in contact with the patient and the local physician and also at the check-up at our unit after 3 months. At 1, 3 and 5 years after the transplantation, an interview was conducted by our team and the addiction team.

Table I. Diagnoses of the control group.

<table>
<thead>
<tr>
<th>Diagnoses of the control group</th>
<th>94 patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSC</td>
<td>43</td>
</tr>
<tr>
<td>PBC</td>
<td>15</td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>9</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>8</td>
</tr>
<tr>
<td>AIH cirrhosis</td>
<td>5</td>
</tr>
<tr>
<td>Alpha-1-antitrypsin deficiency</td>
<td>4</td>
</tr>
<tr>
<td>Secondary sclerosing cholangitis</td>
<td>4</td>
</tr>
<tr>
<td>Others</td>
<td>6</td>
</tr>
</tbody>
</table>

Abbreviations: PSC = primary sclerosing cholangitis; PBC = primary biliary cirrhosis; AIH = autoimmune hepatitis.

Alcohol history

The following variables were obtained from the medical records concerning alcohol consumption history: the duration of excess consumption in years and the duration of abstinence before transplantation in months. Furthermore, information was obtained about whether or not the patients had previously undergone treatment for alcoholism and the use of illicit drugs, including i.v. drugs, as well as benzodiazepine use. Information was obtained from the medical records about the number of patients who returned to drinking after transplantation. When the information about recidivism was not clear from the medical records, the doctor responsible was contacted in order to obtain this information. Alcohol relapse was defined as any alcohol use revealed in either an interview survey or during clinical follow-up. Alcohol relapse was based on the clinical judgement of the doctor responsible, a gastroenterologist/hepatologist or a member of the transplant team, and the patient’s own report and sometimes a report from close relatives. The pattern of drinking was also analyzed. The patients were considered to be heavy drinkers if they had periods of repetitive and excessive drinking observed by the doctor responsible. Excessive drinking was considered drinking on many occasions where the patient had obviously been drunk. These patients were distinguished from patients who were known to have only used alcohol on special occasions but had not abused alcohol through repetitive and excessive drinking. Information was also obtained
about the treatment of alcoholism after transplantation whether or not other narcotics had been used and the use of benzodiazepine-type drugs.

**Marital and employment status**

Marital status was analyzed before and after transplantation (in those surviving >3 months). Employment status before and after transplantation was also determined and a comparison was made between the patients transplanted for ALD and the controls. Those who were older than 65 years and those who did not survive 3 months were excluded from the post-transplantation employment analysis.

**Medical history**

Laboratory investigations conducted immediately before transplantation were obtained from the medical records, including: ASAT, ALAT, bilirubin, alkaline phosphatase (ALP), International Normalized Ratio (INR), albumin, creatinine and glomerular filtration rate (GFR). Child-Pugh and model of end-stage liver disease (MELD) scores were calculated, and the need for dialysis pre-Tx and post-Tx, the occurrence of ascites, esophageal varices, encephalopathy, portal vein thrombosis, diabetes mellitus and also biliary tract surgery prior to transplant and HCC were recorded and analyzed and compared between the groups.

Furthermore, a history of malignancy in the past and the development of cancer after the transplantation were analyzed and compared between the two groups. The causes of death were assessed and also compared between the two groups.

**Statistics**

The patient and graft survival rates were analyzed and compared between the groups using Kaplan-Meyer curves. Laboratory investigations and clinical parameters were compared between patients transplanted for ALD and the controls using an unpaired Student’s t-test and the Fisher’s exact test. These variables were also compared between those with recidivism and those who did not drink after transplantation by using Fisher’s exact test. The association between patient and graft survival and biochemical and clinical parameters between the groups was assessed using a permutation test. In order to investigate independent predictors of graft and patient survival, all variables were entered in a stepwise multivariate logistic regression analysis. For model discrimination, the c statistics were calculated. Results are expressed as medians and interquartile range (IQR). All tests were two-tailed and conducted at a 5% level of significance.

The study was approved by the Ethics Committee of the University of Gothenburg.

**Results**

**Patient characteristics**

Of the 103 patients with ALD, 81 were men and 22 were women, with a median age of 53 (range 39–68 years) (Table II). One patient was Child-Pugh A (1%), 26 (24%) were Child-Pugh B and 77 (75%) were Child-Pugh C patients. The control group consisted of 94 patients with a median age of 52 (range 34–71 years) (Table I). Fourteen (15%) were Child-Pugh A patients, 40 (42.5%) Child-Pugh B and 40 (42.5%) Child-Pugh C patients. The proportion of ALD patients with Child-Pugh C was significantly higher than that in the controls (Table II). The median MELD score in the ALD group was significantly higher than that in the controls (Table II). The proportion of men or women was not significantly different between the groups (Table II).

<table>
<thead>
<tr>
<th>ALD</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>53 (39–68)</td>
</tr>
<tr>
<td>Gender, M/F</td>
<td>81/22</td>
</tr>
<tr>
<td>Donor age</td>
<td>48 (9–80)</td>
</tr>
<tr>
<td>Cold-ischemia time</td>
<td>10 (2.5–21)</td>
</tr>
<tr>
<td>Rejection</td>
<td>54%</td>
</tr>
<tr>
<td>Median follow-up (months)</td>
<td>31 (6–60)</td>
</tr>
<tr>
<td>Median follow-up survivors</td>
<td>35 (12–61)</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>70 (34–180)</td>
</tr>
<tr>
<td>INR</td>
<td>1.6 (1.3–1.9)</td>
</tr>
<tr>
<td>Albumin</td>
<td>27 (22–31)</td>
</tr>
<tr>
<td>Kreatinin</td>
<td>105 (81–132)</td>
</tr>
<tr>
<td>GFR</td>
<td>70.5 (54–91)</td>
</tr>
<tr>
<td>Child-Pugh score</td>
<td>11 (9.2–12)</td>
</tr>
<tr>
<td>Child-Pugh C (%)</td>
<td>75%</td>
</tr>
<tr>
<td>MELD score</td>
<td>19.7</td>
</tr>
<tr>
<td>(mean)</td>
<td>Ascites</td>
</tr>
<tr>
<td>Esophageal varices</td>
<td>82%</td>
</tr>
<tr>
<td>Encephalopathy</td>
<td>55%</td>
</tr>
<tr>
<td>HCC known</td>
<td>4%</td>
</tr>
<tr>
<td>Previous biliary surgery</td>
<td>5%</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>20%</td>
</tr>
<tr>
<td>Previous malignancy</td>
<td>9%</td>
</tr>
<tr>
<td>Smoking</td>
<td>77%</td>
</tr>
</tbody>
</table>

Abbreviations: ALD = alcoholic liver disease; INR = International normalized ratio; GFR = glomerular filtration rate; MELD = model of end-stage liver disease; HCC = hepatocellular cancer.
Baseline characteristics of the laboratory values are summarized in Table II. No difference was observed in serum bilirubin values between the groups, although INR and creatinine were significantly higher and serum albumin was significantly lower in the ALD group (Table II). Other clinical features associated with liver cirrhosis and portal hypertension, such as history of ascites, esophageal varices and hepatic encephalopathy, were more common in the ALD group (Table IV). Furthermore, diabetes mellitus was observed before transplantation in 20% of ALD patients, but only in 9% of the control group \( (p = 0.03) \) (Table II). Current smokers (53% versus 15%) or former-smokers (23% versus 16%) were also significantly more common in the ALD group than in the control group. The proportion of patients who were either smokers at the time of the transplantation or ex-smokers is recorded in Table II. A history of malignancy was also more common in the ALD group (Table II). However, the only factor associated with adverse outcome of liver transplantation, which was more frequent in the control group, was previous biliary surgery (Table II). Other factors of potential importance to the final outcome of the transplantation, such as donor age, cold-ischemia time and the occurrence of rejections postoperatively, were similar in the two groups (Table II).

**Survival analysis**

The median follow-up in the two groups was similar, as shown in Table II. Forty-seven of the 93 (50.5%) patients who survived 3 months were followed for at least 3 years among those with ALD and 55 out of 84 (64.7%) in the control group (NS).

Ten (9.7%) of the 103 ALD patients died during the first 3 months and 9 out of 94 died (9.6%) in the control group. The overall survival rates at 1 and 5 years were, respectively, 81% and 69% for the ALD group and 87% and 83% for the control group (NS) (Figure 2). Graft survival was not significantly different in the two groups (Figure 2). When the proportion of patients in the ALD group with concomitant hepatitis C was compared with the rest of the group, no significant difference was observed in terms of survival (Figure 3).

At the end of the follow-up, 28 (27%) patients in the ALD group and 19 (20%) patients in the control group had died. The causes of death are listed in Table III. Among the ALD patients who died, 8 (29%) died of cancer and 3 (16%) out of 19 controls died of cancer (of those who did not survive the follow-up period).

The median period of abstinence in all ALD patients before transplantation was 8 months (IQR 6–15 months). We made an analysis of recidivism after transplantation in the 93 patients surviving at least 3 months. Despite all the patients being given strict instructions about total abstinence from alcohol after the transplantation, 32 (33%) patients resumed some alcohol use and 61 (67%) were abstinent at the end of follow-up (median follow-up of 42 months). Out of the 32 patients, 17 (18%) were considered by their physician to be heavy drinkers, defined by periods of repetitive and excessive drinking and this continued despite advice from their doctors and families. The other 15 patients were considered to be occasional drinkers who admitted to having resumed alcohol drinking but with only very small or very moderate amounts of alcohol. The median time from the transplantation until alcohol...
consumption was resumed was 12 months (IQR 6–24 months). There was no correlation between the abstinence time prior to transplantation and the likelihood of abstinence after the transplantation (Figure 4). In those patients who had more than 6 months of abstinence, there was an alcohol relapse in 33% of cases after transplantation compared with a 31% relapse rate in those with less than 6 months of abstinence (NS). A comparison between the patients who had resumed alcohol consumption post-Tx and those who had been abstinent did not reveal any significant differences in terms of sex and age at transplantation. A reassessment of causes of death in those four patients who had resumed alcohol consumption and who died during follow-up did not reveal any obvious direct impact of alcohol consumption. One patient died of dilated cardiomyopathy, which was known prior to the transplantation, another died of sepsis and one patient died of a heart attack. The fourth patient died as a result of gastrointestinal (GI) bleeding and associated multiple organ failure. In some cases morbidity has been related to recidivism. Two patients developed alcohol-related organ damage. One patient developed alcoholic hepatitis and was hospitalized for that condition 6 years after the transplantation. The other patient had diabetes mellitus and on resuming alcohol consumption developed hypoglycemia due to excessive alcohol intake and suffered from ischemic brain damage 4 years after the transplantation.

A liver biopsy was undertaken in a total of 68 (66%) of 103 patients transplanted for alcoholic liver disease and in 63 (67%) of the 94 controls. The liver biopsy showed steatosis in 13 of the ALD patients, 11 of whom had resumed alcohol consumption (8 were excessive drinkers) but none of the controls had steatosis in their liver biopsies. Among those who survived 3 months and who were abstinent after the transplantation, 14 out of 61 died. Seven of these patients died of malignancy, 4 of HCC recurrence, 2 of pancreatic cancer and 1 of lung cancer, a median of 8 months post-Tx (range 6–28 post-Tx months). Three patients died of liver-related causes (liver infarction, portal vein thrombosis and GI bleeding) and 4 deaths were not liver related.

The compliance of the patients post-Tx was considered to be inadequate in 6 (18.8%) of 32 patients who had resumed alcohol consumption and in 2 (3%) out of 61 who remained abstinent (p=0.02). There was no significant difference in those who resumed alcohol intake and the rest with ALD in terms of ASAT, ALAT, ALP, gamma-GT, bilirubin, INR and albumin at the last follow-up (data not shown). Only mean cell volume (MCV) showed a tendency to be higher post-Tx in those who had relapsed (95 versus 89; p=0.057).

Among the patients who relapsed, 36% had undergone treatment for alcoholism before transplantation compared with 30% of the non-relapsers.

Table III. Causes of death in patients with alcoholic liver disease and in controls.

<table>
<thead>
<tr>
<th>Causes of death</th>
<th>ALD</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCC recurrence</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Malignancy, other</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Multorgan failure</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>GI bleeding</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Cardiopulmonary disease</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>Infections</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Hospital mortality (survived)</td>
<td>10 (9.7%)</td>
<td>9 (9.6%)</td>
</tr>
</tbody>
</table>

Abbreviations: ALD = alcoholic liver disease; HCC = hepatocellular cancer; GI = gastrointestinal.
Similarly, there was no significant difference in the frequency of treatment for alcoholism post-Tx, which had been undertaken in 48% and 46% in the relapers and non-relapers, respectively. Benzodiazepines were used or had been used regularly before transplantation by 19% of the relapers and by 15% among the non-relapers (NS). After transplantation, the use of benzodiazepines decreased and these substances were used by 9% of the relapers and 6% of the non-relapers (NS). Among the ALD group, 23 patients (22%) had a history of i.v. drug abuse at some point in time (in most patients many years previously) prior to transplantation. There was no significant difference in the frequency of recidivism among those with a history of i.v. drug abuse and those who had not used i.v. drugs previously (data not shown).

**Impact of structured management**

An analysis was performed separately in the patients with ALD transplanted from 1998 to 2003 (63 patients) and those with ALD transplanted during the period 1988–1997 (40 patients). From 1998, patient survival rate in the ALD group at 1 and 5 years was 83% and 78%, respectively, and for the control group 92% and 90%. Analysis of the rate of recurrence of alcohol use showed significantly better results after 1998 in terms of abstinence. Nineteen out of 40 patients had resumed alcohol intake (48%) in comparison with 13 (22%) among the 58 (who survived 3 months) transplanted between 1998 and 2002 (p=0.003). The number of patients who completed treatment for alcoholism post-Tx when Kaplan-Meyer curves are compared was 58% in those transplanted from 1998 onwards compared with only 30% transplanted before 1998 (p=0.03).

**Employment and marital status**

Before transplantation, 36 (35%) out of 103 alcoholic patients were either divorced or separated from their partners, compared with only 14 (15%) out of 94 patients transplanted for other causes (p=0.0017). Among these, 36 (38%) out of 93 with ALD lived alone, but only 13 (15.6%) out of 83 controls (p=0.0007). Analysis of the situation post-Tx for those who had resumed alcohol intake in comparison with those who remained abstinent showed that 56% of the former were either divorced or separated from their partners but only 29% of those who remained abstinent lived alone (p=0.004).

As regards employment status before transplantation, 37% of the alcoholic patients were working compared with 56% of the controls (p=0.02). Only 18% of the alcoholic patients resumed employment post-Tx, compared with 52% of the non-alcoholic patients (p<0.0001).

**Rejection**

The occurrence of rejection episodes was diagnosed in 56 (54%) of the 103 alcoholic patients and in 54 (57%) of the 94 non-alcoholic patients (NS). (Table II). The vast majority of episodes were acute.
rejections and in a minority of patients in both
groups they were chronic rejections (data not
shown).

Malignancy

In the alcoholic group, 8 patients had been diag-
nosed with hepatocellular cancer (HCC) prior to
transplantation. In another 13 patients, HCC was
discovered in the explanted liver, giving a total HCC
frequency of 20.4% in the ALD group. Among the
ALD patients, 5 died of HCC recurrence (Table III).
Patients transplanted for malignancy per se were
excluded from the control group. However, in 9
patients with end-stage liver disease caused by
hepatitis C cirrhosis (in patients without alcohol
abuse), 4 patients also had HCC prior to Tx,
causing death in only one patient during follow-up.
Two other patients in the control group also had
HCC in the explanted liver. In the alcoholic group, 7
patients (6.8%) developed cancer de novo (Table
IV). This was not significantly different from the
non-alcoholic group, which had 6 (6.4%) patients
with cancer de novo.

Factors of potential to survival and alcohol recidivism

We used multivariate analyses to elucidate potential
factors of importance to overall patient and graft
survival as well as predicting alcohol recidivism. We
entered the following variables into a multivariate
analysis for patient and graft survival: age at Tx,
donor age, cold-ischemia time, ASAT, ALAT, ALP,
bilirubin, albumin, GFR, Child-Pugh score, MELD
score, ascites, esophageal varices, encephalopathy
and previous biliary surgery. None of these factors
influenced overall patient or graft survival.

The following variables were entered into a multi-
ivariate analysis with respect to alcohol recidivism:
duration of abstinence from alcohol prior to trans-
plantation, sex, age, alcoholic treatment, previous
malignancy, marital status, employment status, ben-
zodiazepine use and history of illicit drug abuse.

None of the factors significantly predicted the risk of
alcohol relapse.

Discussion

In Scandinavia, a follow-up of patients with end-
stage liver disease of various etiologies is reported to
the Nordic Liver Transplantation Registry [3].
Although alcoholic cirrhosis has been a more fre-
fquent indication for Tx in recent years no systematic
evaluation has been reported in the patient popula-
tion undergoing transplantation in the Scandinavian
countries.

This study confirms the good results of previous
studies on comparisons of patient and graft survival
in patients transplanted for ALD with comparable
results at both 1 and 5 years as obtained in patients
transplanted for other indications [4–11]. Most of
the patients (75%) in the current study had Child-
Pugh C cirrhosis compared with only 41% in the
control group. Similarly, the MELD score was
significantly higher in the ALD patients. Factors
that were likely to impact on patient survival, such as
diabetes mellitus and smoking, were also signifi-
cantly more prevalent in the ALD group. More
severe liver failure and the additional risk factors for
poor outcome of liver transplantation did not impact
significantly on patient or graft survival. However,
when the Kaplan-Meyer curves are compared, there
is a tendency towards lower survival in the ALD
between 3 and 5 years post-Tx. It is conceivable that
the lack of difference in survival during this period is
due to a type-II error. The more severe the liver
disease prior to transplantation, the more impact it
has on survival compared with patients not trans-
planted for ALD [6]. Almost all studies on survival
in patients transplanted for ALD have shown results
at 1- and 5-year follow-up that were similar to the
results in non-alcoholic transplanted patients. How-
ever, a long-term follow-up study from Pittsburgh
showed a significantly lower survival rate after 5
years in the alcoholic patients compared with the
non-alcoholic group [12]. This was probably due to
the development of extrahepatic malignancies post-
Tx, which was more common in the alcoholic group.
In the current study, there was no significantly
poorer long-term survival in the alcoholic patients
and the frequency of de novo cancer was no different
in the alcoholic group compared with the non-
alcoholic group. This is at variance with the recently
reported French multicenter study, which showed an
increase in cancer post-Tx at the 2-year follow-up
[22]. In the current study the alcoholic group was
followed for a mean period of 42 months. The
incidence of de novo cancer was only 6.8% com-
pared with 19.5% in the study by Jain et al. [12].

<table>
<thead>
<tr>
<th>Table IV. De novo malignancy post-Tx in patients with alcoholic liver disease (ALD) and in controls.</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALD</td>
</tr>
<tr>
<td>------------------</td>
</tr>
<tr>
<td>Pancreatic cancer</td>
</tr>
<tr>
<td>Skin cancer</td>
</tr>
<tr>
<td>Lung cancer</td>
</tr>
<tr>
<td>Lymphoma</td>
</tr>
<tr>
<td>Esophageal cancer</td>
</tr>
<tr>
<td>Cholangiocancer</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>(6.8%)</td>
</tr>
</tbody>
</table>
However, in the study by Jain et al., the longer follow-up of 94 months might possibly explain the differences compared with our results as, for example almost half of the patients who died of cancer developed these tumors 60–96 months post-Tx [12]. No cases of de novo oropharyngeal cancer were observed in our cohort and the low incidence of de novo cancer in general is of interest and cannot be explained readily by our results and requires further investigation. The low incidence is hardly due to fewer numbers of smokers in our population, as 77% of the alcoholic patients were current or ex-smokers. We found no significant difference in survival in the subset of patients with concomitant hepatitis C. However, the number of patients with concomitant hepatitis C was low and this could be due to a type-II error. Our results, however, are in agreement with results from Wiesner et al. showing no difference between patients with ALD and those with ALD and concomitant hepatitis C post-Tx [23].

The risk of recidivism of alcohol use post-Tx has been one of the most important reasons for the reluctance to accept patients with ALD for liver transplantation. Even with careful selection of patients with alcoholic cirrhosis for transplantation, 20–50% of patients in the published studies acknowledge some alcohol use after transplantation [24]. In the current study, 33% of patients resumed some alcohol intake post-Tx with approximately half of these returning to heavy drinking. Unfortunately, in some patients this resulted in damaging effects, causing some morbidity in a number of patients. However, the overall impact on patient and graft survival was surprisingly low and is in line with the results from other studies [12,25,26]. No deaths in our patients could be clearly attributed to the recurrence of alcohol use but we cannot exclude that alcohol use might have contributed as a cofactor to some of the deaths. The recidivism in our patients is very similar to the 31% recidivism in a recently reported study from Montpellier in France and Austria [10,7]. Furthermore, Lucey et al. reported a recidivism rate of 34% in patients transplanted in the US [9]. In the US, patients usually need to satisfy financial requirements for liver transplantation, which is not the case in Scandinavia, which has a publicly funded healthcare system. Our patient selection is based purely on medical and psychosocial issues and not on the patient’s financial situation and this does not seem to impact on the rate of recidivism.

All transplant professionals seem to agree that abstinence from alcohol is an important criterion in the selection of ALD patients for liver transplantation [17,24]. This is also the opinion of the investigators in the present study. Most transplant centers use some fixed period of abstinence, usually 6 months, in order to accept patients for transplant listing. However, although widely used, the so-called 6-month rule is controversial and has come under increasing criticism [17,24]. Although it is important to evaluate the effects of abstinence on the patient’s clinical condition, and in many cases this can obviate the need for liver transplantation, the problem with those who do not improve with abstinence is challenging. At our center, the 6-month rule has been followed when possible. However, if the prognosis of the patients without Tx is very poor, some patients have been transplanted before this time limit. In the current study, 19 (18%) patients transplanted for ALD had a pre-Tx sobriety period of less than 6 months. Analysis of the rate of recidivism with regard to duration of abstinence prior to transplant did not reveal any correlation with the duration of abstinence and the risk of recidivism post-Tx. Our results thus contrast with the results of some published studies, which show less recidivism in those abstinent for more than 6 months [10,20,27], but support the results from other studies, which have shown that sobriety of less than 6 months did not predict recidivism [12,25,28,29]. In fact we were not able to identify any factor, such as length of sobriety, treatment of alcoholism, prior illicit drug use history, benzodiazepine use, employment status or marital status, to predict abstinence after transplantation.

In the current study, the most important factor with regard to the rate of recidivism was the start of structured management of these patients in 1998. Patients transplanted before this change of management had a recidivism rate of 48% but only 22% of patients who were transplanted thereafter relapsed. Although the follow-up of patients transplanted during the early period, between 1988 and 1997, was longer, the patients transplanted in1998 and later had a median follow-up of 27 months and the median time to relapse was 12 months in those who resumed alcohol post-Tx. Most patients who relapse within our population thus seem to do so fairly early and the shorter follow-up in those transplanted during the late period probably does not explain the different results for recidivism occurring before and after 1998. The structured management perhaps increased the likelihood of abstinence of the patients after the Tx but it cannot be excluded that this change in management improved the selection of patients and therefore decreased recidivism.

In the light of our results and those of others [29], showing a lack of predictive factors for recidivism and showing favorable outcome after the start of structured management of the ALD patients by a dedicated group of specialists in alcohol and
addiction medicine, social workers and a transplant coordinator, this might be more important than a fixed abstinence period before transplantation. A crucial element in the pre-transplant process is the acceptance by the patient and the relatives of his/her alcoholism. Although difficult to evaluate in a retrospective survey, we believe that the evaluation process by this dedicated team is of great importance. The evaluation of the acceptance of the alcohol problem by the patient should be done by an experienced specialist in addiction medicine and thereafter a worked-up plan for therapy should be proposed, which has been the case at our center since 1998. We found an increase in the divorce rate in the ALD group compared with the non-alcoholic controls and 56% of those who resumed alcohol consumption were living alone compared with only 29% of those who remained abstinent. Whether this is the cause or the effect of the relapse is unclear and it cannot be explained by our results.

The employment status of the alcoholic group in the current study was somewhat discouraging. In line with the results of others, more ALD patients were out of work prior to transplantation in comparison with the non-ALD group [30]. Unfortunately, only 18% of our ALD patients resumed employment post-Tx compared with 37% working pre-transplant. However, an employment rate as low as 13% in alcoholic patients has been reported from the USA (11) and Bravata et al. have shown that 30% fewer transplant recipients with ALD were working more than one year after transplantation than before [31].

One of the possible weaknesses in our study is its retrospective nature, with no formal instrument for the detection of recidivism. We relied on clinical judgements by the doctor responsible and no biochemical markers for alcohol use were obtained as a part of the study. However, careful prospective studies by DiMartini et al. have shown that clinical interviews by a psychiatrist were the most successful method for identifying post-Tx alcohol use [2,16]. Biochemical markers for alcohol use do not seem to be reliable [2] and the lack of sensitivity and specificity of the alcohol markers has been reported previously in this clinical situation [30].

In conclusion, our results show that ALD is a good indication for liver transplantation in a selected group of patients with ALD. Only a rather small proportion of patients return to excessive drinking although the impact on survival is surprisingly low. No factors could predict relapse after transplantation and instead of applying a strict period of abstinence prior to transplantation, a dedicated team including a specialist in addiction medicine should evaluate the patient and help the patient to accept the alcohol problem in order to minimize the risk of recidivism.

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References


