ORIGINAL ARTICLE

Good outcome after liver transplantation for ALD without a 6 months abstinence rule prior to transplantation including post-transplant CDT monitoring for alcohol relapse assessment – a retrospective study

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SUMMARY

Alcoholic liver disease (ALD) is the second most common indication for liver transplantation (LT). The utility of fixed intervals of abstinence prior to listing is still a matter of discussion. Furthermore, post-LT long-term observation is challenging, and biomarkers as carbohydrate-deficient transferrin (CDT) may help to identify alcohol relapse. We retrospectively analyzed data from patients receiving LT for ALD from 1996 to 2012. A defined period of alcohol abstinence prior to listing was not a precondition, and abstinence was evaluated using structured psychological interviews. A total of 382 patients received LT for ALD as main (n = 290) or secondary (n = 92) indication; median follow-up was 73 months (0–213). One- and five-year patient survival and graft survival rates were 82% and 69%, and 80% and 67%, respectively. A total of 62 patients (16%) experienced alcohol relapse. Alcohol relapse did not have a statistically significant effect on patient survival (P = 0.10). Post-transplant CDT measurements showed a sensitivity and specificity of 84% and 85%, respectively. In conclusion, this large single-center analysis showed good post-transplant long-term results in patients with ALD when applying structured psychological interviews before listing. Relapse rates were lower than those reported in the literature despite using a strict definition of alcohol relapse. Furthermore, post-LT CDT measurement proved to be a useful supplementary tool for detecting alcohol relapse.

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Key words
alcohol relapse, alcoholic liver disease, carbohydrate deficient transferrin, liver transplantation

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Introduction

Liver transplantation is the only definitive and long-lasting treatment for end-stage alcoholic liver cirrhosis. The outcome of liver transplantation for alcoholic liver disease (ALD) is similar to that for other indications [1]. Long-term survival rates in Europe were reported to be 73% after 5 years and 59% after 10 years [2,3]. According to the European Liver Transplant Registry, ALD is currently the second most frequent indication

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for liver transplantation, preceded by liver cirrhosis because of viral infection. Combined ALD and hepatitis C infection is a common indication for LT while the clinical outcome for this condition is similar or even better than it is for transplantation because of hepatitis C alone [4]. Nevertheless, the listing criteria for LT in patients with ALD are controversially discussed. One of the most disputed aspects is the pretransplant abstinence period [5–7]. While some centers, especially those in the United States, prescribe a minimum abstinence period of 6 months prior to transplantation [8], in others the opinion of an addiction specialist is decisive for the inclusion of patients on the waiting list [9–11]. Additionally, the identification of a potential alcohol relapse in post-LT surveillance is a challenging aspect. The diagnosis of alcohol relapse is mainly based on psychological examination. The detection of post-LT alcohol relapse on the basis of laboratory findings is rendered difficult by the large number of biomarkers available and their lack of standardization [12]. One of the best-investigated biomarkers in patients with alcoholic disease is carbohydrate-deficient transferrin (CDT). CDT is a very useful aid in detecting alcohol disorders [13]. The consumption of 50–80 g of alcohol/day for two weeks alters the glycosylation profile of transferrin [14], also known as CDT [15]. Once a person stops consuming alcohol, the glycosylation status of CDT returns to normal within 1–3 weeks [16,17]. A high-performance liquid chromatography (HPLC) method to measure CDT proved to be a highly accurate test for patients with active drinking disorders [15]. In this study, outcome (patient and graft survival) from patients transplanted for ALD was analyzed retrospectively in regard to alcohol relapse rates. We further evaluated CDT levels, measured routinely post-LT, and correlated their diagnostic value with results of psychological examinations.

Patients and methods

Study design and study population

Patients listed for LT between 1996 and 2012 at the Department of Transplantation, Medical University of Vienna, with alcoholic cirrhosis as the main or secondary indication were included in this study. Patients with acute alcoholic hepatitis were not transplanted in the observation period. Patients' data were analyzed retrospectively using our institutional LT database. This database includes standard demographic data, indications for liver transplantation, date of listing, date of transplantation, the occurrence, and date of alcohol relapse, and CDT values including dates of analysis, the date of death, and the cause of death.

Inclusion criteria and listing policy

All patients included in the study suffered from ALD, based on a history of alcohol consumption combined with corresponding clinical and laboratory data and the histologic morphology of the explanted liver after LT. A specialized transplant psychologist evaluated all patients pretransplant by regularly conducted, structured psychological interviews when patients with ALD where considered for LT. During these interviews, patients' characteristics as demographic data, social anamnesis, causes for alcohol consumption, coping mechanisms (past and future), compliance (past and future), agreement to therapy (medical, psychological), and future goals were evaluated. When there was a suspicion of drinking any time prior to transplantation, patients were sent to specialized institutes/rehab centers for further treatment. Patients, who did not appear regularly to the appointments or denied consulting a rehab center, were taken from the list because of noncompliance. A specified period of alcohol abstinence prior to transplantation was not used at our institution. Patients on the waiting list were asked to strictly abstain from alcohol, and sobriety was assessed at every interview.

Follow-up

Medical records during the patients' hospital stay as well as records from visits at the outpatient clinic were collected in our LT database. Follow-up was performed once a week during the first month after LT, twice a month during the second and third month after transplantation, twice a year during the first 2 years after LT and once a year thereafter, or when required. At these visits, a member of the transplant team and a specialized psychologist interviewed the patients. After the first two years with frequent visits at our transplant center, patients' follow-up was partly taken over by referring physicians with regular blood examinations for liver function and levels of immunosuppression. Besides, patients were obligatory invited for yearly follow-up visits in our transplant center. If there were any significant changes in liver function parameters, patients were immediately allocated to our hospital. Post-LT CDT and routine blood values including liver function parameters were measured at every follow-up appointment at our transplant center. Until February 2002, the

Transplant International 2016; 29: 559–567

reference value for CDT was less than 20 U/l for men and less than 26 U/l for women; the test was based on a commercially available double antibody radioimmunoassay (Pharmacia Diagnostics AB, Uppsala, Sweden). An HPLC method was introduced in February 2002 with a cut-off value of 2.3%. There are no different cut-offs between male and female patients [18]. Alcohol relapse was strictly defined as any kind of post-transplant alcohol consumption. Besides regular post-transplant blood tests including CDT measurements, patient's compliance and alcohol consumption was assessed during every post-transplant visit using structured psychological interviews.

All outcome parameters were evaluated until October 2013. Graft survival was calculated from the time of transplantation to the time of end-stage organ failure – either resulting in retransplantation or the patient's death.

Statistical analysis

Statistical analysis was performed using SPSS 20 (SPSS, Inc., Chicago IL, USA) and the statistics program R 3.2.2 (R-packages survival, mstate, cmprsk) [19–22]. Qualitative data are shown as counts (n) and percentages (%). Patient survival and graft survival were analyzed by Kaplan–Meier curves. Reasons for death were compared between patients with vs. without alcohol relapse by Chi-square tests. To compare patients transplanted for ALD as the main indication vs. secondary indication with respect to the time until alcohol relapse, a competing risk analysis was applied with alcohol relapse as the event of interest and death because of graft loss or other reasons as competing event. For patients who experienced both events (alcohol relapse and death) during the observation period (n = 31), only the event alcohol relapse was considered. Group differences were analyzed using the Gray's test. Cumulative incidence curves were plotted for all patients and for the subgroups (main indication, secondary indication) separately. For evaluation of CDT as diagnostic test, sensitivity, specificity, positive and negative likelihood ratio, and positive and negative predictive value were calculated and 95% confidence intervals were reported. To analyze the effect of alcohol relapse on patient survival, an extended Cox model was calculated with patient survival as dependent variable and alcohol relapse as time-dependent covariate. For patients who died, we used the time until death for analysis. Patients who had not died during the observation period were censored at the time of last observation. All tests were two-sided, and P-values <0.05 were considered statistically significant.

Results

Demographic data

Between 1996 and 2012, 1034 patients received a liver transplant at the Medical University of Vienna. In the aforementioned observation period, 458 patients with ALD were put on the waiting list for liver transplantation. A total of 382 patients (83.4%) were transplanted (study group), 36 (7.9%) died while on the waiting list, and 40 patients (8.7%) were removed from the list (noncompliance because of nonadherence to appointments or alcohol relapse n = 6, deterioration of general condition n = 6, tumor progression n = 17, clinical improvement n = 11) (Table 1). ALD was the main indication for LT in 290 patients and the secondary indication in 92 patients (Table 2). The median duration of follow-up was 73 months (range, 0–213 months). The median waiting time from listing until transplantation was 3.8 months (range, 0–37 months). The proportion of male and female patients in the transplanted group was 300:82.

Survival times

One- and 5-year patient survival rates were 82% and 69%, and graft survival rates for first transplants were 80% and 67%, respectively (Fig. 1). Nineteen patients required retransplantation. The indications for retransplantation were primary graft dysfunction (n = 3), thrombosis of the hepatic artery (n = 6), thrombosis of the portal vein (n = 2), complications of the bile duct (n = 3), acute rejection (n = 1), and chronic rejection (n = 4). Kaplan–Meier curves for patients with ALD as primary indication (n = 290) or as secondary indication (n = 92) are shown separately in the Figs S1 and S2.

Table 1. Patients considered for liver transplantation (LT) from 1996 to 2012.

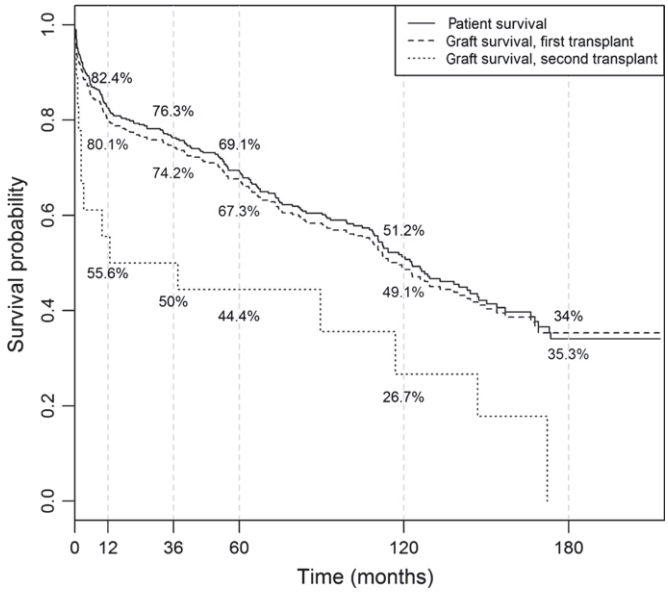
Patients considered for LT (n = 458, 100%)	
Transplanted	382 (83.4%)
Died on list	36 (7.9%)
OFF-list	40 (8.7%)
Clinical deterioration	n = 6
Noncompliance	n = 6
Tumor progression	n = 17
Clinical improvement	n = 11

Table 2. Indication for liver transplantation.

Patients with LT for ALD (n = 382; 100%)			
ALD as primary indication (n = 290; 75.9%)		ALD as secondary indication (n = 92; 24.1%)	
ALD only	249 (65.2%)	HCC	42 (11%)
+HCC	17 (4.4%)	HCV/HBV	30 (7.9%)
+HCV/HBV or other	24 (6.3%)	HCC+HCV/HBV or other	20 (5.2%)

ALD as primary indication (n = 290): ALD was the sole indication for LT (n = 249, 65.2%); ALD + Hepatocellular carcinoma (HCC) – ALD was the main indication, HCC was found incidentally from histological examination of the explanted liver (n = 17, 4.4%); ALD + HCV/HBV or other (n = 24, 6.3%).

ALD as secondary indication (n = 92): HCC + ALD – Hepatocellular carcinoma was diagnosed before transplantation (n = 42, 11%); HCV/HBV (Hepatitis C or B Virus) + ALD – Hepatitis C or B was interpreted as a primary indication for LT (n = 30, 7.9%) or HCC + HCV/HBV + ALD or other (n = 20, 5.2%).



Number at risk at different time points, all patients

months	0	12	36	60	120	180
patient survival	382	315	275	220	107	19
graft survival, first transplant	382	306	267	215	102	19
graft survival, second transplant	18	10	9	6	3	-

Figure 1 Kaplan–Meier curve for patient survival and graft survival including all patients. Number at risk at different time points is shown for all patients. One Patient received a third transplant (graft loss of third transplant (death of the patient) 4.8 months after transplantation of the second transplant).

Reasons for death

Thirty-one patients with alcohol relapse died during the observation period. The causes of death were liver related n = 13 (41.9%) (Recurrence of disease, sequelae of recirrhosis n = 11; biliary complication n = 1; chronic rejection n = 1), sepsis n = 4 (12.9%), *de novo* tumor n = 6 (19.4%), cerebrovascular or cardiac reasons n = 3 (9.7%), and others n = 5 (16.1%). None of the patients died from acute alcoholic hepatitis. A total of 155 patients without evidence of alcohol relapse died during the observation period; the causes were liver related n = 16 (10.3%) (Biliary complications n = 7; chronic rejection n = 2, HCV recurrence n = 1; others n = 6), sepsis n = 36 (23.2%), tumor recurrence n = 11 (7.1%), *de novo* tumor n = 33 (21.3%), cerebrovascular or cardiac reasons

Transplant International 2016; 29: 559–567

n = 24 (15.5%), and other n = 35 (22.6%). The cause of death was significantly more often liver related in patients with alcohol relapse than it was in those without alcohol relapse (Chi-square test $P < 0.0001$) (Table 3).

Alcohol relapse

Until October 2013, alcohol relapse occurred in 62 patients (16.2%) transplanted for ALD. The cumulative incidence curve for the endpoint alcohol relapse is shown in Fig. 2a. A total of 165 of 382 patients did not have an event (alcohol relapse or death) during the observation period. A total of 62 patients had an alcohol relapse, and 155 patients without alcohol relapse died during the study period. The cumulative incidence for alcohol relapse after 1, 3, and 5 years was 3.9%, 10.4%, and 13.9%, respectively (Fig. 2a). The cumulative incidence curves for the endpoint alcohol relapse for indication (primary vs. secondary) separately are shown in Fig. 2b. The cumulative incidence of alcohol relapse was significantly higher in patients with ALD as primary indication vs. secondary indication (Gray's test: P = 0.03).

CDT values

In all 6756 CDT measurements were performed routinely at every post-LT follow-up appointment in 321 of 382 patients with a mean of 17 measurements per patient. A total of 61 patients without regular CDT measurements died early (n = 29) or underwent clinical follow-up at another hospital without the possibility of CDT measurements (n = 32). Of 62 patients with alcohol relapse, 6 had no CDT measurement. When alcohol relapse was suspected in patients whose follow-up was performed by another hospital without the possibility of CDT measurements (n = 32), they were submitted to a specialized psychologist where alcohol relapse was confirmed. Forty-seven of 56 patients with CDT screening had positive CDT values when an alcohol relapse occurred, whereas 9 patients were negative for CDT. Of those 9 patients, 6 reported alcohol consumption only once after the LT, referred to as "slip". The sensitivity of CDT for alcohol relapse was 84% (95% confidence interval (CI): [71.67%; 92.38%]) (47/56) and the specificity 85.3% (95% CI: [80.43%; 89.32%]) (226/265). When defining the 6 patients with a slip as patients without alcohol relapse, a sensitivity of 94% was found. All patients with slips had ALD as their primary indication, except one patient with HCC as the leading indication. Positive likelihood ratio was 5.7 (95% CI: [4.18; 7.79]) showing a good association with a positive CDT value and alcohol relapse. We found a negative likelihood ratio of 0.19 (95% CI: [0.10; 0.34]); thus, a negative CDT value was highly associated with the absence of alcohol relapse. Positive and negative predictive values of CDT were calculated as 55% (95% CI: [43.55%; 65.42%]) and 96% (95% CI: [92.85%; 98.23%]), respectively (Fig. 3).

Influence of alcohol relapse on patient survival

The extended Cox model with alcohol relapse as time-dependent covariate did not reveal any statistically significant effect of alcohol relapse (P = 0.10) on patient survival. The estimated hazard ratio [95% CI] was 1.4 [0.94; 2.1], indicating that at any given time, the risk of death for a patient who has already experienced an alcohol relapse at that time is 1.4 times the risk for a patient who has not yet experienced an alcohol relapse.

Discussion

This report summarizes the experience at our institution concerning patients who underwent LT for ALD. Although our data are based on a retrospective analysis, an accurate prospectively fed database was available for patients transplanted for ALD, including post-transplant alcohol relapse rate, patient and graft survival, and the

Table 3. Reasons for death in patients with and without alcohol relapse.

Reasons for death	Died (n = 186)	Died without alcohol relapse (n = 155)	Died with alcohol relapse (n = 31)	P-Value
Liver-related	29 (15.6%)	16 (10.3%)	13 (41.9%)	<0.0001
Sepsis	40 (21.5%)	36 (23.2%)	4 (12.9%)	0.202
HCCA recidivism	11 (5.9%)	11 (7.1%)	–	–
Tumor – *de novo*	39 (21%)	33 (21.3%)	6 (19.4%)	0.809
Cerebrovascular-cardiac	27 (14.5%)	24 (15.5%)	3 (9.7%)	0.402
Other	40 (21.5%)	35 (22.6%)	–	–

For statistical analysis, chi-square test was applied.

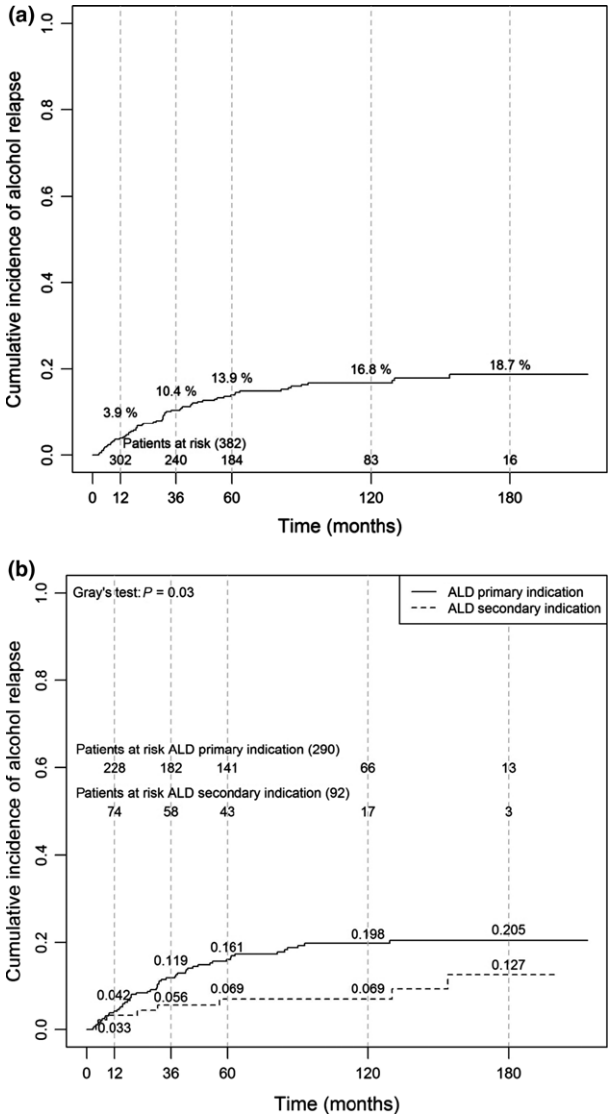


Figure 2 (a) Cumulative incidence curve for alcohol relapse (competing risk = death because of graft loss or other reasons), $n = 382$. One-, 3-, 5-, 10-, and 15-year alcohol relapse rates are marked and labeled with the respective percentages. (b) Cumulative incidence curve for alcohol relapse (competing risk = death because of graft loss or other reasons) for patients transplanted for ALD as primary indication ($n = 290$) vs. secondary indication ($n = 92$). The cumulative incidence of alcohol relapse was significantly higher in patients with ALD as primary indication vs. secondary indication (Gray's test: $P = 0.03$).

usability of CDT in post-LT alcohol relapse monitoring. Over the entire observation period, the median waiting time was only 3.8 months and mortality on the waiting list was only 7.9%. One reason for this low mortality could be the use of structured psychological interviews instead of a required abstinence period of six months. This strategy leads to a timely evaluation without any delays.

Despite this evaluation strategy, our 1-, 3-, and 5-year patient survival rates of 82.4%, 76.3%, and 69.1%, respectively, are similar to the survival rates reported in the European Liver Transplant Registry. The latter were calculated for all patients with ALD, including those with additional diseases like HCC, HCV/HCB infection, or others. Of patients who died during the observation period, more than half (57%) died because of "not-directly-graft-related" reasons, namely cerebrovascular-/cardiac events, *de novo* tumors or other reasons. Liver transplant recipients with a proven alcohol relapse died significantly more often because of liver-related reasons, whereas in patients without alcohol relapse sepsis was the most prevailing cause of death. Interestingly, death because of *de novo* tumors was relatively high with 19% and 21% in both groups. According to the literature, post-transplant malignancies can be found in up to 25% of patients [23]. The reason for these high rates of *de novo* tumor in patients with ALD could be the carcinogenic impact of alcohol. Besides, many patients in our study cohort are either smokers or ex-smokers adding an additional risk for tumor development. Our data confirm a previous study from Dumortier *et al.* showing that long-term survival in patients with ALD is limited by aero-digestive malignancies rather than morbidity and mortality because of alcohol relapse [24].

In a previous study comprising 118 patients transplanted for ALD between 1982 and 1993 at the Medical University of Vienna, patients were found to be compliant regarding post-LT clinical investigations and appointments for psychological counseling [23]. Including any consumption of alcohol, 16.2% of our patients experienced an alcohol relapse during the observation period. Published data on alcohol relapse after LT, including all drinking patterns, vary from 3–49% [25]; heavy drinking was observed in less than 10% [26]. Egawa *et al.* recently reported risk factors for alcohol relapse after living donor LT for ALD in Japan [27]. The incidence of alcohol consumption after LT in their cohort was 22.9%, and the risk was significantly higher in patients with a history of treatment for psychological diseases other than alcoholism, noncompliance with clinical visits after LT, and smoking after transplantation; preoperative alcohol consumption was no risk factor [27]. When selecting patients for LT, socio-medical support appears to be a more critical factor than pretransplant alcohol consumption [11]. In contrast to Egawa *et al.*, we found no significant effect of alcohol relapse on patient survival (Hazard ratio [95% CI]: 1.4 [0.94; 2.1], $P = 0.10$) [27]. Patients experiencing alcohol relapse were told that they would not be eligible to a

Transplant International 2016; 29: 559–567

Patients with alcohol relapse:	CDT test results:			
62/382 (16%)		relapse	no relapse	sum
6756 CDT-measurements from 321 patients	positive	47	39	86
	negative	9	226	235
	sum	56	265	321

Statistic	Value	95% CI
Sensitivity	83.93%	71.67% to 92.38%
Specificity	85.28 %	80.43% to 89.32%
Positive Likelihood Ratio	5.70	4.18 to 7.79
Negative Likelihood Ratio	0.19	0.10 to 0.34
Positive Predictive Value	54.65%	43.55% to 65.42%
Negative Predictive Value	96.17 %	92.85% to 98.23%

Figure 3 CDT test results performed after LT. Statistical analysis of CDT as diagnostic test was performed.

second liver transplantation, and besides more-frequent visits at our transplant unit they were allocated to regular appointments with the psychologist. By this strategy, most patients with a relapse stopped their alcohol consumption again.

Owing to organ shortage and concerns about post-LT alcohol relapse, LT in patients with ALD is still controversially discussed. This also reflects the discussion on required period of alcohol abstinence before transplantation. In our center, no specific period of abstinence before transplantation is required. The decision if patient with ALD is eligible for LT is primarily based on a combination of the psychological interview and compliance. In view of the fact that some patients with ALD would probably be unable to survive an abstinence period of six months, we give greater importance to a structured psychological interview evaluating sobriety and coping mechanisms rather than a predefined alcohol abstinence period. Our data showed good survival rates and low alcohol relapse rates for patients transplanted for ALD, despite our strict definition of relapse. Unfortunately, because of the retrospective nature of this study we were not able to distinguish between various drinking patterns, apart from identifying six patients with a slip.

In our cohort, the measurement of CDT after LT for ALD yielded valuable information about a potential alcohol relapse. It is known that pretransplant CDT monitoring of patients with ALD, still waiting for a transplant, is not helpful because elevated CDT levels may not correlate with the consumption of alcohol [28]. CDT levels can be elevated in patients with alcoholic as well as in patients with nonalcoholic end-stage liver diseases awaiting LT [29]. However, this simple test, which was performed routinely after LT in our cohort, revealed a sensitivity of 84% in all patients (95% CI: [71.67%; 92.38%]) and raised up to 94% when patients experiencing only a slip were defined as "nonrelapsers". Furthermore, negative test results were highly associated with absence of alcohol relapse (negative predictive value of 96%). Detecting alcohol relapse in patients after LT is challenging, and therefore, CDT is an important tool in monitoring post-LT compliance. While keeping in mind the low sensitivity of the test in patients with one-time slips, it does help to filter patients who need psychological aid for drinking abnormalities. However, when CDT is normal, the test can release patients from a suspicion of alcohol relapse. A weakness of CDT is its low positive predictive value. This is because of the fact that heightened CDT could be caused by a variety of cofounders including drugs, immunosuppression or recurrence of cirrhotic liver disease. Nevertheless, a major advantage of this test is the easy applicability after routine blood draw with low costs. Although other tests, as for example, urinary or hair ethyl glucuronide, have been proofed to be useful for detecting alcohol relapse after liver transplantation, they are not yet available for routine diagnosis in many centers [30–32]. We believe that in the future, a combination of these tests and structured psychological interviews will deliver the highest chance to detect alcohol consumption after liver transplantation.

In summary, this large single-center analysis showed good long-term outcome in patients who underwent LT for ALD. Our alcohol relapse rates were low despite a strict definition of relapse. Thus, the policy of performing LT in patients with ALD on the basis of psychological and social evaluation, without a six-month abstinence period, proved to be a valid concept. Furthermore, our data showed that regular measurement of CDT after LT is simple to perform and is

useful to identify patients with alcohol relapse and especially to confirm the absence of relapse.

Authorship

DK: collection of complete data, statistical analysis, design of the work, writing the manuscript, final approval of the version to be published. SR-R: follow-up of patients, collecting data, final approval of the version to be published. IS: statistical analysis, final approval of the version to be published. EF: structured psychological interviews, collection of data, final approval of the version to be published. GG: Drafting the work or revising it critically for important intellectual content, final approval of the version to be published. GS: Drafting the work or revising it critically for important intellectual content, final approval of the version to be published. TS: supervision of the project, interpretation of data for the work, final approval of the version to be published. GAB: supervision of the project, design of the work, writing the manuscript, interpretation of data for the work, final approval of the version to be published.

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Conflicts of interest

The authors have declared no conflicts of interests.

SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Figure S1. Kaplan–Meier curve of patient survival and graft survival for patients transplanted for ALD as the primary indication (n = 290).

Figure S2. Kaplan–Meier curve for patient survival and graft survival including patients transplanted for ALD as the secondary indication (n = 92). One patient received a third transplant (graft loss of third transplant (death of the patient) 4.8 months after transplantation of the second transplant).

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