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ORIGINAL ARTICLE

Significance and clinical impact of routinely tested urinary ethyl glucuronide after liver transplantation – development of a risk score

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SUMMARY

Alcohol abuse after liver transplantation can seriously impact graft and patient survival. However, to date, there is no defined standard procedure to identify patients consuming alcohol after liver transplantation. The aim of this study was to analyze the diagnostic value and clinical impact of routinely measured urinary ethyl glucuronide (uEtG) – a metabolite of ethanol – in patients after liver transplantation. Data of 362 consecutive patients after liver transplantation who visited the University Hospital of Tuebingen for outpatient follow-up were analyzed. Forty-eight patients (13%) displayed positive uEtG results. The uEtG positive group contained significantly more patients with pretransplant alcoholic liver disease. However, two thirds of the uEtG positive patients had no history of pretransplant alcoholic liver disease. Several clinical parameters were significantly associated with positive uEtG. In order to enable a more cost-effective application of uEtG in the future, a clinical risk score was developed (specificity 0.95). In conclusion, routine testing for uEtG reveals a considerable percentage of patients practicing alcohol intake after liver transplantation. Application of our proposed risk score could help focusing uEtG testing on patients at risk.

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Key words
alcohol consumption, alcohol screening, clinical risk score, follow-up care, liver transplantation, urinary ethyl glucuronide

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Introduction

The impact of alcohol abuse after liver transplantation is best documented in patients transplanted for alcoholic liver disease (ALD). In these patients, alcohol relapse can lead to diminished graft survival as well as contribute to reduced patient survival, especially when higher amounts of alcohol (>30 g/day) are consumed [1–5]. Furthermore, alcohol abuse is associated with reduced patient compliance and the occurrence of

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nonhepatic cancers, which further endanger graft and patient survival. However, excessive and harmful alcohol use after liver transplantation and its negative consequences are not limited to patients transplanted for ALD [6–8]. Therefore, it is a challenge to identify those patients who are at risk of drinking after liver transplantation in order to enable timely intervention.

The importance of patient interviews as a component in the detection of alcohol abuse is well documented [9]. In addition, there are several diagnostic tools available to detect signs of alcohol consumption: (i) Ethanol itself can be measured in blood samples, with short-term detectability being the major drawback of this method [10]. (ii) Carbohydrate-deficient transferrin (CDT) represents an indirect marker for alcohol intake with longer detectability, but only the consumption of rather high amounts of alcohol over more than one week will turn this test positive [11,12]. (iii) Ethyl glucuronide (EtG) acts as a direct metabolite of ethanol [13] and can be measured either in hair (hEtG) [14,15] or in urine (uEtG) [16,17]. uEtG can be detected for up to and sometimes more than 90 h after alcohol intake in a dose-dependent manner [13,18]. Allowing for interindividual differences, already ingestion of very small amounts of alcohol (≤3 g) can lead to the detection of uEtG [19]. In order to rule out unintentional low-dose ethanol exposure, a cut-off value for uEtG of 500 ng/ml is recommended [18]. In recent years, uEtG has been established as a marker for proof of abstinence from alcohol for various purposes [13,20]. For instance, uEtG is widely used in monitoring sustained alcohol abstinence in patients on the liver transplant waiting list in Germany [10,21,22].

However, to date, there is no defined standard procedure to identify patients practicing alcohol abuse after liver transplantation. Considering the above mentioned profound negative consequences of alcohol abuse after liver transplantation, this stands in marked contrast to other thoroughly implemented strategies in follow-up care after liver transplantation, such as systematic therapy of chronic viral hepatitis B and C [23].

As a first attempt to address this shortcoming, we introduced uEtG as a routinely used parameter for post-transplant outpatient visits at the University Hospital of Tuebingen, and positive uEtG results were made a topic of discussion and education with the patient.

The study presented here was carried out to analyze the diagnostic value and clinical impact of routinely measured uEtG alone or in combination with other clinical markers indicating alcohol consumption in patients after liver transplantation. In order to enable a more tailored approach in the future, one important goal of this study was to identify either special groups of patients and/or clinical risk constellations that could point to alcohol abuse after liver transplantation. In the following, the terms 'abuse' and 'dependence' are used according to DSM-4 [24].

Patients and methods

Patients and collected data

This analysis was performed after introducing uEtG as a screening parameter into routine laboratory work for outpatient visits post liver transplantation at the University Hospital of Tuebingen. All consecutive adult patients in follow-up care after liver transplantation who visited the outpatient clinic between April 2017 and July 2018 (n = 362) have been included. For analysis, data of the first visit and – if available – of the visit closest to one year after the first visit were collected. For 12 patients, the first visit in the observation period had to be substituted with a later visit because of missing uEtG. Exclusion criterion at all times was missing uEtG.

Collected data contained uEtG as well as additional laboratory results including liver enzymes, bilirubin, INR (international normalized ratio), albumin, and creatinine. Furthermore, patient histories were obtained, including primary diseases leading to liver transplantation. If the patient's statement about alcohol consumption was included in the patient records, alcohol intake per week was classified following Andresen-Streichert *et al.* [11] (see Figure 3). Alcohol anamnesis was embedded into routine conversation with the patient and obtained via unstructured interview. In case of a positive uEtG result, the conversation got extended towards the detection of signs of alcohol abuse or alcohol dependence as well as the need for specialized therapy. Information about graft steatosis was obtained either from histology or from ultrasound examination.

uEtG was measured semiquantitatively by urine homogenous enzyme immunoassay (HEIA; Immunalysis Corporation, Pomona, USA) at the central laboratory of the University Hospital of Tuebingen. Test results exceeding the cutoff value of 500 ng/ml were positive by definition.

In case of positive uEtG, patients were informed about the test result and the issue of alcohol consumption was addressed more thoroughly. At our centre, we recommend basically abstinence from alcohol after liver

transplantation regardless of the underlying disease, which is communicated to the patients on the wards and during outpatient visits.

For this retrospective chart analysis, the institutional review board gave its approval (project number 259/2018BO2) and waived the need for patient consent.

Statistical analysis

Unless otherwise stated, data are given as median [interquartile range (IQR)]. Data analysis was performed using IBM SPSS Statistics (Version 26; IBM corporation) and GraphPad Prism (Version 8.4.0; GraphPad Software, LLC). Mann-Whitney-U test was used for continuous variables. Chi-square test was performed for categorical variables. Furthermore, receiver operating characteristic (ROC) curves were created for parameters of interest, and the area under the ROC curves was examined with a confidence interval (CI) of 95% in order to evaluate the predictive value of the different parameters with respect to uEtG. For the individual continuous parameters used in the risk score, cutoff values were determined using Youden's J statistic. Odds ratios were determined using Cox regression analysis. A multivariable analysis to predict uEtG was performed using a linear regression analysis. Statistical tests were considered significant when P values < 0.05.

Results

Patient characteristics

Three hundred and sixty two consecutive patients were included in the study. Patient characteristics are displayed in Table 1. 30 patients were transplanted twice, two patients were transplanted three times. Median time since last transplantation was 5.5 years (minimum 14 days, maximum 30.8 years). Primary diseases are shown in Figure 1. Eighty-five patients had ALD, of which 16 had further hepatic comorbidities, mostly chronic viral hepatitis B or C.

Results of uEtG testing

Forty-eight patients (13%) presented with positive uEtG. Of these, 18 patients showed a uEtG value between 500 and 1000 ng/ml, nine patients were located within the range of 1000–3000 ng/ml and 21 patients displayed uEtG values of >3000 ng/ml.

Regarding the underlying primary diseases of patients with positive uEtG, the distribution is shown in Figure 1. Seventeen uEtG positive patients (35% of all uEtG positive patients and 20% of all patients with ALD) were formerly transplanted for ALD as the primary disease. There was a significant difference between the uEtG positive and the uEtG negative patient group regarding the percentage of patients with ALD ($P = 0.036$). Further characteristics that were tested between the two groups are displayed in Table 1: the uEtG positive group comprised a significantly higher percentage of male patients, exhibited a significantly longer time since transplantation, suffered significantly more often from graft steatosis and had a significantly higher body mass index (BMI). Notably, there was no significant difference for complications of the biliary tract between the two groups.

As for laboratory results, a significant difference between the two groups could be detected only for gamma-glutamyltransferase (GGT) and the mean corpuscular volume (MCV), with the medians of GGT and MCV in both groups still within normal ranges (Figure 2). Also, medians of alanine transaminase (ALT) and aspartate transaminase (AST) were slightly higher in the uEtG positive than in the uEtG negative group, but the difference was not significant (Figure 2). Bilirubin, creatinine levels, INR, and albumin were within normal ranges, and there were no significant differences for these laboratory results between the two groups (data not shown).

In 225 patients, a history of alcohol consumption was noted, indicating whether and to which degree alcohol was used. The results, grouped by uEtG, are displayed in Figure 3. Patients in the uEtG positive group reported alcohol consumption more often and to a higher degree than patients in the uEtG negative group. The difference between the uEtG positive and the uEtG negative group for history of alcohol consumption was significant ($P < 0.001$). Notably, six patients in the uEtG positive group had reported complete alcohol abstinence.

Development of a clinical risk score for positive uEtG

In order to better predict which patients are good candidates for further uEtG testing, ROC curves were created for several parameters. For these parameters, areas under the curves (AUC) are displayed in Figure 4. Significant results with respect to the prediction of positive uEtG could be obtained for patient history ($P < 0.001$), time since liver transplantation ($P = 0.002$), sex ($P = 0.015$), age ($P = 0.034$), allograft steatosis ($P = 0.024$), BMI ($P = 0.001$), GGT ($P = 0.005$) and

Table 1. Patient characteristics.

		Total	uEtG negative	uEtG positive	*P*
Number of patients	*n*	362	314	48	-
Age (yrs)	Median	59	59	61	0.058
	IQR	49-66	48-65	53-69	
	Range	18-82	18–82	22–77	
Sex (male)	*n* (%)	220 (61%)	182 (58%)	38 (79%)	**0.0051**
Time since (last) transplantation (mos)	Median	66	63	102	**0.0036**
	IQR	26–121	20–117	50–139	
	Range	0–369	0–369	2–367	
ALD	*n* (%)	85 (23%)	68 (22%)	17 (35%)	**0.036**
Immunosuppression	*n* (%)				
Tacrolimus		239 (66%)	211 (67%)	28 (58%)	0.23
Ciclosporine		77 (21%)	67 (21%)	10 (21%)	0.94
Graft steatosis*	*n* (%)	33 (9%)	21 (6.7%)	12 (25%)	**<0.0001**
BMI (kg/m^2)	Median	25.2	25.0	27.5	**0.0008**
	IQR	22.1–29.1	21.6–28.4	25.3–30.0	
Use of nicotine	*n* (%)	45 (12%)	41 (13%)	4 (8.3%)	0.96
Psychiatric comedication	*n* (%)	33 (9%)	32 (10%)	1 (2.1%)	0.49
Any complications of the biliary tract	*n* (%)	42 (12%)	35 (11%)	7 (15%)	0.49

Numbers given for the collective group (total) and for subgroups divided by positive or negative urinary ethylglucuronide (uEtG), respectively. *P* values < 0.05 were considered significant (bold letters).

n, number; yrs, years; IQR, interquartile range; mos, months; ALD, alcoholic liver disease; BMI, body mass index.

*Information obtained either from histology or from ultrasound examination.

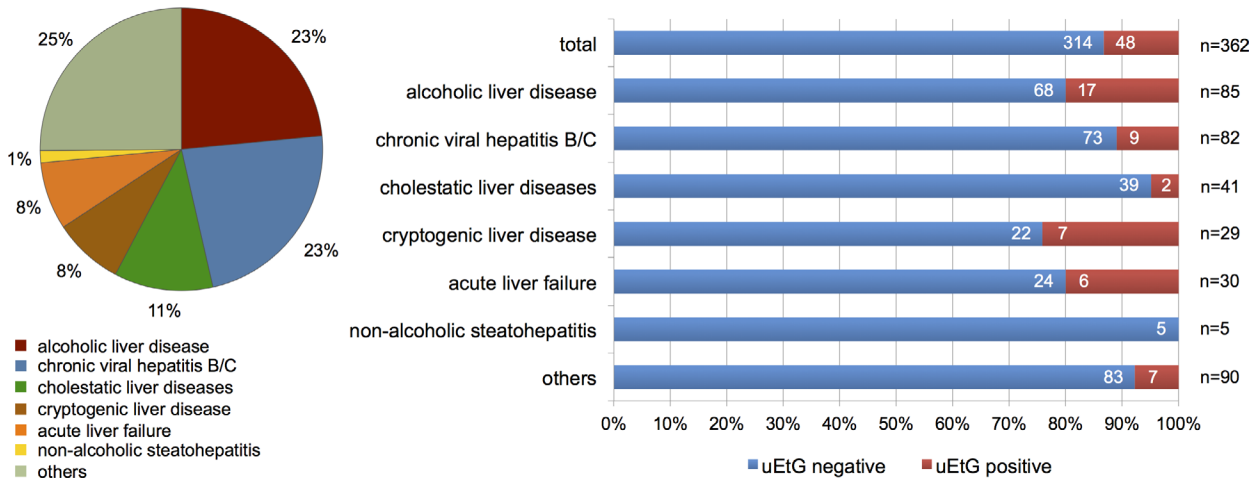

Figure 1 Distribution of negative and positive urinary ethyl glucuronide (uEtG) among the different primary diseases. The distribution of primary diseases among the patients is visualized on the left side as pie chart and given in percentage terms. The absolute number of patients per primary disease is displayed to the right of the bar chart. In the bar chart, the percentage of patients with negative or positive uEtG per primary disease is given as colored bars. The white numbers within the bars show the absolute numbers of patients with negative or positive uEtG per primary disease.

MCV ($P = 0.012$). The result for ALD was not significant.

For the following generation of a uEtG risk score, no laboratory results were included because the medians of all laboratory results were within normal ranges for both groups yielding no clinically sensible cutoff value. Using the other six parameters (patient history, time since transplantation, sex, age, graft steatosis, and BMI), which yielded significant results in the AUC analysis, a risk score was created to better predict alcohol consumption represented by positive uEtG measurement (see Table 2). For the continuous variables, that is, time

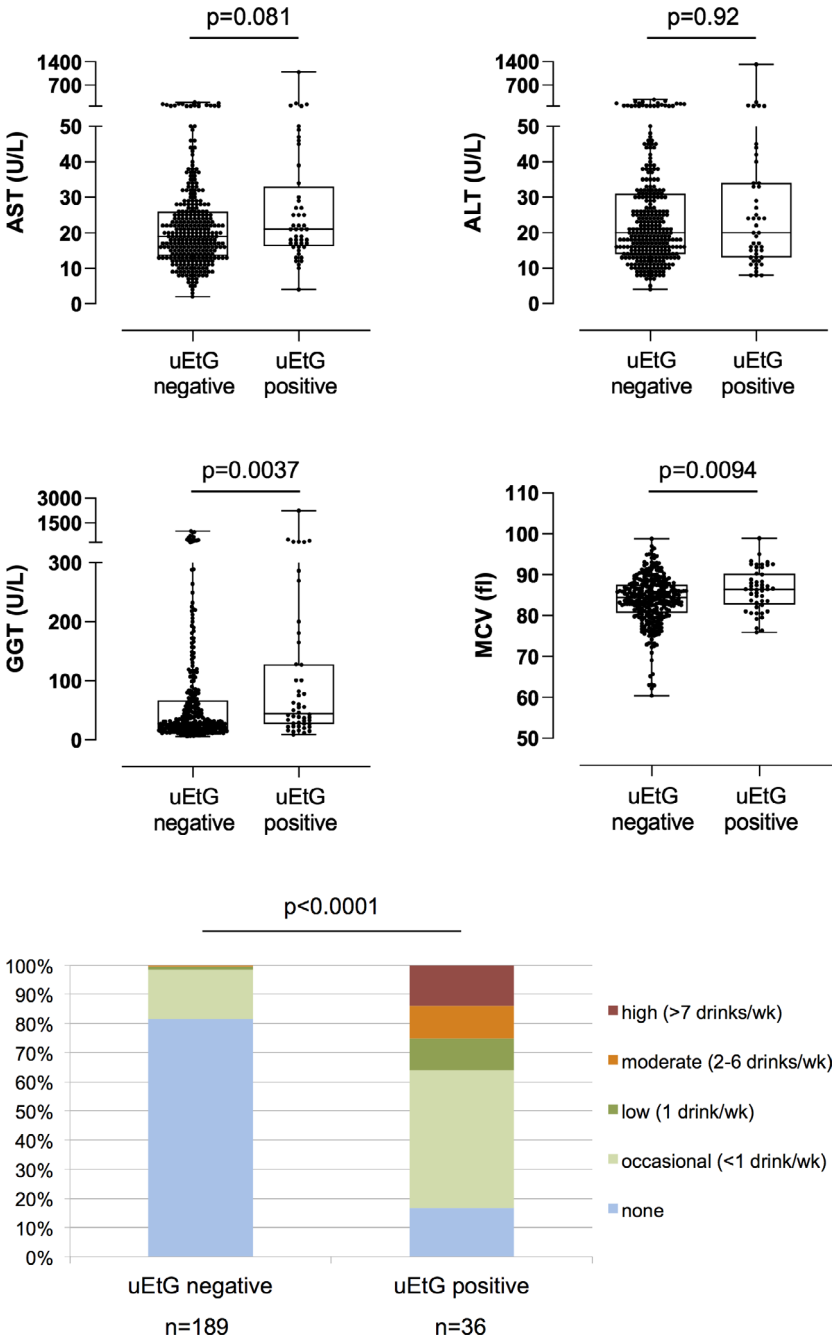

Figure 2 Comparison of selected laboratory results between the two groups of patients with negative and positive urinary ehtyl glucuronide (uEtG), respectively. Box plots: median and interquartile ranges; whiskers: minimum to maximum. ALT = alanine transaminase, AST, aspartate transaminase; GGT, gamma-glutamyltransferase; MCV, mean corpuscular volume. *P* values <0.05 were considered significant.

Figure 3 Patient history of alcohol consumption in patients with negative (left) and positive (right) urinary ethyl glucuronide (uEtG). Degrees of alcohol consumption are given by analogy with Andresen-Streichert *et al* [11]. Wk = week.

since transplantation, BMI, and age, collective specific cutoff values were calculated using Youden's J statistic (calculated cutoff values: time since liver transplantation ≥7.1 years, age ≥ 65.5 years BMI ≥ 25.6 kg/m²). The other parameters, that is, patient history (reported alcohol consumption), sex (male), and graft steatosis, were included dichotomously.

In order to determine the weight of the individual parameters in comparison to each other, odds ratios were determined with respect to uEtG, which yielded the following results: patient history 13.3 (95% confidence interval (CI): 6.7–26.3), time since liver transplantation 3.4 (95%CI: 2.7–9.3), male sex 2.8 (95% CI: 1.3–5.7), graft steatosis 4.7 (95%CI: 2.1–10.2), BMI 3.5 (1.7–6.5), and age 2.1 (95%CI: 1.1–3.9). Granting the heaviest parameter (patient history) 1 point, points were assigned to the other parameters with regard to the relation of their respective odds ratio to this maximum as shown in Table 2.

After definition of the risk score, calculations were performed for all patients with documented patient histories (n = 225). A cutoff value of 1.35 points was

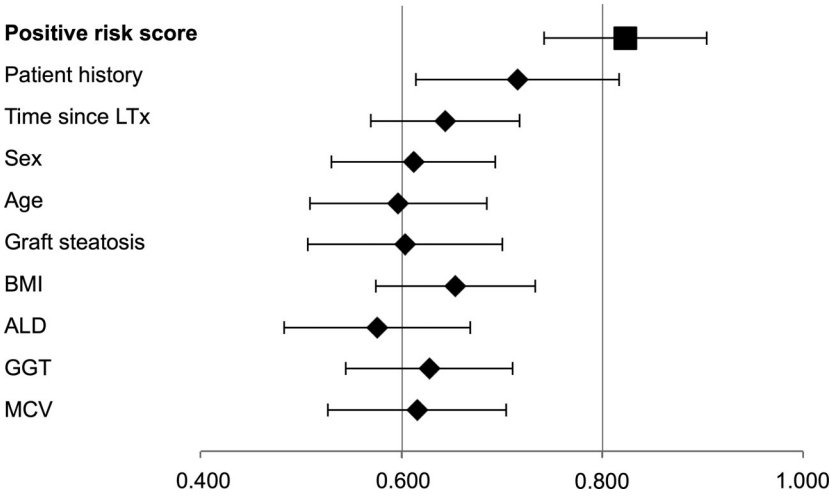

Figure 4 Area under the ROC (receiver operating characteristic) curve for several parameters with respect to prediction of positive uEtG (urinary ethyl glucuronide). At the top, area under the ROC curve for the uEtG risk score. Dots represent the result of the respective area under the ROC curve, whiskers indicate the 95% confidence interval. Patient history = patient reported alcohol consumption, ALD, alcoholic liver disease; LTx, liver transplantation; GGT, gamma-glutamyltransferase; MCV, mean corpuscular volume; BMI, body mass index.

Table 2. Risk score for positive urinary ethyl glucuronide (uEtG).

Parameter	Points
Patient history: reported alcohol consumption	1.0
Time since liver transplantation ≥ 7.1 years	0.3
Male sex	0.2
Age ≥ 65.5 years	0.4
Graft steatosis	0.3
BMI ≥ 25.6 kg/m²	0.2
Score	**0–2.4 points**

A score of ≥ 1.4 points is defined as positive score result.
BMI, body mass index.

determined via Youden's J statistic. As the risk score can only have one decimal place, a risk score of ≥1.4 points was defined as 'positive' (see Table 2). The application of the risk score to our data yielded an area under the ROC curve of 0.823 (95%CI: 0.742–0.905), which is superior to all tested individual parameters (see Figure 4). Specificity and sensitivity of the risk score were 0.95 and 0.67, respectively. The negative predictive value was 0.95.

One-year follow-up

One-year follow-up data on uEtG could be obtained from 345 patients (see Figure 5). Regarding the other 17 patients, four had died from various causes (cardiogenic shock, subdural haematoma, inoperability at time of liver-re-transplantation and biliary pancreatitis) all of which were in the uEtG negative group. Two patients transferred to another transplant centre, and one patient had no residual urine excretion at one-year follow-up. Furthermore, three patients in the uEtG positive group and seven patients in the uEtG negative group did not have their regular follow-up appointment at the outpatient clinic until after the end of the study.

Twenty-eight patients (8%) had a positive uEtG at one-year follow-up: 10 patients showed a uEtG value between 500 and 1000 ng/ml, seven patients were located within the range of 1000–3000 ng/ml, and 11 patients displayed uEtG values of >3000 ng/ml. Sixteen of these patients had already presented with positive uEtG at first visit while 12 patients were 'newly positive' (see Figure 5). Twenty-nine patients who were in the uEtG positive group at first visit were 'newly negative' at one-year follow-up, including most of the patients (89%, $n = 16$), who had uEtG values <1000 ng/ml and 40% ($n = 12$) of the patients with higher uEtG results. Of the newly positive patients, three had reported alcohol consumption at first visit (all: occasional) and six reported alcohol consumption at one-year follow-up (four: occasional, one: low, one: moderate).

For a first validation of our newly developed risk score, we calculated the risk score for all follow-up patients in whom a patient history concerning alcohol use had been documented ($n = 256$). This yielded results similar to the cohort at first visit with a specificity of 0.88, a sensitivity of 0.65 and a negative predictive value of 0.96.

Discussion

To our knowledge, this is the largest post liver transplant cohort to date in which uEtG was used as a screening parameter for alcohol consumption, comprising all kinds of pretransplant primary liver diseases.

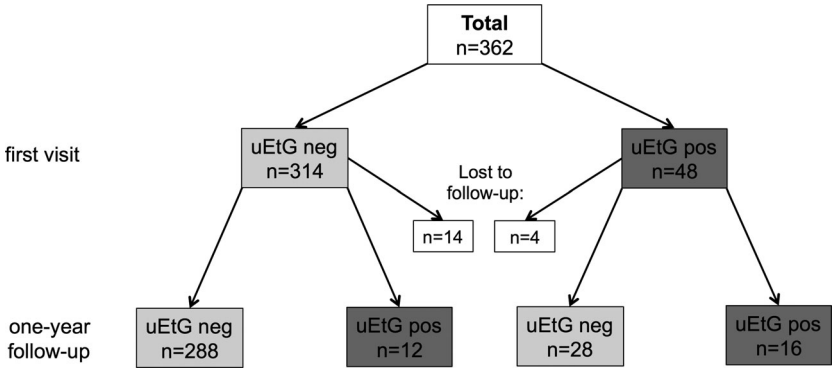

Figure 5 Distribution of patients with negative or positive urinary ethyl glucuronide (uEtG), respectively, at first visit and at one-year follow-up. neg, negative; pos, positive.

The time point prevalence of 13% for positive uEtG – and thus for probable alcohol consumption – in our study is lower than in the average German population, where heavy episodic drinking alone is reported for 34% of the population [25]. In the literature, for ALD patients, return to alcohol consumption after liver transplantation (detected mainly based on patient interviews [3,26]) is reported in about 22–26% of the cases. In our study, time point prevalence for positive uEtG was 20% in ALD patients, which lines up with the literature. Even though one positive uEtG result does not necessarily mean the consumption of higher amounts of alcohol on a regular basis, positive uEtG should always result in further inquiry about alcohol consumption and possible relapse in patients transplanted for ALD, as ALD patients should strictly adhere to alcohol abstinence after liver transplantation [23].

However, approximately two thirds of the patients with positive uEtG in our study had non-ALD primary diseases. Thus, ALD patients are not the sole risk group for alcohol consumption or possible abuse after liver transplantation as a few studies have already pointed out [6–8]. Yet, the interpretation of uEtG results in non-ALD patients is more difficult, as alcohol consumption does not necessarily mean alcohol abuse or alcohol dependence in these patients.

Prior studies have identified various parameters that are heterogeneously correlated with alcohol abuse after liver transplantation, such as tobacco smoking [2,26], social status/support [2,26], time since transplantation [2], age [5], and psychiatric comorbidity [26]. In our study, there was no significant difference for most of these factors between the uEtG negative and the uEtG positive group. Instead, factors such as male sex, BMI, and time since transplantation stood out. In order to evaluate the association of different factors with uEtG more independently, we additionally calculated a multivariable model to predict uEtG ($P < 0.001$, $R^2 = 0.315$), which yielded statistically significant results for sex ($P = 0.019$), ciclosporin ($P = 0.023$), MCV ($P = 0.031$), gGT ($P = 0.025$), steatosis ($P = 0.000$) and patient history ($P = 0.000$). Putting the results of this model into perspective, the relatively small number of uEtG positive patients has to be taken into account as a limiting factor.

Besides the great heterogeneity in different studies' results, no single parameter could be identified in our analysis or in other studies that sufficiently identifies patients at risk for alcohol abuse, with the best single parameter still being the patient interview.

This is why we developed a simple risk score to identify patients who qualify for uEtG testing and who should be addressed on the topic of alcohol consumption. Our uEtG risk score has a specificity and a negative predictive value of 0.95 each and it shows a considerably higher area under the ROC curve than any single parameter by itself. For validation, we applied the risk score to our one-year follow-up cohort obtaining similar results. Thus, patients with a negative uEtG risk score have a very high probability of proving negative for uEtG as well. Accordingly, uEtG testing is not recommended to be performed routinely in these patients. Consequently, our score can help substantially in narrowing numbers of uEtG testing down. Furthermore, it is easy to apply and, thus, could prove very useful in everyday clinical settings.

It must be emphasized again that alcohol consumption is not to be equated with alcohol abuse or alcohol dependence. Unlike in the case of patients with ALD, there is no general recommendation for strict alcohol abstinence after liver transplantation for non-ALD patients [23]. Transplant centers may thus give different instructions regarding the consumption of small amounts of alcohol. As a consequence, uEtG as well as the proposed risk score can only identify patients who are at risk. They require further interpretation on a case by case basis. In case of positive uEtG, the patient should be informed about the laboratory result and

drinking habits should be assessed more thoroughly in order to ascertain the need for intervention. In case the suspicion is confirmed, help should be offered to the patient including referral to specialist care for addiction medicine providing, among others, cognitive behavioural and motivational enhancement treatment [27].

Our follow-up data provides preliminary evidence for the success of addressing the issue of alcohol consumption in conversation with the patient. Over half of the patients who presented with positive uEtG at first visit had a negative uEtG result after one year of follow-up. Furthermore, only 12 patients had a 'newly positive' uEtG, leaving the time point prevalence of positive uEtG at one-year follow-up at 8% as compared with 13% at first visit.

Keeping uEtG's short-term detectability of 3–5 days in mind, patients might deliberately abstain from alcohol consumption only in the days prior to their visits. This, on the one hand, might help differentiate between mere consumption and actual dependence [28], especially when considered in combination with the absolute level of the initial uEtG value. Furthermore, looking at the absolute uEtG level can also help to differentiate between alcohol consumption and the accidental ingestion of alcohol through food or medication (i.e. sauces, cough drops and the like). On the other hand, additional EtG testing in hair (hEtG), where EtG accumulates over time [15], should be considered when abuse is still suspected after repeated negative uEtG testings. A cost-effective alternative to hEtG could be the testing for phosphatidylethanol (PEth), which is another direct marker for alcohol consumption besides EtG. Like the determination of EtG, this marker is also recommended in the recently updated German treatment guideline for harmful or dependent alcohol consumption [29], although it is not yet routinely used nationwide. PEth is measured in EDTA blood; recently, detection in saliva has also become possible. The advantage of PEth over EtG is the longer half-life, which enables detection over a period of up to 3 weeks [27,30].

As for graft and patient outcome, the fact that the uEtG-positive group tended to have higher transaminases and displayed significantly more graft steatosis can be interpreted as a first indicator of a possible worse outcome in this group of patients. However, further studies focusing specifically on outcome in association with positive uEtG are needed.

In conclusion, alcohol consumption after liver transplantation is a common phenomenon in patients with ALD as well as in patients with non-ALD primary liver diseases. Screening tools need to be applied in order to identify those patients at risk for alcohol abuse to enable timely intervention. Further research will be necessary for the prospective evaluation of the proposed risk score and for the assessment of possible implications of uEtG results on graft and patient outcome.

Authorship

JMG, CRW and CPB: designed this study. JMG, AKo, AS, CH, SMB, TK, MH and CPB: involved in data acquisition and analysis. JMG, AKo, CH, TK, AKö, AB, NPM, SN and CPB: analyzed and interpreted data. JMG and CPB: wrote the initial draft of the manuscript, which was revisited for important intellectual content by AS, CH, SMB, TK, CRW, MH, Akö, AB, NPB and SN. All authors approved of the final version of the manuscript.

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Conflicts of interest

The authors declare no conflicts of interest in association with this study.

Ethics approval and patient consent

For this retrospective chart analysis, the institutional review board gave its approval (project number 259/2018BO2) and waived the need for patient consent. The study was conducted in accordance with the Declaration of Helsinki.

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