Role of Alcohol and Drug Detection by Regular Urine Sample Testing in pre-transplant evaluation for Alcohol Liver Disease

Papel de la detección regular de sustancias en orina en pacientes en valoración pre-transplante hepático por hepatopatía alcohólica

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Abstract

Alcohol Liver Disease (ALD) is one of the most prevalent conditions leading to liver transplantation for end-stage liver disease. There is lacking evidence of regular urine screening testing (RUST) impact on survival or liver transplantation of ALD patients. The aims of this study were to compare the sensitivity of RUST, to assess its impact on survival and liver transplantation, and to evaluate factors associated with adherence to RUST. We performed a single-centered retrospective study (N = 84) with ALD candidates for liver transplantation. Demographic, biochemical and clinical variables were recorded at baseline. Adherence to RUST was evaluated during follow-up. The sensitivity of both RUST and self-reports were calculated for all drugs. Multivariable logistic and survival regression analyses were performed to explore associated factors and the impact of adherence to RUST, and positive results on survival. RUST had high sensitivity for identifying active drinkers (76.9%), smokers (78.9%) and cannabis users (83.3%). High adherence to RUST was inversely associated with mortality during follow-up. Presence of personality disorders negatively impacted (OR 0.29, CI 95% 0.08-0.97) adherence to RUST. Both RUST and self-reports should be carried out in this setting. Professionals involved in liver transplantation programs must promote adherence to RUST, primarily in patients with personality disorders.

Keywords: Alcohol; Liver transplantation; Alcohol liver disease; Adherence; Alcohol dependence; Drug dependence.

Resumen

La enfermedad hepática alcohólica (EHA) es una de las causas más frecuentes de trasplante hepático en enfermedad hepática terminal. No hay evidencia de impacto de la detección regular de sustancias en orina (DRSO) sobre la supervivencia de los pacientes con EHA. Los objetivos de este estudio fueron comparar la sensibilidad de la DRSO, evaluar su impacto en la supervivencia y en el trasplante de hígado, y evaluar el impacto de la adherencia a la DRSO. Realizamos un estudio retrospectivo (N = 84) con candidatos para trasplante de hígado por EHA. Registramos las variables demográficas, bioquímicas y clínicas al inicio del estudio. Evaluamos la adherencia a la DRSO durante el seguimiento. Calculamos la sensibilidad tanto de la DRSO como de las declaraciones de los pacientes para todas las sustancias. Realizamos análisis multivariables (regresión logística) y de supervivencia para explorar los factores asociados y el impacto de la adherencia a la DRSO, y de los resultados positivos en la DRSO sobre la supervivencia. La DRSO tuvo una alta sensibilidad para identificar bebedores activos (76,9%), fumadores (78,9%) y consumidores de cannabis (83,3%). Alta adherencia a la DRSO tuvo una asociación inversa con mortalidad durante el seguimiento. La presencia de trastornos de la personalidad tuvo un impacto negativo (RM ,29, IC 95% ,08-,97) sobre la adherencia a la DRSO. Tanto la DRSO como las declaraciones deben llevarse a cabo en este perfil de pacientes. Los profesionales que participan en programas de trasplante hepático deben promover el cumplimiento de la DRSO, principalmente en pacientes con trastornos de la personalidad.

Palabras clave: Alcohol; Trasplante hepático; Enfermedad hepática terminal; Adherencia; Dependencia del alcohol; Dependencia a sustancias.

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Alcohol liver disease (ALD) is a leading cause of liver-related morbidity and mortality worldwide (Rehm, Gmel, Sierra & Gual, 2018) and a major cause of end-stage liver disease (ESLD) and death among adults with prolonged alcohol abuse (Mathurin & Bataller, 2015). Liver transplantation (LT) is a well-established treatment for ESLD caused by ALD (Dawwas, Gimson, Lewsey, Copley & van der Meulen, 2007). Survival after a liver transplantation in patients with ALD is similar to that in patients with other ESLD etiologies (Burra et al., 2010).

Prevalence of drug or alcohol metabolites in patients with ALD candidates for Liver Transplantation is high (Carbonneau et al., 2010; Erim et al., 2007; Webzell et al., 2011). Most liver transplantation programs require 6-month alcohol abstinence and 12-month drug abstinence for listing patients (Beresford & Everson, 2000; Lligoña, Freixa, Bataller, Monràs & Rimola, 2009). However, some exceptions are considered (e.g. cannabis or tobacco) (Lligoña et al., 2009). However, there is no international consensus.

In our program, assessment of patients with ALD for liver transplantation includes psychiatric and psychological interviews, in order to identify the presence of psychiatric illnesses, which may preclude transplantation. The use of alcohol and other drugs is also evaluated in these interviews as part of the standard protocols. Detection of alcohol and other drugs on regular urine sample tests (RUST) at least once per week, is recommended in the follow-up of these patients (Lligoña et al., 2009). However, there is mixed evidence about RUST for monitoring alcohol dependant patients (e.g. short half-life) (Barrio et al., 2016; Niemelä, 2016) and limited evidence in candidates for ALD liver transplantation (Allen, Wurst, Thon & Litten, 2013; Carbonneau et al., 2010; Piano et al., 2014; Staufer & Yegles, 2016; Webzell et al., 2011). Further, the majority of these studies were conducted under research protocols, in which adherence might have been overestimated by Hawthorne effect and consequently the validity of RUST. In addition, self-reports are considered a valid strategy to assess alcohol and drug use in many conditions, even in clinical trials (CDER, 2015; EMA, 2010). Further, self-reports of alcohol and drug use is a cost-effective strategy. However, candidates for liver transplantation are considered a special population since they can underestimate alcohol use if they believe their current intake may delay or contraindicate transplantation (Allen et al., 2013).

On the other hand, treatment adherence predicts a good outcome in several conditions, including alcohol use disorders (Oslin, Pettinati & Volpicelli, 2002) and ALD (Rustad, Stern, Prabhakar & Musselman, 2015; Telles-Correia, Barbosa, Mega & Monteiro, 2009). However, there is a lack of studies about the impact of adherence to RUST or its positive results on prognosis for ALD patients.

The aims of this study, focused on patients assessed for liver transplantation, were: 1) to compare the sensitivity of self-reports and RUST for detecting alcohol /drugs use; 2) to assess the impact of adherence to RUST and its positive results on liver transplantation and survival; and 3) to explore baselines factors associated with high adherence to RUST.

Material and Methods

Study design

Observational single-centered retrospective (post-hoc) study.

Participants

All patients with ALD over 17 years old, consecutively evaluated in the pre-transplant (accepted or not for waiting list to liver transplantation) Liver Outpatient Service between January 2008 and January 2014 were recruited.

Exclusion criteria: those patients who did not provide RUST within our addiction unit and did it elsewhere because geographical restrictions

Setting

The current evaluation protocol for liver transplantation in patients with ALD at Hospital Clinic Barcelona requires an exhaustive assessment by a psychiatrist and a psychologist, and RUST for most common drugs of abuse (alcohol, benzodiazepines, nicotine, cocaine, opiates and cannabis) at least once per week (Lligoña et al., 2009). Frequency of RUST was decided according to clinical criteria of the treating psychiatrist, who considered the primary and secondary drugs used and the individual capacity to attend RUST (physical, geographical, work or family restrictions). The psychiatrist usually prescribed RUST twice per week according to common clinical practice, difficulties to attend consultation and resources' availability in our outpatient clinics. Twice per week is enough to identify drug relapse because of the long half-life of most drugs and regular alcohol use, but it is likely insufficient for the detection of occasional alcohol intake. However, this was the real practice in our environment between 2008 and 2014 and before the generalization of ethyl-glucuronide in urine samples for detection of alcohol intake, which took place in our hospital in October 2016.

Recruitment started in January 2008, once the ethics committee of the HCB approved the current protocol for liver transplantation of patients with ALD. Our data refers to the first six year of protocol implementation. Follow-up start-point was first appointment with psychiatrist and end-point was: death or until October 2015.

Data collection was done prospectively during assessment for the liver transplantation with the exception of MELD (Model for End-stage Liver Disease), adherence

to RUST and follow-up, survival and performance of liver transplantation, which were collected during last trimester of 2015.

Variables

During the psychiatric interview, the following data were systematically and prospectively recorded:

1) Socio-demographic data: age (at the first urine sample test day) and gender
2) Psychiatric and clinical data:
   - Current and History of psychiatric illness, according to DSM-IVTR criteria based on clinical diagnosis of the psychiatrist in charge: including Affective Disorders (Depression, Dysthymia, Bipolar Disorder), Psychotic Disorders (Schizophrenia, Schizoaffective disorder and other related disorders) and Anxiety Disorders (Obsessive Compulsive Disorder, Panic Disorder, Generalized Anxiety Disorder, Posttraumatic Stress Disorder, Phobia). Personality Disorders was clustered according to three categories based on DSM IV-TR classification: A (Paranoid, Schizoid, and Schizotypal Personality Disorders), B Borderline, Narcissistic, Histrionic and Antisocial Personality Disorder) and C (Avoidant, Dependent and Obsessive-Compulsive Personality Disorder)
   - Life-time and current alcohol use pattern: using a frequency and quantity questionnaire called Systematic Interview of Alcohol Consumption (SIAC) (Gual, Contel, Segura, Ribas & Colom, 2001) The SIAC sensitivities are 70-81% for men and 46-100% for women. The SIAC specificities are 82-99% and 97-100%, respectively.
   - Life-time and current drug use.
   - The High-Risk Alcohol Relapse (HRAR) score: HRAR is a 3-item scale that evaluates total alcohol consumption per day, years of heavy alcohol use and the previous treatments for alcohol misuse. This system scores 0-2 each evaluated item (maximum total score 6), stratifying patients into 2 alcoholism relapse risk categories (high risk (<4) or low risk (≥4). HRAR score higher than 3 is a risk factor for relapsing in alcohol use after liver transplantation (OR, 10.7; 95% CI, 3.8-30.0) (De Gottardi et al., 2007; DiMartini et al., 2000).

At the end of the study, the following information was retrospectively collected from clinical records:

1) Number of programmed urine samples.
2) Number of accomplished urine samples.
3) Follow-up in the Addictions and/or Hepatology Unit.
4) Performance of liver transplantation.
5) Survival status (Dead/Alive): For the purpose of the study, the combined endpoint of alive at last follow-up or liver transplantation was the main variable used for survival analysis.
6) Adherence to RUST: Adherence was calculated as follows: (number of urine samples performed/number of programmed urine samples) x 100. We stratified adherence in 3 categories: low adherence (<25%), intermediate adherence (25-75%) and high adherence (≥75%). For inferential analysis two categories were considered: high adherence (≥75%) versus non-high adherence (<75%)
7) Model for End-stage Liver Disease (MELD) at the moment of first urine sample testing (Malinchoc et al., 2000).

The following metabolites were analyzed using the Hospital Clinic laboratory-established cut-offs and window of detection:

1) Alcohol: ethanol (cut-off: 100 ng/mL; window of detection ≤12h)
2) Tobacco: cotinine (cut-off: 100 ng/mL; window of detection: 3 days)
3) Opiates: morphine (cut-off: 300 ng/mL; window of detection: 3 days)
4) Cocaine: benzoilecgonine (cut-off: 300 ng/mL; window of detection: 3 days)
5) Benzodiazepines: diazepam (cut-off: 200 ng/mL; window of detection: 10 days-5 weeks)
6) Cannabis: 11-nor-d9-THC (cut-off: 50 ng/mL; window of detection: 5 days-5 weeks)

Statistical Analysis

Descriptive analysis of the sample was carried out. Continuous variables were described as mean (standard deviation). Categorical variables were described by counts and percentages. Comparisons between groups were performed using Student's *t* test, analysis of variance (ANOVA) or Mann-Whitney's *U* test, depending on variable distribution. Differences between categorical variables were assessed by the Chi-squared test or Fisher's exact test, when appropriate. A p-value <.05 was considered significant.

The sensitivity and area under the curve were individually calculated for self-reports and RUST taking both methods (self-reports and RUST) together as the gold standard (objective 1). We chose this gold standard because the combined outcome was the way to identify the largest number of active users considering the previous experiences in research protocols, in which both outcomes separately showed low sensitivity. To investigate variables with prognostic information for the combined end-point (alive/liver transplantation) during patient follow-up (objective 2), Cox regression univariate and multivariable analyses were fitted, entering variables at initial evaluation and during follow-up. The results of the multivariable Cox regression analysis (hazard ratio –HR-) were considered to be the main outcome. In order to evaluate the influence of adherence to RUST in patient survival during follow-up (objective 2), a comparative risk analysis using the Kaplan-Meier

method compared by the log-rank test was performed. To investigate variables associated with a high adherence to RUST (objective 3), those variables with a p<.10, and those that were considered clinically relevant in the univariate analysis were entered into a *backward stepwise* elimination variable selection procedure (multivariable logistic regression). The p-values for the univariate tests were not corrected for multiple testing, because those tests were taken as exploratory. The SPSS statistical package (SPSS Inc., version 15.0, Chicago, IL.) was used for all analyses.

Ethical Issues

This study was approved by the ethical committee of Hospital Clínic de Barcelona, (HCB/2015/0845) according to the Helsinki declaration and Spanish national laws. Informed consent was not required due to the retrospective design (using only routine clinical information) and after guaranteed absolutely anonymity of the participants.

Results

Patient Characteristics

The final sample included 84 patients with 88.1% male and a mean age of 53.7 (SD 6.2) years. 67.9% (n=57) were alive and 34.5% (n=29) were transplanted at the end of the study. The mean MELD at first urine sample test was 14.2 (SD 5.6). Overall mean follow-up was 15.9 (SD 11.4) months. Clinical characteristics are widely described in Table 1.

Mental illness was present in 29.8% patients, being cluster B personality disorder the most frequent diagnosis (n=9; 10.7%). Other diagnoses were depression disorder (n=6; 7.1%), anxiety disorder (n=4; 4.8%), cluster A personality disorder (n=3; 3.6%) and cluster C personality disorder (n=3; 3.6%).

Table 1. *Socio-demographic and clinical characteristics of evaluated patients in the pre-transplant assessment for Alcohol Liver Disease Liver Transplantation.*

		n (%)
Gender (male)		74 (88.1)
Age (mean, SD)		53.7 (6.2)
Baseline MELD (mean, SD)		14.2 (5.6).
Mental illness (history or current)		25 (29.8)
SDU[a]/day	<= 9	40 (47.6)
	9-17	36 (42.9)
	>17	8 (9.5)
Years with heavy use	<= 11	26 (31)
	11-25	40 (47.6)
	>25	18 (21.4)
Previous treatment for alcohol use disorder	0	65 (77.4)
	1	13 (15.5)
	>1	6 (7.1)
HRAR[b]	Low risk (<4)	74 (88.1)
	High risk (=>4)	10 (11.9)
Death		27 (32.1)
Follow-up in Addictions service		13 (15.5)
Follow-up in Hepatology service		56 (66.7)
Lifetime Alcohol use		84 (100)
Lifetime Benzodizepine use		10 (11.9)
Lifetime Cannabis use		28 (33.3)
Lifetime Cocaine use		12 (14.3)
Lifetime Tobacco use		39 (46.4)
Lifetime Opiod use		11 (13.1)

Note. [a]SDU: standard drink units (10 gram of pure alcohol); [b]HRAR: High Risk Alcohol Relapse.

Objective 1. Compare sensitivity of Self-reports and RUST for Alcohol and Drugs Use Detection (Combined Gold Standard)

The sensitivity and area under the curve using urine samples + self-reports as a gold standard is shown in Table 3. In the case of alcohol, cannabis and tobacco, sensitivity is better for RUST than self-reports, being worse for benzodiazepines and cocaine.

Objective 2. Impact of RUST (adherence and results) concerning both Liver Transplantation and Mortality

Adherence/At least one positive in RUST and Liver Transplantation. We studied those variables potentially associated with liver transplantation (n=29) in the included patients. Adherence (high adherence n=19, 37.3% versus non-high adherence n=10, 30.3%; p=.531) was not associated with liver transplantation. Neither at least one positive result for alcohol (30% versus 35.1%; p=.749), at least one positive result for nicotine (23.3% versus 40.7%; p=.108) or at least one positive result for other drugs (38.1% versus 33.3%; p=.89) were associated to liver transplantation outcome. Table 4 shows exclusion reasons for liver transplantation.

Adherence/At least one positive in RUST and Mortality. Finally, we studied those variables associated with mortality during follow-up of the included patients. Mean adherence was similar among those who received liver transplantation or were alive at the end of the study and those who died (74.5% versus 64.6%; p=.08) but it was less likely to be classified as high adherent if the outcome was the death (71.9% versus 37%, p=.02). Excluding those who received liver transplantation (target population=55), at the end of the study 26.1% (n=6) of low adherent were alive and 73.3% (n=22) of high adherent were (p=.003). The univari-

Table 2. *Adherence and positive results in urine sample test in evaluated patients in the pre-transplant assessment for Alcohol Liver Disease Liver Transplantation.*

		All sample (n=84) n (%)	**Psychiatric** (n=25) n (%)	**Non-psychiatric sample** (n=59) n (%)
Adherence to urine sample test	Low (‹= 25%)	5 (6)	3 (12)	2 (3.4)
	Intermediate (26-75%)	27 (32.1)	10 (40)	17 (28.8)
	High (›= 75%)	52(61.9)	12 (48)	40 (67.8)
Mean adherence of RUST (mean, SD)		35 (30.1)	37.5 (35.8)	33.9 (27.6)
				n (%)
Number of patients with at least one urine sample positive for alcohol				10 (11.9)
Number of patients with at least one urine sample positive for benzodiazepine				8 (9.5)
Number of patients with at least one urine sample positive for cannabis				15 (17.9)
Number of patients with at least one urine sample positive for cotinine				30 (35.7)
Number of patients who self-report current alcohol use				6 (7.1)
Number of patients who self-report current benzodiazepine use				12 (14.3)
Number of patients who self-report current cannabis use				12 (14.3)
Number of patients who self-report current cocaine use				2 (2.4)
Number of patients who self-report current cotinine use				23 (27.4)

Note. [a] There were no cases of positive for opioid or cocaine in RUTS, or for opioid in self-reporting.

Table 3. *Psychometric characteristics of self-reporting or RUST (gold standard RUST+self-reports) in evaluated patients in the pre-transplant assessment for Alcohol Liver Disease Liver Transplantation.*

	Self-reporting	**Regular Urine Sample Test**	**Differences (Regular Urine Sample Test -self-reporting)**
Alcohol users (n=13, 15.5%)[c]			
Sensitivity (%)	46.2	76.9	30.7
[a]AUC	0.73 (CI95% 0.549-0.913)	0.89(CI95% 0.00-1.00)	0.16
Benzodiazepines users (n=17, 20.2%)[c]			
Sensitivity (%)	70.6	47.1	- 23.5
[a]AUC	0.85 (CI95% 0.72-0.99)	0.74 (CI95% 0.58-0.90)	-0.11
Cannabis users (n=18, 21.7%)[c]			
Sensitivity (%)	66.7	83.3	16.6
AUC	0.83 (CI95% 0.70-1.00)	0.92 (CI95% 0.00-1.00)	0.09
Cocaine users (n=2, 2.4%)[c]			
Sensitivity (%)	100	0	-100
[a]AUC	1.00 (CI95% 1.00-1.00)	0.5 (CI95% 0.09-0.91)	-0.5
Tobacco users (n=38, 45.2%)[c]			
Sensitivity (%)	60.5	78.9	18.9
[a]AUC	0.80 (CI95% 0.70-0.91)	0.90 (CI95% 0.82-0.97)	0.10

Note. [a]AUC: Area Under Curve; [b]CI: Confidence Interval. [c]According to combined gold standard (RUST+self-reports)

ate Cox regression identified high adherence to RUST and the HRAR score positively associated with mortality during follow-up. To further analyze the independent value of variables predicting mortality, statistically significant and clinically relevant variables were entered in a final multivariable model. We found that low adherence to RUST (HR 0.44; *p=.04*), HRAR score >3 points (HR 2.95; *p=.02*) and MELD score (HR 1.08; *p=.03*) were independently associated with mortality during follow-up. From 51 patients with high adherence to RUST 22 (43%) were alive (without liver transplantation) at last follow-up (mean follow-up 15 [SD 10] months) and 19 (37.3%) patients were transplanted (mean time to LT: 11 [SD 5] months). Patients with low adherence to RUST showed a higher mortality when compared with patients those with high adherence (17/33 [51.5%] vs. 10/51 [19.6%]; *p=.01*). Finally, high adherence to RUST positively influenced overall survival at last follow-up (Figure 1). The presence of at least one positive result for alcohol, nicotine or other drugs during the follow-up was not associated with mortality (*data not shown*).

Objective 3: Baseline factors that predict adherence to RUST

Overall, mean adherence was 71.3% (SD 24.4). During follow-up, 60.7% (51 out of 84 patients) showed high adherence to RUST, as did 66% of transplanted patients. No differences in length of follow-up were found between patients with high vs. low adherence to RUST (16.9 versus 15.3 months, respectively; *p=.52).* In the univariate analysis the presence of mental illness, personality disorder and HRAR scores were negatively associated with high adherence to RUST (Table 5). Patients affected by personality disorders (PD) were less adherent to RUST than patients without this condition (31% *vs.* 10 %; *p=.02).* When including these variables in the multivariable analysis, only the presence of personality disorder (OR 0.29; *p=.04*) showed a negative and independent association with high adherence to RUST. Of note, the HRAR score did not reach statistical significance when adjusted for other co-factors. Finally, no differences in the length of total follow-up between patients with and without any mental illness or with

Table 4. *Exclusion reasons for liver trasplantation.*

Reason	n (%)
Active drinkers	15 (27.3%)
Non-adherence to RUST*	11 (20%)
Improvement of Liver Disease	9 (16.4%)
Death during assessment	1 (1.8%)

Note. * Regular Urine Sample Testing.

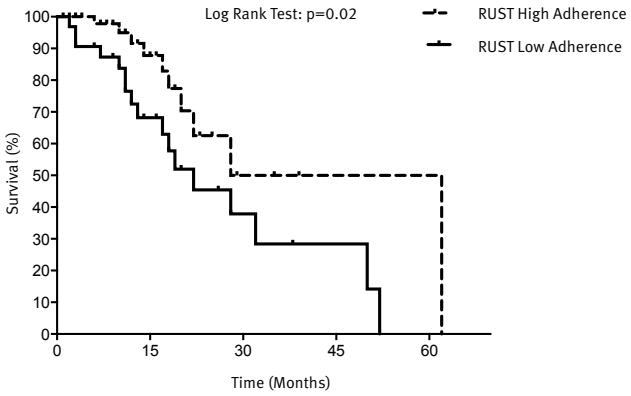

Figure 1. Survival according to RUST adherence during follow-up of patients with ALD.

Table 5. *Univariate and Multivariate Analysis of Factors Associated with High Adherence to RUST in evaluated patients in the pre-transplant assessment for Alcohol Liver Disease Liver Transplantation During Follow-up since enrollment (first appointment with psychiatrist).*

	Univariate analysis			Multivariate analysis		
Variable	**OR**	**95% CI**	**p**	**OR**	**IC 95%**	**p**
Age (years)	1.03	0.96 - 1.11	.5			
Gender (female)	0.38	0.10 - 1.47	.2			
Psychiatric comorbidity, (y/n)	0.37	0.14 - 0.98	*.04*			
Personality disorder (y/n)	0.25	0.08 - 0.82	*.02*	0.29	0.08 -0.97	*.04*
Other drugs of abuse* (y/n)	0.68	0.28 - 1.65	.4			
HRAR score at admission (points)	0.76	0.56 - 1.03	.08	0.81	0.59 -1.11	.2
HRAR score at admission (>3 points)	0.38	0.09-1.47	.16			

and without personality disorder were found (15.7 vs. 16.1. months; p=.8 and 15.8 vs. 16.2 months; p=.9, respectively).

Discussion

Assessment of patients with ALD undergoing liver transplantation is a challenging task for both, hepatologist and psychiatrists. Initial evaluations includes psychiatric and psychological interviews in order to identify psychiatric conditions, which may be a potentially cause of exclusion to the waiting list (Bunzel & Laederach-Hofmann, 2000; Martin, DiMartini, Feng, Brown & Fallon, 2014; Surman, Cosimi & DiMartini, 2009). Although the length of sobriety is a matter of debate for patients with ALD (Di Martino, Sheppard & Vanlemmens, 2012) who are potentially candidates for liver transplantation, a period of abstinence >6 months before liver transplantation is one of the mostly used criteria in the majority of liver transplantation centers and guidelines ("EASL Clinical Practice Guidelines: Liver transplantation.," 2015; Lligoña et al., 2009; Martin et al., 2014). This "6-month rule" has been proposed as necessary to limit relapse into high-risk alcohol consumption that could jeopardize graft integrity (Allen et al., 2013). There is no doubt that a proportion of patients undergoing liver transplantation return to drinking behavior which eventually results in graft loss or death due to lack of compliance of immunosuppressive treatments or direct liver injury caused by alcohol consumption (Cuadrado, Fábrega, Casafont & Pons-Romero, 2005). Therefore, monitoring of abstinence and patient's compliance to protocols in the pre-transplant setting is of paramount importance and a critical step in the evaluation process of patients with ALD undergoing liver transplantation. Use of self-reports is a valid and cost-effective strategy for assessing alcohol consumption and other drug use in many clinical scenarios (EMA, 2010). However, in the liver transplantation setting, self-reports has shown low accuracy to identify active drinkers given the high rate of under-reporting (Allen et al., 2013).

Sensitivity of self-reports and RUST. In our sample, RUST showed better sensitivity to identify active drinkers and active drug users with the exception for benzodiazepines and/or cocaine, but did not identify all active users. Alcohol and benzodiazepines in urine samples were detected in a similar proportion than other samples of ALD liver transplantation candidate (Webzell et al., 2011). In contrast, we were not able to identify any case of opiate consumption when use of these drugs have been reported as high as 20% among ALD patients candidates for liver transplantation in other countries (e.g. United Kingdom). These differences can be explained since patterns of consumption may vary in each country and also technical differences for drug measurement between cohorts (EMCDDA, 2015; Stewart, Koch, Burgess, Willner & Reuben, 2013; Wurst et al., 2003).

The performance of RUST for alcohol allows identifying almost 31% more cases than self-reports but did not achieve to identify all active users (23.1% false-negative in RUST in our study). Self-reports identified less than one out of two current alcohol users. Our results are consistent with other recent studies focused on treatment of alcohol use disorder in liver transplantation candidates (Erim et al., 2016). Using RUST we were able to detect almost eight out of ten alcohol users but we did not identify all alcohol users. Thus, combining both self-reports and RUST is the best strategy, confirming guidelines recommendation ("EASL clinical practical guidelines: management of alcoholic liver disease.," 2012). In addition, underreporting is higher in our population than other sensible populations such as psychiatric inpatients (56%) or pregnant women (0%) (de Beaurepaire et al., 2007; Horrigan, Piazza & Weinstein, 1996). Underreporting of alcohol use means that alcohol use is perceived as contraindication to transplant in the context of high resistance to declare its use. Also, our laboratory analyses are less sensitive than ethyl-glucuronide in urine sample (uEtG) which is potentially more powerful in order to detect any recent alcohol consumption, has excellent validated properties in liver disease patients and is strongly correlated with amount of alcohol intake (Nanau & Neuman, 2015; Wurst et al., 2015). A recent study of our group showed that abstinent patients were 95% in agreement to ethanol in urine sample but they decreased to 60% if we considered uEtG (Barrio et al., 2016). According with a recent study on LT candidates, the most accurate diagnosis of alcohol consumption was found combining short version of Alcohol Use Disorder Identification Test (AUDIT-C) and uEtG (ROC curve 0.98) (Piano et al., 2014).

Underreporting of tobacco use is explained by a general patient's defensive attitude in front of drug assessment during liver transplantation evaluation (Allen et al., 2013). Underreporting of cannabis is equivalent to a recent meta-analysis (19 studies) which reported sensitivity of 0.60 for cannabis self-reports using biological measures as a gold standard in different populations (Hjorthøj, Hjorthøj & Nordentoft, 2012). Two relevant points must be considered in order to explain no positives for cocaine in our sample: small sample with only two positives for self-reports and technical considerations (short-time of metabolites -48 to 96h- presence in urine sample) (Moeller, Lee & Kissack, 2008). Higher sensitivity of self-reporting compared with RUST for benzodiazepine use means that benzodiazepine use is not perceived as contraindication to transplant. In addition, there is technical limitations on detecting different active compounds in urine samples because poor cross-reactivity with conjugated metabolites and non-diazepam benzodiazepine (Melanson, Ptolemy & Wasan, 2013).
Impact of RUST (adherence/positive results) on survival. Previous data has showed that low adherence to pre- liver

transplantation treatments and evaluations is a robust predictor of high-risk alcohol relapse after LT (Egawa et al., 2014; Sansone, Bohinc & Wiederman, 2015). In our study, we found that high-adherence to RUST during the evaluation for liver transplantation, correlates patient survival after adjusting for well-established outcome predictors in patients with ALD undergoing evaluation for liver transplantation (e.g. MELD). This relationship was also independent to liver transplantation among those with high adherence or persistent negatives in RUST. In addition, the presence of at least one positive result for alcohol, nicotine or other drugs during the follow-up did not increase mortality. 66% of transplanted patients showed high-adherence to RUST accounting as good outcome according to our composite end-point alive/ liver transplantation. Therefore, the assessment of this dynamic parameter during the evaluation period of patients with ALD undergoing liver transplantation may provide additional prognostic information that could be taken into account as part of compliance assessment. Future research on this area is needed to confirm our data. Surprisingly, 30.3% of non-adherent patients and 35.1% of alcohol positive patients in RUST received liver transplantation. Non-adherent patients could be considered valid transplant candidates because the team took into account other characteristics as a priority. One positive for alcohol does not imply that the patient drunk during all the pre-transplant assessment and relapses could be managed by healthcare professionals during evaluation.

Factors associated with adherence to RUST. When evaluating the potential factors associated with adherence to RUST during the patient's follow-up, we found that patients affected by personality disorders were less adherent to RUST than patients without this condition (31% *vs.* 10 %; *p=.02*). When adjusted for other co-factors, the presence of personality disorders negatively influenced the development of high adherence to RUST in our cohort (OR 0.29; p=.04). This is not surprising given that patients with personality disorders in general have lower compliance to general health care (Sansone et al., 2015), drug treatment (Peles, Schreiber, Domany & Adelson, 2014) or psychotherapy (Jensen, Mortensen & Lotz, 2014). In addition, personality disorder is a frequent comorbidity of alcohol use disorders (Sánchez Autet et al., 2018). Up to our knowledge, this is the first study, which found that patients with personality disorders have lower compliance to the different approaches followed in the liver pre-transplant evaluations. It does not mean that personality disorder contraindicates transplantation but it is a vulnerable population, which should have a specific approach. Other studies have failed to demonstrate any relationship among personality disorders and poor prognosis after liver transplantation in ALD (Askgaard et al., 2016; Dom et al., 2015). Psychological and pharmacological (Addolorato et al., 2007; Erim et al., 2016) support are the focus of research in the management of ALD liver transplantation candidates. However, there are no studies based on improving the compliance. Motivational Interviewing and patient-centered care increased compliance in other health problems as medication compliance for hypertension (Conn, Ruppar, Chase, Enriquez & Cooper, 2015) or VIH (Hill & Kavookjian, 2012), alcohol use disorders (Bradley & Kivlahan, 2014), or follow-up of diabetic patients (Page et al., 2015), these approaches probably deserve to be tested in patients with personality disorders candidates for liver transplantation.

Limitations and Strengths. It is relevant to acknowledge that our study has several limitations. Given its retrospective nature, a record bias can exist. However, in our institution, the assessment for liver transplantation candidates has a well-established protocol following the international parameters and multidisciplinary evaluations with strict rules that might minimize the risk for this record bias. Detection of alcohol in urine samples instead of ethyl-glucuronide is also a limitation, but it was the real practice before generalization of ethyl-glucuronide in our setting. False-negatives probably exist despite the combined gold standard (self-reports/RUST) and they might explain a potential underestimation of impact of positive RUST results on survival and liver transplantation. Finally, our small sample size precludes us to give more robust and powered information. As we previously mentioned, this is a single-centered study in which due to geographical restrictions of the local health system only those patients providing regular urine sample testing within our addiction unit were included. However, our study has many strengths. To our knowledge this is the first study exploring the additive accuracy for alcohol consumption detection using both, self-reports and RUST approaches in candidates for liver transplantation. We analyzed and provide information about the detection the most frequently used drugs in Western Europe among patients with ALD undergoing evaluation for liver transplantation. Mean adherence to RUST was low (62%), which make more difficult to interpret validity of RUST. While other studies are based on research protocol, in which adherence is stimulated by Hawthorne effect, our study has a naturalistic approach, which allows examining RUST validity in real world practice. In these sense, our sample had high prevalence of psychiatric disorders (30%) being likely more representative of real practice than prospective studies with strict exclusion criteria or did not report psychiatric diagnosis. Finally, even when the impact of personality disorder and adherence to RUST and survival respectively are preliminary results, this is the first time that a study shows this relationship.

Conclusion

Both self-reports and RUST are required in patients assessed for liver transplantation. It seems that, except for cocaine and benzodiazepines, self-reports are less sensitive. Patients with good adherence to RUST have better outcomes compared with those with low adherence. Patients affected by personality disorders require further efforts in order to improve their adherence.

Contributors

The first (HLP), second (JA), third (EL) and sixth (AL) author have contributed in the conception, design, gathering and interpretation of data. All authors have contributed in the analysis, interpretation of data. All authors have contributed in the writing and intellectual content of the article. All authors have read and approved the manuscript for submission to the journal.

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Annex. Abbreviations

ALD, Alcohol Liver Disease
CI, Confidence Interval
DSM IV-TR, Diagnostic and Statistical Manual of Mental Disorders
HR, Hazard Ratio
HRAR, High Risk Alcoholism Relapse
MELD, Model for End-stage Liver Disease
OR, Odd Ratio
RUST, Regular Urine Sample Test
SDU, Standard Drink Unit
UETG, ethyl-glucuronide in urine sample