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REVIEW

Liver transplant for alcoholic hepatitis: a current clinical overview

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ABSTRACT

Introduction: Current management of severe alcoholic hepatitis is based on corticosteroid therapy and abstinence from alcohol. As liver transplantation is lifesaving in alcoholic hepatitis patients at high risk of early death, refractory alcoholic hepatitis has become a new indication for liver transplantation in highly selected non-responders to corticosteroids.

Areas covered: This review summarizes the conditions under which liver transplantation may be considered, the available data on liver transplantation for refractory alcoholic hepatitis and explores the ethical considerations surrounding the use of liver transplantation in these patients.

Expert opinion: Selection of candidates should be made according to available scientific results on post-liver transplantation outcomes and the risk of alcohol relapse. Currently, a strict selection process based on a good psychosocial profile, including social stability, no previous treatments for alcohol dependence, no current drug use, and no co-existing severe mental disorder, seems to be the best way to manage these issues. Well-defined selection criteria for candidate selection and accurate tools to predict alcohol relapse after liver transplantation are still needed.

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Abstinence; alcoholic hepatitis; alcohol relapse; liver transplantation; prognosis

1. Introduction

Alcoholic hepatitis (AH) is a clinical syndrome corresponding to clinical, biological, and histological criteria. Clinically, it is characterized by recent onset of jaundice, with or without other signs of liver decompensation (*i.e.* ascites and/or encephalopathy), in patients with alcohol misuse disorder [1]. Laboratory findings include hyperbilirubinemia (>3 mg/dL), serum levels of AST >50 IU/mL, although rarely above 300 IU/mL, and an AST/ALT ratio greater than 1.5 [2]. Histologically, the presence of steatosis, hepatocyte ballooning, and an inflammatory infiltrate with polymorphonuclear neutrophils are the criteria required for the diagnosis of AH [1]. In its severe form, AH is characterized with mortality rates as high as 50% at 3 months without treatment [3–6] and is the form of alcoholic liver disease that carries the poorest prognosis [3–5].

In this review, we discuss the current management of AH and the conditions under which liver transplantation may be considered, the current available data on liver transplantation for AH, and the ethical considerations surrounding the use of liver transplantation in AH patients.

2. Current management of AH and conditions under which liver transplantation may be considered

2.1. Evaluation of disease severity and selection of patients for therapy

Several prognostic scores have been developed that aim to identify patients at high risk of early death. The Maddrey discriminant function (DF), initially developed in 1978 [6] and then modified in 1989 (mDF) [7], is still the most widely used score in clinical practice and in clinical trials. An mDF greater than or equal to 32 defines patients with severe AH and is the cutoff required for indicating AH-specific therapy. In the absence of specific treatment, 1-month mortality of patients with an mDF score ≥32 was reported to be 50% in early studies but this decreased to 17% in later trials [8,9]. More recently, prognostic scores such as the model for end-stage liver disease (MELD), the Glasgow alcoholic hepatitis score (GAHS), and the age, serum bilirubin, INR, and serum creatinine (ABIC) score, have been developed in the setting of AH [10–12]. These scores appear to have similar performance with regard to predicting short-term survival [13]. The GAHS, which includes age, white cell count, urea, INR, and bilirubin, can also identify patients who may benefit from corticosteroids. The GAHS ranges from 5 to 12 and patients with an mDF ≥32 and a GAHS ≥9 have 84-day survival rates of 59% and 38% with and without corticosteroid treatment, respectively [12].

2.2. Current therapy for patients with severe AH

Corticosteroids given orally (40 mg prednisone for a maximum of 28 days) have been recommended for the last decade as a treatment for severe forms of AH. In a recent meta-analysis with individual participant data, patients treated with corticosteroids had a lower probability of death at 1 month compared to untreated patients [14]. However, the benefit of corticosteroids was more limited in the largest randomized controlled

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Article highlights

- Current management of severe AH is based on corticosteroid therapy and abstinence from alcohol.
- A number of studies have provided evidence that liver transplantation is lifesaving in AH patients at high risk of early death.
- Refractory AH has become a new indication for liver transplantation in highly selected non-responders to corticosteroids.
- Equity should be respected in the setting of AH as in other conditions in which liver transplantation is discussed.
- Selection of candidates should be made according to available scientific results on post-liver transplantation outcomes and the risk of alcohol relapse. Currently, a strict selection process, similar to the one used in the French-Belgian landmark study, seems to be the best way to manage these issues.
- Well-defined selection criteria for candidate selection and accurate tools to predict alcohol relapse after liver transplantation are still needed. These will contribute to ensuring the perpetuation of the liver transplantation program for highly-selected patients with refractory AH from the perspective of both healthcare providers and the public.

trial to date in the field of AH [9]. In this study, a survival benefit of less than 10% was observed at 1 month and this benefit was not sustained at 3 or 12 months. In addition to the limited duration and the low magnitude of the positive effect on survival, the applicability of corticosteroid therapy is further restricted by concerns about the risk of sepsis [15].

Other drugs have been tested in severe AH. The addition of a 5-day course of N-acetyl cysteine to corticosteroid therapy tended to improve survival at 3 months compared to corticosteroids alone in a randomized controlled trial, although the difference in survival was not significant [16]. These promising results should be confirmed in other studies before a recommendation to use this combination therapy can be made. Enteral nutrition added to corticosteroids failed to demonstrate a survival benefit compared to corticosteroids alone in a randomized controlled trial administering nutrition through a naso-gastric tube for 14 days [17]. However, a post-hoc analysis identified a nutritional intake >21.5 kcal/kg as a factor significantly associated with a better survival, indicating that caloric supplementation should be provided to AH patients, which may require a nasogastric tube if tolerated.

2.3. Upcoming medical management

Many anti-inflammatory agents have been studied in AH, with a number of therapies currently under evaluation. Although TNF-α inhibitors (infliximab) have failed to demonstrate a benefit due to increased rates of infection [18], other anti-inflammatory therapies, such as anti-Lipopolysaccharide (LPS) antibodies, anti-Toll-like receptor 4 antibodies, and interleukin (IL)-1 receptor antagonists are currently being investigated [19]. Moreover, the caspase inhibitor emricasan, cytokine IL-22 inhibitors, and the farnesoid X receptor agonist obeticholic acid have also been studied in clinical trials for their hepatoprotective effects [20]. Finally, fecal microbiota transplantation also seems to be a promising therapy [21]. However, larger controlled studies are required for confirmation. By contrast, other therapies, including pentoxifylline, antioxidants, and extracorporeal liver supports are ineffective and should not be used for the treatment of AH [14,22–24].

Granulocyte colony stimulating factor (G-CSF) is a glycoprotein that stimulates the bone marrow to produce and release neutrophils and stem cells (CD34+) into the bloodstream. In animal models, administration of G-CSF was shown to mobilize hematopoietic stem cells, induce liver regeneration, and improve survival. Recent studies performed in Asia have reported a reduced risk of death in severe AH patients treated with G-CSF compared to placebo [25,26]. However, in two European studies, G-CSF did not improve survival compared to placebo [27,28] (Figure 1). Whether these conflicting results between Asian and European studies can be explained by ethnic differences, patient selection, or G-CSF administration schedules remains unknown and needs additional investigation.

2.4. Evaluation of response to therapy

One major improvement in the management of severe AH during the last decade has been the emergence of tools for assessment of patient prognosis according to early response to therapy. An early change in serum bilirubin levels after 7 days of corticosteroid therapy was initially proposed as a means for identifying patients at high risk of death at 6 months [29]. Similarly, a change in MELD score during the first week of therapy has been shown to predict in-hospital mortality [30]. More recently, the Lille model, which is based on age, pretreatment liver function parameters, and the evolution of bilirubin serum levels after a 7-day course of corticosteroids, has been developed. This score ranges from 0 to 1; a score ≥0.45 indicates non-response to corticosteroids and is associated with a very high risk of 6-month mortality (ranging from 70% to 80%) [31]. As corticosteroids provide only a modest improvement in prognosis and because there is currently no other therapeutic option for non-responders to corticosteroids, liver transplantation could be lifesaving in this setting and has been proposed in highly selected patients. In 2005, a French consensus conference recommended pilot studies to evaluate early liver transplantation in carefully selected patients with severe AH who are not responsive to medical therapy [32].

3. Current available data on liver transplantation for refractory AH

3.1. Summary of current available data

Several studies have demonstrated the benefit of liver transplantation to the prognosis of selected patients suffering from severe/refractory AH [33–37] (Table 1). In the first French-Belgian landmark study from Mathurin et al., 26 patients with severe AH not responding to medical therapy (around 7% of all non-responders evaluated for early liver transplantation) were selected using a strict selection process and underwent a liver transplantation after a median waiting time of 13 days [35]. As expected, the 6-month and 2-year survival rates of transplanted patients were better than those of non-transplanted matched non-responders: 77% vs. 23% at

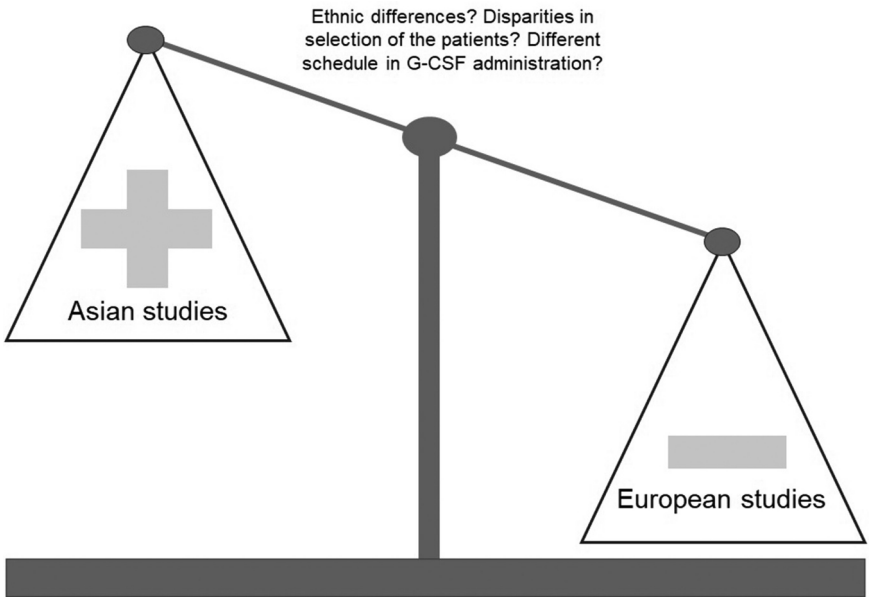

Figure 1. Conflicting results with regard to the survival benefit of G-CSF.
Abbreviations: G-CSF, Granulocyte colony-stimulating factor

Table 1. Main outcomes of studies evaluating early transplantation in patients with severe/refractory alcoholic hepatitis.

Study	Number of patients transplanted	Age *	MELD at time of liver transplantation *	Alcohol relapse (n, %)	Harmful alcohol relapse (n, %)	1-year survival (%)
Mathurin 2011 [35]	26	47	34	3 (12)	1 (4)	77
Singal [36]	55	52 **	26 **	-	-	87
Im [33]	9	41	39	2 (22)	2 (22)	89
Weeks [37]	46	50	33	13 (28)	8 (17)	97
Lee [38]	147	43	38	40 (28)	15 (11)	94

* Expressed as median ** Expressed as mean

6 months and 71% vs. 23% at 2 years, respectively. Alcohol relapse after transplantation occurred in 3 patients after 720 days, 740 days, and 1140 days. One patient engaged in a harmful level of drinking while the 2 others were occasional drinkers. There was no graft loss related to alcohol relapse during the follow-up period.

The following year, a retrospective study was published reporting on outcomes of AH transplanted patients in the United Network of Organ Sharing (UNOS) database. In this study, 55 patients were transplanted for severe AH between 2004 and 2010 and were compared to 165 matched patients transplanted for alcoholic cirrhosis. Compared to patients transplanted for alcoholic cirrhosis, AH transplanted patients had similar 5-year graft survival (75% vs. 73%) and similar 5-year overall survival (80% vs. 78%). Data on alcohol relapse were not reported in this study but no graft losses or deaths were related to recurrent alcohol intake [36].

Experiences with liver transplantation for AH have also been reported in studies from the United States. In a prospective study from Mount Sinai, 9 AH patients selected on the same stringent criteria as those used in the Mathurin study underwent early liver transplantation [33]. Patients transplanted for AH had better 6-month survival than matched non-responders who were not transplanted (89% vs. 11%). A single transplanted patient had alcohol relapse. In the Johns Hopkins' experience, 46 patients were transplanted for severe AH before 6 months of abstinence [34,37]. These patients had similar 1-year survival to 34 patients who were transplanted for alcoholic cirrhosis with at least 6-months sobriety before transplantation (97% vs. 100%). Rates of any alcohol relapse were also similar in the 2 groups (28% vs. 24%), as well as rates of harmful drinking (17% vs. 12%). In these studies, the selection process was less restrictive than in the Mathurin study as patients with a history of psychiatric disease were not systematically excluded if the evaluation made by a transplant psychologist was favorable. Of note, the length of abstinence before liver transplantation was not predictive of either survival or of alcohol relapse in both groups of patients.

Data on outcomes after liver transplantation in patients with AH were evaluated in a meta-analysis in 2018 [4]. This meta-analysis included studies in which patients with recent jaundice and severe AH were transplanted, as well as studies in which AH was discovered on the explant. The overall 6-month survival rate was 85%. Six-month survival was 80% in the subgroup analysis that included only studies in which patients were transplanted for clinically severe AH. The survival rate of AH transplanted patients was similar to that of patients transplanted for alcoholic cirrhosis. Fourteen percent of patients had alcohol relapse in the subgroup analysis

including only studies of patients transplanted for severe AH that used stringent criteria for selecting candidates. Once again, the rate of alcohol relapse after liver transplantation was similar to that of patients with alcoholic cirrhosis who underwent liver transplantation after a sobriety period of at least 6 months.

Since the publication of the meta-analysis, the results of a large multicenter observational US study (ACCELERATE-AH) were reported [38]. This study summarized previously reported experience in the US [33,34,37]. Overall, 147 patients with severe AH without a prior diagnosis of liver disease underwent liver transplantation before 6 months of abstinence from 2006 to 2017 in 12 centers from 8 UNOS regions. While generally following the same inclusion/exclusion criteria as the Mathurin study, criteria for selecting liver transplant candidates were not uniform across centers. The survival rate of the 141 transplanted patients was 94% at one year and 84% at 3 years. Alcohol relapse occurred in 40 liver transplant recipients (28%), with 11% of patients drinking harmfully. The only factor associated with alcohol relapse after transplantation in multivariable analysis was younger age. The only predictor of harmful relapse was the consumption of more than 10 drinks per day at initial presentation.

3.2. Differences between Europe and the US studies

It should be noted that experiences from Europe and from the US differ on several points summarized in Table 2. All transplanted patients included in the Mathurin study had histologically confirmed AH, were non-responders to corticosteroids, and were transplanted following a prospective protocol. By contrast, in the US studies, not all candidates underwent a liver biopsy and not all were treated with corticosteroids, thus, AH cannot be considered to have been refractory in all cases. In addition, in the Mathurin study, even though they were carefully selected to match each transplanted patient, non-responders who served as controls were not exposed to the same stringent criteria as the transplanted patients. If all studies that used non-responders as a control group had observed a survival benefit for transplanted patients, this benefit appears to be less important in the French-Belgian landmark study. Finally, the retrospective design of most of the US studies could also have influenced the results. Nevertheless, in the end, these data provide strong evidence that early liver transplantation could be lifesaving for patients with severe/refractory AH and that alcohol relapse is not a frequent event if a strict process is used to select candidates.

Table 2. Main differences between European and US studies regarding diagnosis of alcoholic hepatitis, initial management of the patients, and selection criteria for early liver transplant.

Study design and location	Diagnosis of AH before liver transplant	Initial AH specific treatment	Criteria for selecting patients for early liver transplant	Number of patients transplanted (n)	AH confirmed on explants (n, %)
Mathurin [35], Prospective, France-Belgium	Clinically and confirmed by liver biopsy in 23/26 (88%) patients	24 (92%) patients received corticoids	• No response to medical therapy • Severe AH as the first liver-decompensating event • Presence of close supportive family members • Absence of severe coexisting or psychiatric disorders • Agreement by patients (with support from family members) to adhere to lifelong total alcohol abstinence	26	26 (100%)
Singal [36], Retrospective, US (UNOS database)	Clinically and not histologically proven in most of the patients	Not clearly reported	• Careful evaluation of the selected patients	55	11(20%)
Im [33], Prospective, US (Mount Sinai)	Clinically and not histologically proven in most of the patients	• One patient (11%) received corticoids alone • 3 (33%) patients received corticoids plus pentoxifylline • One patient (11%) received corticoids plus N-acetyl cysteine • 4 (44%) patients did not receive any specific treatment for AH	Same criteria as in the Mathurin study: • No response to medical therapy • Severe AH as the first liver-decompensating event • Presence of close supportive family members • Absence of severe coexisting or psychiatric disorders • Agreement by patients (with support from family members) to adhere to lifelong total alcohol abstinence	9	9 (100%)
Lee and Weeks [34,37], Retrospective US (Johns Hopkins)	Clinically and not histologically proven in most of the patients	• 21(46%) patients received corticoids • 25 (54%) patients did not receive corticoids because of contraindication to therapy	• Severe AH as the first liver-decompensating event • Presence of close supportive family members • Stably managed disease in case of history of psychiatric disease • Agreement by patients (with support from family members) to adhere to lifelong total alcohol abstinence	46	24 (52%)

Abbreviations: AH, alcoholic hepatitis

4. Ethical considerations surrounding the use of liver transplantation in AH patients

Consideration of using early liver transplantation for management of patients with refractory AH has raised concerns regarding equity in liver graft allocation in the specific setting of alcoholic liver disease. Several arguments have been made for not considering liver transplantation in AH. The most common reasons are: (1) hope that liver function will improve after alcohol withdrawal making liver transplantation unnecessary; (2) fear of recurrent alcohol consumption after liver transplantation which could raise safety issues in post-transplant care, be seen as an unfair behavior on the part of the liver transplant recipient, and impair graft survival, making liver transplant, if not unnecessary, at least of limited utility; (3) fear that considering liver transplantation in patients with a self-inflicted disease could raise a problem of equity in liver graft allocation and in both public opinion and healthcare providers who participate in candidate selection which could reduce the number of potential donors [39,40]; and, finally, (4) organ shortages.

4.1. Hope that liver function will improve after alcohol withdrawal

While the positive effect of alcohol abstinence on liver function is well established in patients with alcoholic liver disease, this effect takes at least 3 months to be significant [41]. As 70–80% of non-responders to corticosteroids die within 3 months after the onset of the disease, this option is not achievable for these patients. In addition, the rationale of using a 6-month sobriety period to predict alcohol drinking behavior after liver transplantation is debated. Previous studies performed among patients with alcoholic cirrhosis have indicated that the 6-month rule of abstinence poorly identifies patients with recurrent alcohol consumption after liver transplantation. Moreover, most patients who do not fulfill 6 months of sobriety before transplantation remain abstinent after transplantation [42,43] (up to 59% in Foster's study [43]). A systematic review of 22 studies evaluating liver transplantation for alcoholic cirrhosis confirmed that the length of pre-transplant abstinence was a poor predictor of alcohol relapse after liver transplantation [44]. By contrast, a good psychosocial profile, including social stability, no previous treatments for alcohol dependence, no current drug use, and no co-existing severe mental disorder, has been associated with long-term abstinence. Hence, the 6-month sobriety period is not a perfect criterion to use for predicting abstinence after liver transplantation and, most importantly, is a poor exclusion criterion to refuse liver transplantation in the setting of refractory AH. New criteria based on a good psychosocial profile but not on the duration of abstinence are needed to identify patients with refractory AH at low risk of alcohol relapse after liver transplantation. It should be outlined that addiction specialists do not encourage to use length of abstinence to predict future alcohol intake. Rather, a good psychosocial profile including social stability, no previous treatments for alcohol dependence, no current drug use, and no co-existing severe mental disorders are associated with long-term abstinence. Table 3 summarizes the main prognostic tools used by addiction specialists to assess risk of alcohol relapse after liver transplantation [45].

4.2. Fear of recurrent alcohol consumption after liver transplantation

Healthcare providers are concerned about alcohol relapse after liver transplantation for alcoholic liver disease. Although rates of alcohol consumption depend on how relapse is defined, alcohol consumption is estimated to occur in 8%-22% and 30%-40% at 1 and 5 years after liver transplantation for alcoholic cirrhosis, respectively, negatively impacting graft and patient survival [42,50,51]. There are a number of reasons to fear alcohol relapse after transplantation. First, alcohol relapse may be associated with poor compliance, which could raise important safety issues in post-transplant care. Second, it may be viewed as an unfair behavior of the transplant recipient. However, recent data indicate that only a few patients with refractory AH who underwent an early liver transplantation returned to alcohol consumption after transplantation [33,35,38] (Figure 2). This favorable result is likely related to the fact that studies that assessed this issue applied a very strict selection process to select candidates. For example, in the Mathurin study, the selection process consisted of several meetings between 4 teams of care providers: first, nurses, residents and fellows; second, addiction specialist; third, senior hepatologist; and fourth, anesthetist and/or surgeons. The 4 groups of care providers had to reach complete consensus on candidate selection for early liver transplantation [39]. Moreover, the following criteria were also used to select candidates for liver transplantation. The patient must present with his/her first liver decompensation event, should have strong family support, should not present with psychiatric disorders, and should adhere to lifelong alcohol abstinence programs. These criteria are considered to be better at predicting alcohol relapse than the length of sobriety by experts in addiction medicine in the setting of alcoholic liver disease [52]. When applying these criteria, only 14% of AH patients transplanted for severe/refractory AH have recurrent alcohol intake after liver transplantation [4], and the rates of alcohol intake after liver transplantation seem to be at least as low as those of patients with alcoholic cirrhosis who were transplanted after a sobriety period of at least 6 months, or those of patients transplanted for other liver diseases. However, this selection process is still imperfect and needs to be refined. For example, using the criterion of a first liver-decompensating event as a prerequisite to select candidates may be considered to be unfairly discriminatory as some patients in whom AH is not the first decompensation event may present with other favorable factors prognostic of future abstinence [53]. In line with this, the ACCELERATE-AH group recently developed the Sustained Alcohol use post-Liver Transplant (SALT) score, a prognostic score ranging from 0 to 11 using 4 objective variables before transplant for identifying candidates for early liver transplant who are considered to be at low risk for sustained alcohol use after transplantation (more than 10 drinks per day at initial hospitalization, 4 points;

Table 3. Alcohol relapse scoring systems.

Instrument	Validation	Interpretation	Item assessed	Points
High-Risk Alcoholism Relapse (HRAR)	Based on a study of relapse following inpatient alcoholism treatment in a cohort of male US veterans This score was validated in a prospective study of 387 patients who underwent liver transplantation for alcoholic cirrhosis in Geneva (Switzerland) and Lyon (France) where a HRAR score > 3 was associated with harmful drinking post liver transplant [46]	HRAR score > 3 was associated with harmful drinking	Duration of heavy drinking (years) • < 11 • 11–25 • > 25 Usual number of daily drinks • < 9 • 9–17 • > 17 Number of prior alcoholism inpatient treatment experiences • 0 • 1 • > 1	0 1 2 0 1 2 0 1 2
Alcohol Relapse Risk Assessment (ARRA)	Based on a retrospective study of 118 transplanted patients in a single US center (Boston) [47]	Patients with ARRA III and IV had significantly higher rates of alcohol relapse ARRA I = 0 ARRA II = 1 to 3 points ARRA III = 4 to 6 points ARRA IV = 7 to 9 points	(1) Absence of hepatocellular carcinoma (2) Tobacco dependence (3) Continued alcohol use after liver disease diagnosis (4) Low motivation for alcohol treatment (5) Poor stress management skills (6) No rehabilitation relationship (7) Limited social support (8) Lack of nonmedical behavioral consequences (9) Continued engagement in social activities with alcohol present	1 1 1 1 1 1 1 1 1
The Stanford Integrated Psychosocial Assessment for Transplant (SIPAT)	Based on a prospective study of heart, lung, liver, and kidney transplant recipients [48]	Higher SIPAT scores associated with increased rejection episodes, hospitalizations, infection rates, and psychiatric decompensation. Score 0–6: Excellent candidate 7–20: Good candidate 21–39: Minimally acceptable candidate 40–69: Poor candidate >70: High-risk candidate	(1) Patient's readiness level and illness management (2) Social support system level of readiness (3) Psychological stability and psychopathology (4) Lifestyle and effect of substance use	0–28 0-20 0–37 0-25
The Michigan Alcoholism Prognosis Score (MAPS)	Stratification of potential transplant candidates into low- and high-risk categories for alcohol relapse in alcoholic cirrhosis [49]	Higher score indicated reduced risk for relapse	(1) Isolation (2) Previous treatment (3) Insight into alcoholism (4) Psychological health	
The Sustained Alcohol use post-Liver Transplant (SALT) score	Developed by the ACCELERATE-AH group in patients with severe AH and evaluated for early liver transplantation (multicentric US centers) [54]	A SALT score < 5 had a 95% negative predictive value for sustained alcohol use after liver transplantation	(1) More than 10 drinks per days at initial hospitalization (2) Multiple prior rehabilitation attempts (3) Prior alcohol-related legal issues (4) Prior illicit substance abuse	4 4 2 1

Abbreviations: AH, alcoholic hepatitis

Adapted from; Lim J and Sundaram V. Risk factors, scoring systems, and interventions for alcohol relapse after liver transplantation for alcoholic liver disease. Clin Liver Dis (Hoboken) 2018;11:105–110 [45].

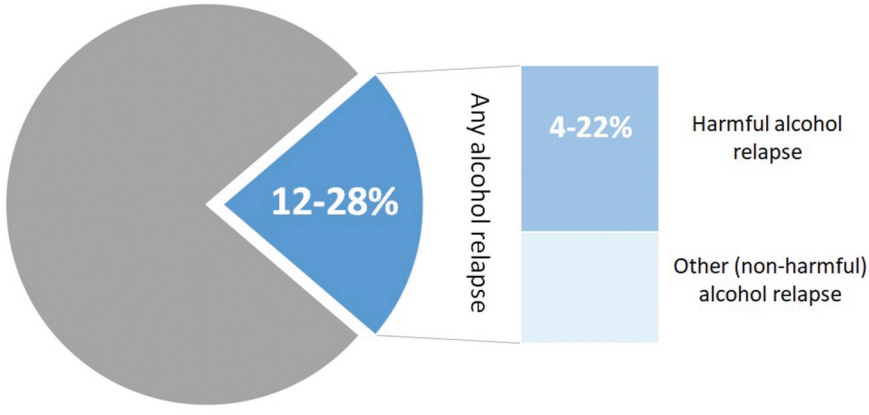

Figure 2. Alcohol relapse rate after early liver transplantation.

multiple prior rehabilitation attempts, 4 points; prior alcohol-related legal issues, 2 points; prior illicit substance abuse, 1 point). A SALT score <5 had a 95% negative predictive value for sustained alcohol use after liver transplantation [54]. Although this score shows promise, it must be validated before it can be applied in clinical practice. In the same line, the first results of an ongoing prospective observational trial focusing on alcohol relapse after liver transplantation (NCT01756794) expected in 2020 will be of interest. This study may contribute to the identification of factors that predict alcohol relapse after liver transplantation in daily practice and may help to develop objective tools to predict relapse. It may also provide more data on the frequency of slips (occasional relapses) versus severe relapses (harmful drinking) and on their respective impacts on prognosis after transplantation.

Another concern is that alcohol relapse could have a negative impact on patient prognosis, as is the case for patients transplanted for alcoholic cirrhosis. In a recent study, half of the patients with severe alcohol relapse after transplantation for alcoholic cirrhosis developed recurrent alcoholic cirrhosis 15 years after transplantation and most of the patients with recurrent alcoholic cirrhosis died during follow-up [55]. Thus, one may anticipate that alcohol relapse will also negatively affect the prognosis of patients transplanted for refractory AH. Although there are currently very few studies that have evaluated this question, an interesting modeling approach has just been reported. It estimated that 7 years of life would be lost in cases of severe alcohol relapse after liver transplantation for refractory AH [54]. As most alcohol relapse occurs within the first 3 months after a first episode of AH, measures to ensure abstinence should be implemented as soon as possible after liver transplantation for refractory AH.

4.3 Fear that considering liver transplantation in patients with a self-inflicted disease could raise a problem of equity in liver graft allocation

One common moral judgment against AH patients is that AH is a self-inflected disease. This argument is discriminating when considering the principles of beneficence, non-maleficence, equity, and justice that are essential in human care [39]. In addition, AH results from a combination of many factors, including individual genetic predisposition. This has been known for a long time and is supported by the observation that a minority of excessive drinkers suffer from AH. Thus, AH patients cannot be considered to be entirely responsible for their disease and refusing liver transplantation in these patients can be seen as a second punishment after the occurrence of AH [40]. Moreover, clinicians and the public are accustomed to considering liver transplantation for other self-induced diseases such as suicide-related acetaminophen-induced liver failure or obesity-induced cirrhosis without raising any ethical issues regarding graft allocation. Thus, the notion of 'merit to be treated' is against all ethical principles in medicine and should not, in itself, be considered an obstacle to have access to any treatment. In line with these points, it should be noted that public opinion regarding liver transplantation for AH may have changed in the last few years. While an older study indicated that public opinion was against liver transplant in patients with alcoholic liver disease [56], a recent survey indicated that more than 80% of participants were at least neutral to the idea of considering early liver transplantation in these patients, while other participants were not willing to consider liver transplantation in this setting [57]. Thus, early liver transplantation for carefully selected patients with refractory AH seems to be not as controversial with the public as previously thought. It also seems to be less controversial with healthcare providers than before. A recent survey on the impact of the Mathurin study on the management of liver transplantation candidates for alcoholic liver disease in France has indicated that 88% of responders had changed their practice regarding liver transplantation for refractory AH [58]. Similarly, the number of liver transplantation centers that performed at least one liver transplantation for AH has doubled in the United States over the last 3 years [53].

4.4. Organ shortages

Lastly, the impact of refractory AH as a new indication for liver transplantation on liver transplantation activity has to be as clear as possible. If we consider that among the 38% of AH patients who are non-responders to corticosteroids less than 10% are eligible for liver transplantation when a strict selection process is applied (a percentage similar to the one observed in the Mathurin study [35]), then only 3% of all patients with severe AH would be candidates for liver transplantation (Figure 3). In a country the size of Belgium, in which we assume that 120 patients with severe AH are diagnosed every year, 4 of them would be candidates for liver transplantation, a number that should not impact liver transplant activity that much. Another matter of concern may be related to the possible increase in the number of patients with alcoholic liver disease in whom liver transplantation could be considered before 6 months of sobriety outside the setting of AH, such as those with acute-on-chronic liver failure (ACLF) not related to AH. However, as the place of liver transplantation is currently controversial for this specific entity and limited to highly selected patients, very few patients with ACLF and without severe AH will be candidates for liver transplantation before 6 months of sobriety [59].

5. Expert opinion

Corticosteroids given orally have been recommended for the last decade as a treatment for severe forms of AH. However, the benefit of this treatment is limited. A large amount of data indicates that a survival benefit of less than 10% is observed at 1 month and that this benefit is not sustained at 3 or 12 months. Non-response to corticosteroids is associated with a 70% to 80% risk of death at 6 months. As most non-responders to corticosteroids die within 3 months after the onset of the disease, waiting for the positive effect of alcohol abstinence on liver function is not an option for these patients. Thus, the 6-month sobriety period, which is not a perfect criterion to use for predicting abstinence after liver transplantation, is not appropriate for non-responders and other criteria based on a good psychosocial profile but not on the duration of abstinence are needed to identify patients with refractory AH at low risk of alcohol relapse.

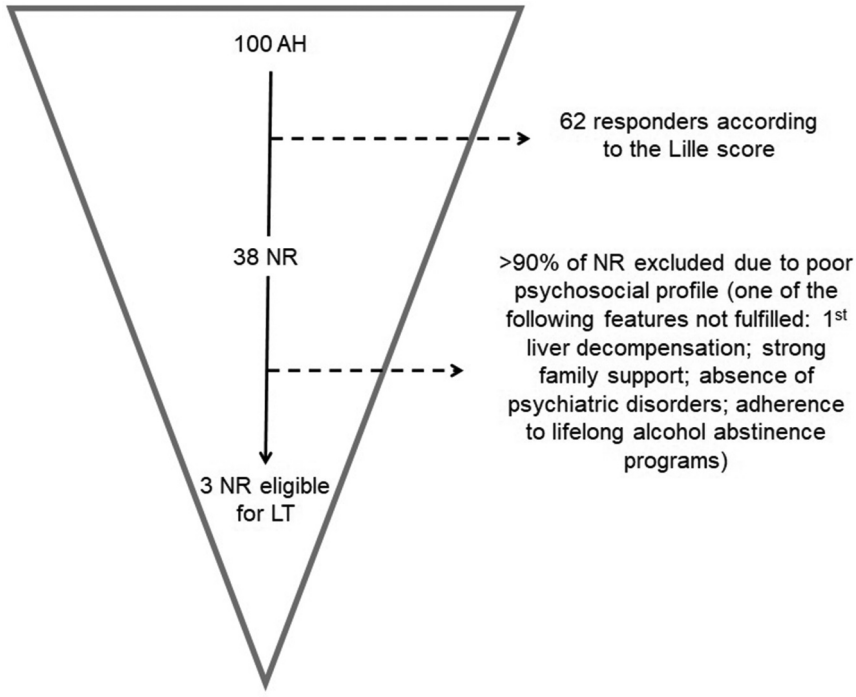

Figure 3. Selection process for patients with severe/refractory AH who are candidates for liver transplantation.
Abbreviations: AH, alcoholic hepatitis; LT, liver transplantation; NR, non-responders

As liver transplantation could be lifesaving in AH patients at high risk of early death, refractory AH has become a new indication for liver transplantation. Indeed, current available data indicate that liver transplantation for refractory AH is lifesaving in highly selected non-responders to corticosteroids. A limited number of non-responders are eligible for liver transplantation. Current data indicate that only 3% of all patients with severe AH would be candidates for liver transplantation when a strict selection process is applied similar to the one observed in the Mathurin study, which should not impact liver transplant activity that much. Consideration of using early liver transplantation for management of patients with refractory AH has raised a lot of concerns regarding equity in liver graft allocation in the specific setting of alcoholic liver disease. Equity should be respected in the setting of AH as in other conditions in which liver transplantation is discussed. Medical care providers should pay particular attention to ethical considerations surrounding the use of liver transplantation in refractory AH. The notion of 'merit to be treated' is against all ethical principles in medicine and should not, in itself, be considered an obstacle to have access to any treatment. Based on available scientific results on post-liver transplantation outcomes and the risk of alcohol relapse, only a few patients with refractory AH who underwent an early liver transplantation returned to alcohol consumption after transplantation when a strict selection process is applied. Currently, a strict selection process similar to the one used in the French-Belgian landmark study seems to be the best way to manage these issues and to ensure the perpetuation of the liver transplantation program for highly-selected patients with refractory AH. However, this selection process is still imperfect and needs to be refined. In the future, well-defined selection criteria for candidate selection and accurate tools to predict alcohol relapse after liver transplantation are needed. These will contribute to ensuring the perpetuation of the liver transplantation program for highly-selected patients with refractory AH from the perspective of both healthcare providers and the public.

6. Conclusions

Refractory AH has become a new indication for liver transplantation in highly selected non-responders to corticosteroids. Currently, a strict selection process based on a good psychosocial profile, including social stability, no previous treatments for alcohol dependence, no current drug use, and no co-existing severe mental disorder, should be applied. Well-defined selection criteria for candidate selection and accurate tools to predict alcohol relapse after liver transplantation are still needed.

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Declaration of interest

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