Review

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Liver transplantation for alcoholic hepatitis

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Summary

While liver transplantation (LT) has become a standard therapy for life-threatening alcohol related cirrhosis, LT as a treatment for severe alcoholic hepatitis (AH) has remained a taboo owing to concerns about the limited organ supply and the risk that the AH liver recipient will return to harmful drinking. The adoption of a 6-month abstinence requirement (the so-called '6-month rule') by many centres made AH a contraindication to LT. Given the high short-term mortality of severe AH, the lack of effective medical therapies and an increasing recognition that the 6-month rule unfairly excluded otherwise favourable candidates, a seminal European pilot study of LT for AH was performed. The success of the European study, which has been corroborated in retrospective analyses from the United States, represented a paradigm shift in therapy for highly selected patients with severe AH who are not responding to medical therapy. However, prospective studies are urgently needed to resolve the controversies that still surround the criteria for selection of patients with AH for LT and the long-term outcomes of the associated alcohol use disorder.

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Key points

By 2017, alcohol-related liver disease was the most common indication for liver transplants in the US, with survival rates similar to other indications.

Alcoholic hepatitis as an indication for liver transplantation – a brief history

In 1983, the National Institutes of Health convened a consensus development conference about liver transplantation (LT).[1] The consensus statement, which declared LT a 'therapeutic modality for end-stage liver disease that deserves broader application', was a key turning point in the establishment of LT within mainstream therapeutics in the United States (US). In addition, the assembled experts offered the following assessment regarding 'alcohol-related liver cirrhosis and alcoholic hepatitis': 'patients who are judged likely to abstain from alcohol and who have established clinical indicators of fatal outcomes may be candidates for transplantation. Only a small proportion of alcoholic patients with liver disease would be expected to meet these rigorous criteria'. This statement set the tone for the debate on transplantation of patients with alcohol-related liver disease (ALD) that has continued for the subsequent 35 years and is illustrative for several reasons. Firstly, it established that a judgment about future drinking was an essential part of the assessment of patients in this population. Secondly, it took as accepted truths that we had the means to accurately foretell future drinking and that it was appropriate to deny LT to patients deemed to be at high risk of relapse. Finally, the experts speculated that few patients with ALD would be found acceptable. Cynics might suggest that the latter projection was really a concession to those who feared that endorsing LT for patients with ALD would jeopardise the acceptance of LT among the wider public.

In the ensuing years, a couple of interesting phenomena arose in parallel. Firstly, the prediction that very few patients with ALD would meet criteria for selection for LT proved inaccurate. The first indication that patients with ALD could undergo successful LT came from Thomas Starzl *et al.* in 1988.[2] They reported on 41 patients with ALD who underwent LT in the 'cyclosporin era' with a 1-year patient survival of 71%. Furthermore, the paper asserted that return to alcohol use was infrequent. The latter issue has been a topic of contention ever since (Table 1). Following this pioneering study, ALD had risen to become the most common liver disease aetiology for LT in the US by 2017, with 1- and 5-year patient and graft survivals that are similar to other indications.[3]

The second phenomenon was the emergence of the recognition of alcohol use disorder (AUD) as a fundamental element in the clinical care of patients with ALD under consideration for LT. In 1996, a NIH workshop entitled, 'Liver Transplantation for Alcoholic Liver Disease' brought together experts from the fields of addiction and ALD.[4] The workshop emphasised that future advances would require a focus on AUD as much as on ALD. 'Thus, the major needs in clinical research on liver transplantation for ALD are better documentation of the relapse rate after transplantation and the factors that predict relapse especially over an extended period (5 to 10 years) using reliable and objective means of documenting alcohol use. Study of relapse after transplantation may be helpful in developing better selection criteria but may also provide insights into treatment of alcoholism in patients that do not receive transplants'.

Table 1. Arguments against and in favour of liver transplantation for alcoholic hepatitis.

Arguments against LT for AH	Arguments in favour of LT for AH
A required interval of abstinence (6-month rule) allows for liver recovery to obviate the need for LT.	Many patients with severe AH without response to medical care will die during a required interval of abstinence, so LT saves lives. Validated and widely used models (Lille ± MELD) can accurately predict survival, especially in life-threatening AH.
A required interval of abstinence (6-month rule) allows a patient to demonstrate a commitment to abstinence and gives the opportunity to implement preventive strategies against future relapse.	While duration of pre-LT sobriety predicts the likelihood of post-LT relapse, it is imprecise at 6-months as a single predictor, with 20% relapsing at 5 years. Reliance on the 6-month rule discriminates against patients with favourable psychosocial profiles, who have a low risk of relapse despite recent drinking.
Public perception of LT for AH is negative and it will lead to reduced organ donation.	Evidence for this is lacking and recent public surveys demonstrate that a majority has a neutral opinion of LT for AH.
AH is a self-inflicted condition, so these patients are less deserving of this limited resource, than patients with other forms of liver disease.	AUD is a disease with a complex genetic, psychological and social foundation. Personal behaviour also influences many other indications for LT such as ALF (suicide attempt), NAFLD (excessive caloric intake), HBV/HCV (high risk behaviours), HCC related to NAFLD, HBV, HCV.
Transplantation of patients with AH in greater numbers will lead to more recipients with post-LT alcohol relapse and greater rates of allograft loss.	While alcohol relapse post-LT is associated with more rapid fibrosis in grafts and eventually more graft loss, current data do not support the argument that transplanting patients with AH will lead to more relapse. However, this argument emphasises the need for more prospective studies of LT in patients with AH.

AH, alcohol-related hepatitis; LT, liver transplantation; MELD, model for end-stage liver disease; AUD, alcohol use disorder; ALF, acute liver failure; NAFLD, nonalcohol-related fatty liver disease; HBV, hepatitis B virus; HCV, hepatitis C virus; hepatocellular carcinoma HCC.

The '6-month rule'

Even while the need to understand AUD became more widespread within the transplant community, LT as a therapy for patients with severe AH remained 'beyond the pale'. The key to this attitude was a resistance to offering LT to patients who had a short, or no, interval of abstinence. The origin of the 6-month abstinence requirement prior to LT is obscure. In a survey conducted in 1996, 85% of responding LT programmes in the US said that they required at least 6 months abstinence as a pre-requisite to LT in patients with any form of ALD.[5] This requirement effectively excluded patients with severe AH. The 6-month interval was justified on the grounds that it would allow patients to recover from the acute effects of alcohol-toxicity to the liver.[6] In practice however, the so-called '6-month rule' became a surrogate for prediction of future drinking by ALD candidates for LT.

From the start of LT for ALD, experts in addiction medicine were not supportive of the 6-month rule. Indeed some studies suggested that abstinence in men with ALD was secure only after 5 years.[7] Beresford offered, as an alternative, a more nuanced approach based on a careful psychosocial assessment.[8] He proposed that patients with ALD undergoing evaluation for LT should be assessed by an addiction specialist, and that risk should be gauged according to the presence of factors that characterise the risk of relapse in patients with AUD beyond the LT setting. He identified 4 domains in the candidate's psychosocial profile: social isolation/social integration; acceptance of a drinking problem; prior history of treatment of AUD and finally, presence of other psychological disorders. He attempted to classify these elements into a predictive score, but found that the predictive ability was limited to identifying high- and low-risk candidates. Since then, several additional protocols and prognostic tools to assess risk of alcohol relapse have been proposed (Table 2),[10–13] In all cases, these need to be used within an integrated evaluation involving experts in addiction medicine.

The present era

Within this historical perspective, the 6-month rule and with it the interdiction of LT for patients with ALD and short intervals of abstinence has persisted in the US. The change in attitude arose in Europe, most significantly in France, where a consensus conference in 2005 came to the conclusion that a therapeutic trial of early LT in patients not responsive to corticosteroid therapy was recommended 'despite the brevity of the required abstinence'.[14] This important determination prepared the way for the landmark French-Belgian pilot study of rescue LT in patients with non-responsive severe AH. Around the same time, consensus statements in favour of LT for selected patients with ALD and shorter intervals of abstinence were produced in the United Kingdom and Italy, indicating a more widespread shift in European approaches.[15–17] Most recently, Lee *et al.* have shown, albeit in retrospective data, that selected patients with severe AH who underwent LT in the US had excellent short-term survival. We will discuss these data below.

Database studies

It is possible to gain insight into the success of LT for AH by examining what has already been done, in some cases unknowingly. In 2002, Tome *et al.* reported a review of liver explants from 68 patients transplanted for ALD and compared them to 101 explants from patients transplanted for miscellaneous non-ALD causes in Spain.[18] The authors looked for histologic evidence of alcoholic steatohepatitis (ASH) in explants, implying more recent alcohol use (perhaps hidden) at the time of LT. There was no difference in survival or alco-

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Table 2. Four prognostic instruments used to predict future drinking after liver transplantation.

Instrument	Nature of instrument	Elements assessed
University of Michigan Alcoholism Prognosis Score[9,10]	Specific to LT in ALD	1. Isolation 2. Previous treatment 3. Insight 4. Psychological health
Alcohol Relapse Risk Assessment (ARRA)[11]	Based on retrospective review of alcohol outcomes in 118 ALD LT recipients at a single US centre	1. Absence of HCC 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 behavioural consequences 9. Continued engagement in social activities with alcohol present
High-Risk Alcoholism Relapse (HRAR)[12]	Predicts harmful drinking; based on a study of relapse following inpatient AUD treatment of male US veterans	1. Duration of heavy drinking 2. Usual number of daily drinks 3. Number of prior alcoholism inpatient treatment experiences
Stanford Integrated Psychosocial Assessment for Transplantation (SIPAT)[13]	Devised for all solid organ transplantation, not solely LT	Comprehensive interview instrument; complex to administer

LT, liver transplantation; ALD, alcohol-related liver disease; AUD, alcohol use disorder; HCC, hepatocellular carcinoma; US, United States.

Key points

In 2011, a pioneering study demonstrated a significant survival benefit in patients receiving liver transplants for severe alcoholic hepatitis, which would encourage further study in Europe and the US.

hol relapse between ALD LT recipients with superimposed ASH on explant and those without. Similar survival was also noted between patients with and without ALD. A similar study came from Wells *et al.* in 2007, which reviewed 1,097 explants from the University of Wisconsin over a nearly 20-year period.[19] The authors examined livers from 148 LT recipients with "pure" ALD (22% with ASH on explant) compared to 125 non-ALD controls "with similar demographics". There was a correlation between reported abstinence <1 year and ASH on explant but not with abstinence <6 months, perhaps reflecting a disincentive to be forthright about abstinence <6 months. Patient and graft survival were no different between ALD and non-ALD LT recipients, nor between ALD with ASH and ALD with "bland cirrhosis" on explant. The relapse rate was 16% amongst patients with ALD. Additionally, relapse was not associated with ASH on explant and did not impact on graft or patient survival compared to non-ALD controls. These studies of explants, although retrospective, subject to selection bias and involving less-sick patients (average model for end-stage liver disease [MELD] 21) than recent experience, demonstrate no impact on graft or patient survival referable to pre-LT abstinence or post-LT relapse.

A similar retrospective effort from Singal *et al.*, utilised the United Network for Organ Sharing (UNOS) national database from 2004–2010 to compare patients undergoing LT with a listing diagnosis of AH and matched controls with a listing diagnosis of alcohol-related cirrhosis (AC).[20] Patients were also compared based on explant pathology of ASH *vs.* cirrhosis. The findings in this combined national report were no different from those seen in single-centre reports: there was no difference in 5-year graft or patient survival between patients based on listing diagnosis and likewise no difference when explant findings were used. The authors concluded that patients with AH or its histopathologic correlate have similar post-LT graft and patient survival and thus LT may be considered in select patients. They further added that "prospective studies are needed".

Landmark French-Belgian trial

This call was answered in 2011. Mathurin *et al.*, performed a prospective study of LT for severe AH carried out at 7 liver transplant centres (6 across France, 1 in Belgium) that included patients with severe AH not responding to medical therapy (DF >32, Lille ≥0.45) and stringent selection criteria: no prior liver decompensation episodes, supportive family members, commitment to abstinence and complete consensus amongst relevant providers.[21] Twenty-six patients with life-threatening AH (median listing MELD 34) underwent LT with a significant survival benefit compared to matched controls without LT (6-month survival 77% and 23%, respectively; p <0.001). After a 2-year follow-up, 3 of the 20 (15%) surviving patients returned to some alcohol use without it impacting on graft function. The authors stressed the selectivity of their programme: <2% of all patients admitted with AH were selected for LT, and centres used only 2.9% of available liver grafts for this indication. The results of this trial challenged the notion of the 6-month rule as the sole alcohol-related criterion for LT eligibility in ALD and generated significant commentary, particularly regarding reproducibility, candidate selection and potential impact on an already limited organ supply.[22,23]

The impact of this study in France was immediate. Antonini *et al.* sent a 20-item online survey to 163 practitioners working at 18 French LT centres "to evaluate the impact...on the management of elective LT candidates for AC in France".[24] They received a 38% response, with participation from 17 of 18 centres. A remarkable 88% of respondents reported that they had changed their practice regarding AH since 2011, and 97% now considered

AH to be a potential indication for LT, with 71% of French centres now performing LT for AH. While three-quarters of centres reported applying the 6-month rule prior to 2011, this declined to 29% at the time of the survey, while 65% reported moving to a 3-month rule after 2011. Overall, 46% of centres had reduced the duration of abstinence required prior to LT for ALD. The authors concluded "the seminal publication of Mathurin exerted a significant impact on French clinical practice".

Liver transplantation for alcoholic hepatitis crosses the Atlantic

The US response to the French-Belgian trial was more hesitant, with only a handful of centres reporting on single-centre pilot studies initiated in response. (Table 3) The initial report came in 2016, with Im *et al.* reporting on the Mount Sinai experience with LT for severe AH in a single-centre report of 9 patients compared to a matched control group that were managed medically, similar to the French-Belgian trial.[25] Out of 111 patients with severe AH from 2012–2015, 94 patients with severe AH not responding to medical therapy were evaluated and 9 underwent LT. This number represented 3% of liver transplants performed at the centre during that time period and the results were excellent with a 6-month survival of 89%, compared to the 11% survival in the control group. One patient with poor insight and prior liver decompensation relapsed, giving a relapse rate of 11% because of the small sample size in this series.

The other single-centre US study came from Johns Hopkins, with a report and update on 46 patients transplanted in their programme over a 5-year period from 2012–2017.[26,27] The authors compared 46 patients who underwent LT for severe AH with a control group of 34 patients with AC and 6-month sobriety transplanted during the same time period. Patients with severe AH were overall similar but were slightly younger, had a considerably higher MELD score (average MELD score >35), and a shorter duration of abstinence from drinking. Survival was similar in both groups (97% and 100% respectively at 1 year), and relapse was also similar in both groups (24% and 28%, respectively). The selection criteria in this study were more liberal than Mathurin, allowing inclusion of patients with a recent gastrointestinal haemorrhage. Pathology results from explanted livers were informative: 96% of explants from patients with AH showed cirrhosis, and 52% of explants from patients transplanted for AH with <6 months of sobriety showed pathologic features of ASH *vs.* 9% of explants from patients reporting >6 months sobriety. The interval of sobriety pre-transplant was not predictive of survival or relapse in either group. Another takeaway from the report is that reported rates of relapse in these series may be a function of how it is defined and how rigorously it is pursued on surveillance.

A large observational, multicentre study by a US consortium (ACCELERATE-AH) retrospectively analysed patients with AH without a prior diagnosis of liver disease, who underwent LT before 6 months of abstinence from 11/2006 to 3/2017 at 12 centres, including data from both the Mount Sinai and Johns Hopkins reports mentioned above.[28] One hundred and forty-seven patients with life-threatening AH (median MELD 39, Lille 0.82) underwent LT, with excellent 1- and 3-year survival (94% and 84%, respectively). These results further confirm the medical and surgical feasibility of LT for AH. While generally conforming to the inclusion/exclusion criteria from the European trial, candidate selection practices (medical and psychosocial) reflected real-world experiences and were not uniform. Unlike the previously mentioned case series from the US, only 59% had histologic steatohepatitis on explant despite the majority meeting National Institute on Alcohol Abuse and Alcoholism (NIAAA) definitions. However, whether AH or a form of acute-on-chronic liver failure, the need for rescue LT given the severity of illness (median MELD 39) was clear. Although one-quarter of LT recipients had any alcohol use at 1-year post-LT, a smaller minority (11%) had sustained (harmful) alcohol use at a median follow-up of 1.6 years. While most alcohol use after LT was detected by clinical interview, the surveillance methods and interventions were heterogeneous. Sustained alcohol use after LT was significantly associated with increased mortality (hazard ratio 4.59; $p = 0.01$). Median return to harmful drinking was about 6 months post-LT, with significant alcohol-attributable mortality (39%) occurring after 1-year post-LT. In multivariable analysis of a small set of pre-LT variables, only younger age was associated with alcohol

Table 3. Recent outcomes of liver transplantation for alcoholic hepatitis.

Study	Number of LT for AH	Age*	Male	Abstinence prior to LT*	MELD at time of LT*	1-year patient Survival	Return to harmful drinking
Mathurin[21]	26	47	58%	<90 days	34	77%	10%
Im[25]	9	41	56%	33 days	39	89%	12.5%
Weeks[27]	46	50	72%	50.5 days	33	97%	17%
Lee[28]	147	43	73%	55 days	38	94%	11%

AH, alcoholic hepatitis; LT, liver transplantation; MELD, model for end-stage liver disease.
* Data reported as median.

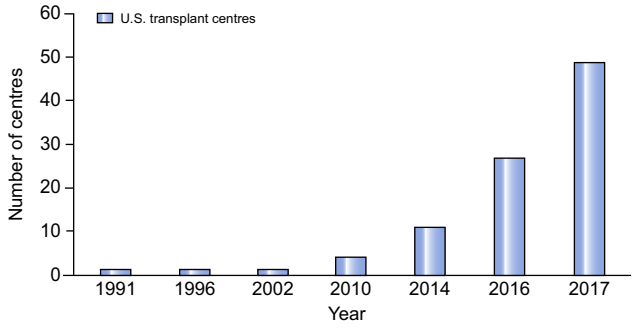

Fig. 1. Centres having performed liver transplantation for alcoholic hepatitis in the United States over time. Data based on references[2,14–15,26–28,48] and unpublished data.

Key points

Improving candidate selection with easily measurable pre-transplant variables that accurately predict the likelihood of relapse are essential for the successful implementation of liver transplantation for alcoholic hepatitis.

post-LT (odds ratio 0.96; $p = 0.02$). Although limited by its retrospective nature and heterogeneous LT centre practices, this study was large, represented a majority of UNOS regions and provided a timely assessment of the changing landscape for this controversial indication for LT in the US.

Impact of liver transplantation for alcoholic hepatitis

Coinciding with highly effective therapies for hepatitis C virus infection and despite the rising burden of non-alcohol-related fatty liver disease, ALD is now the most common liver disease aetiology for patients waitlisted and undergoing LT in the US.[29,3] LT for AH is likely contributing to this trend. Two surveys of LT centre directors in the US, reflecting data from 2014 and 2017 with similar response rates, illustrate the broader interest in LT for AH.[30–31] Over 3 years, the number of LT centres that had performed ≥1 LT for AH doubled (11 to 23), now representing about one-quarter of all centres, with a case from every UNOS region. However, a large majority (83%) had performed very few (≤5) (Fig. 1). Another UNOS-based study demonstrated a 4-fold increase in waitlisting for AH as the primary diagnosis from 2011 to 2016.[32] While Germany now allows LT centres to request that highly selected patients with ALD, abstinent for <6-months, be waitlisted for LT, a pilot program in the UK failed to recruit any patients over 3 years, probably because of stringent selection criteria.[33,34] The latest US survey also found that about half of the responding centres had not performed LT for AH primarily because of the perceived high risk of alcohol relapse, but not due to concerns relating to public recrimination. The latter reassurance may be due to a public survey study demonstrating a large majority (81.5%) expressing at least neutrality about LT for AH.[35] These issues highlight the shifting landscape and current uncertainty surrounding appropriate candidate selection in LT for AH.

Box 1. Common study criteria in liver transplantation for alcoholic hepatitis.

Inclusion criteria
- Maddrey Discriminant Function >32
- Non-responder to (according to Lille ≥0.45) or ineligible for medical therapies (mainly corticosteroids)
- First liver-decompensating event
- Favourable psychosocial profile
- Good social support
- Agreement of transplant selection committee

Exclusion criteria
- Uncontrolled infection
- Comorbid systemic illness likely to prevent recovery
- Poor prognostic profile: failure to accept addiction as a problem; history of previous failed alcohol use disorder treatments
- Lack of social support: no home, supporting family or friends, lack of transport
- Prior liver-decompensating events
- Severe, uncontrolled psychiatric disorder

Improving candidate selection

Distinguishing between AH, decompensated AC and acute-on-chronic liver failure can be difficult. The diagnostic criteria outlined by the NIAAA can be useful for classifying patients as having definite, probable or possible AH.[36] Liver biopsy should be performed, usually by transjugular route, when there is diagnostic uncertainty (like in possible AH) and treatment is being considered (including LT for AH), as recommended by clinical guidelines.[37,38]

The French-Belgian trial set very restrictive standards for candidate selection, meaning only a small minority of highly selected patients with favourable psychosocial profiles were eligible for LT for AH (Box 1). The first liver-decompensating event criterion prioritised those who were previously unaware of their liver disease from alcohol, making this criterion a surrogate of patient insight. However, the complexity of AUD and ALD are such that this criterion may still unfairly discriminate against patients who have other favourable prognostic factors. The ideal prediction model for LT for AH would include a set of easily measurable pre-LT variables that accurately predicted harmful drinking after LT, and future patient resistance to accept AUD treatment. Derivation and validation of such a model would likely increase the number of centres performing LT for AH. Lee *et al.* derived a psychosocial scale identifying relapse post-LT in their cohort which allows for overt hepatic encephalopathy, but it has not been validated.[21]

Areas of future study

As with any new indication for LT, a learning curve for candidate selection is expected. Akin to the early days of LT for hepatocellular carcinoma, the search for pre-LT psychosocial "Milan criteria" informing and pushing the boundaries for optimal selection in LT for AH should be pursued by the transplant community in well-designed prospective studies. Equally important, studies of AUD treatment (psychosocial and/or pharmacologic) after LT are needed. Since AUD is not cured by LT, early or otherwise, LT centres should encourage

structured support like alcohol rehabilitation after LT for AH. In the most recent US survey, there was uniform consensus regarding the fundamental criteria for selection, but less than half of centres offered support group therapy or encouraged patients to attend external support groups after LT for AH.[27] In the US consortium study, the median time to first drink was around 6 months, so AUD treatment should start when feasible and target the time period prior to this.[23] That young patients (<40 years of age) appear to be more likely to return to harmful drinking in several initial LT for AH studies should not be a surprise. Evidence from the study of AUD identifies subtypes (Type B or type 2 or clusters 4/5) defined by younger age with familial AUD predicting recalcitrant addiction to alcohol.[39–41] Since young patients may also elicit a positive emotional response during selection meetings, this common selection conundrum highlights the need for addiction specialist input in LT for AH.[42] Similarly, more research collaborations with specialists in the addiction community would also yield valuable insights.

Studies of LT for ALD typically have reported post-LT alcohol use as a binary (yes/no) outcome measure, leading to wide ranges that are difficult to interpret. Expert opinion recommends more detail like differentiating slips (occasional lapses) from relapse (harmful drinking) in an attempt to capture the often relapsing-remitting course of alcohol addiction that is not cured by LT.[43] However, even these outcomes can be difficult to interpret. For example, an early relapse with graft injury followed by regaining of sobriety, recovery of graft health and prolonged survival can be seen through the lens of a negative outcome of relapse or a positive one of survival, depending on its reporting.[44] A more nuanced and valuable approach would standardise surveillance of alcohol use using interviews and biomarkers (like urine ethyl glucuronide and phosphatidylethanol) and use long-term trajectories of alcohol use and patient-reported outcomes post-LT as endpoints.[45–47] This approach would capture the relapsing-remitting course of AUD and would allow LT centres to personalise treatment and support for those who return to drinking. Understanding the impact of LT for AH at the centre level, including changes in clinical workload (including those ineligible for LT) and healthcare costs, could serve as a guide for LT centres considering LT for AH. On a wider scale, studies to evaluate disparities in access to LT for AH and evolving provider/public perception are needed.[3]

In summary, LT for AH has evolved from being a taboo in the early era of LT to become an emerging and effective rescue therapy for highly selected patients with severe AH not responding to medical therapy. Further studies on the use of LT for AH are warranted.

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Supplementary data

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