

REVIEW ARTICLE

Severe Acute Alcoholic Hepatitis and Liver Transplant: Ethical and Legal Responsibility

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ABSTRACT

Background Since more than 30 years ago, it is well understood that the survival of patients with a severe stage of hepatic damage due to alcohol, is no longer influenced by abstinence. Often, liver transplantation is the only way for these patients to survive. The arbitrary exclusion of these critically ill patients from an adequate therapy, in itself, is a substantial violation of the human rights of the patients and the national constitutional law in several countries. Not transplanting patients with alcoholic hepatitis simply because they failed to demonstrate long-term abstinence appears to be very hard to defend and preserve, particularly in view of the high fatality risk without LT. SAAH patients deserve to be included in the life saving organ donation system and deserve to be treated equally. The outcome of patients transplanted for severe acute alcoholic hepatitis is at least as good as patients transplanted for other diagnoses. **Summary** Emerging studies have verified the excellent survival advantage of LT in carefully selected patients with severe alcoholic hepatitis who failed medical therapy. **Conclusion** Patients with severe acute alcoholic hepatitis should have legitimate equal access to LT compared to other LT candidates.

INTRODUCTION

The severe acute alcoholic hepatitis is a well recognized separate entity from chronic alcoholic liver disease. It generally occurs in certain cases of extended alcohol misuse. Acute alcoholic hepatitis usually presents with the clinical syndrome of encephalopathy, jaundice and signs of liver failure. Mortality risk in patients with alcoholic hepatitis might be predictable using the Maddrey discriminant function [1, 2].

The development of severe acute alcoholic hepatitis (SAAH) is associated with a short-term mortality in excess of 70% in patients who fail glucocorticoid therapy [3]. Severe acute alcoholic hepatitis is commonly affects young patients. Liver transplant is life saving and the only treatment option after failing medical therapy.

Many historical retrospective studies and literature reviews, consider severe acute alcoholic hepatitis a contraindication for liver transplantation. Two points of view have been set forward to argue against liver transplant in the life-threatening SAAH. First, valuable organs should not be given to patients whose actions

resulted in liver damage by self-harm. Second, the risk of recidivism is uncontrollably high in patients who have a history of alcohol abuse in urgent LT situations.

A milestone multicenter study by Mathurin *et al.* from France showed a significant survival advantage in patients with SAAH not responding to glucocorticoid therapy by early liver transplant (LT) in carefully selected patients [3].

They presented mortality rates for patients with SAAH from the 7th to the 14th day of intensive care unit (ICU) admission. Accordingly, a lack of clinical improvement in patients with SAAH during the first weeks of ICU treatment indicates a poor outcome and the crucial need for LT. In less than 3% of the patients screened with SAAH and selected to undergo LT the 6-month survival was 77% vs. 23% in corresponding controls ($P < 0.001$), while only three of the 26 transplanted patients resumed alcohol consumption during follow-up time.

In response to the breakthrough trial by Mathurin, Testino *et al.* published an Italian position statement, which represents several Italian transplant centers and the World Health Organization Collaborating Centre for Research and Health Promotion in Italy who are supporting and adopting an approach similar to their French colleagues' [4].

DISCUSSION

A US study by Im *et al.* aimed at finding out, if a policy of early LT for SAAH might be used effectively in the United States. They reviewed 111 patients with SAAH between 2012 and 2015. The primary end point was mortality at 6 months or early LT, with a secondary end point of alcohol relapse after LT. Survival was compared between those who received early LT and matched patients who did

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not. Using a procedure analogous to the European study, 94 patients with SAAH not responding to medical therapy were evaluated for early LT. Only 9 (9.6%) patients with positive psychosocial reviews underwent early LT, comprising 3% of all adult LT during the study period. The 6-month survival rate was higher among those who received early LT compared with matched controls (89% vs. 11%, $p < 0.001$) [5]. Eight patients who received LT were alive after a median of 2 years with only 1 alcoholic relapsed. They concluded that early LT for SAAH can achieve outstanding clinical results with low impact on the organ donor pool and low rate of alcohol relapse in well-selected patients in the United States. Despite the fact that the number of transplanted patients was small, Im *et al.* have demonstrated great survival advantage and reproducible results like Mathurin *et al.* On behalf of the International Liver Transplant Society, Addolorato *et al.* have recently recommended LT in selected SAAH patients [6].

Thus the prerequisite period of alcohol abstinence for transplant eligibility in patients who fail medical treatment in SAAH, is ethically unfair, but also is degrading and inhumane, since the majority of these patients will die before they reach the six-month abstinence period [7, 8, 9]. Hence, excluding and denying these patients a proper treatment that could save their lives is morally intolerable, and is a failure to provide medical assistance. Despite this convincing outcome, major disagreement persists regarding LT prior to the six months rule, which is till this day, is mandated by most liver transplant centers worldwide [10].

Since many decades it is obvious that once a severe stage of hepatic damage has been reached, abstinence has no impact on the patient's survival [11, 12]. Newly, Lee *et al.* published a pilot study with carefully selected SAAH patients for LT. Early liver transplant resulted in outstanding short-term survival rates and the alcohol relapse rate was similar compared with the patients in the six month abstinence group [13].

Public opinion in general, did not support LT for patients with ALD. Several studies showed that public backing for LT was greater for other diseases than for diseases such as ALD [14-16]. Consequently, the transplant community is concerned that people will be less willing to donate if their organs will be allocated to patients with ALD. This was shown in the paucity of LTs for ALD in the 1980s and early 1990s [17]. But today, public opinion seems to have changed towards affording greater support for therapy to all individuals. A recent survey of 503 participants reported that the majority (81.5%) was at least neutral toward early transplantation for patients with ALD [18].

We definitely agree that resources are limited. Nonetheless, patients with recurring hepatitis C infections get transplanted, patients with recurring PSC get transplanted and obese patients suffering from NASH get transplanted. Even patients, who suffer from self-inflicted liver damage, who abused drugs like ecstasy or overdosed on paracetamol for instance, get transplanted. We should

not ignore this fact when we discuss an exclusive rule that is biased against patients suffering from ALD to participate in liver organ allocation.

The indication for LT is clear medically and the LT results are excellent. We the treating Physicians, are morally responsible by oath, should take action to save the lives of this selected group of patients, contrary to the policy of exclusion that denies the physicians the proper treatment of their patients. Rejecting LT to patients with severe alcoholic hepatitis because of failure to demonstrate long-term abstinence appears to be very hard to defend, particularly in view of the high risk of death without OLT [19].

In Contrast with alcoholic cirrhosis, patients with severe acute alcoholic hepatitis has comparable posttransplantation patient and graft survival [20].

Selection criteria for OTL in SAAH

Patients with first episode of SAAH, a Maddrey score value ≥ 32 , unresponsive to medical therapy after 1-2 week and positive psycho-social evaluation by a multidisciplinary team without any other medical contraindication (heart failure, extrahepatic tumor, etc.), not considering the 6-month abstinence rule.

Additionally, it should be acknowledged that the exclusion of these patients from an adequate therapy itself is both, a substantial violation of the patients' rights and the national constitutional law in several countries. SAAH patients equally deserve to participate in a deceased donation system. Human dignity and human rights apply to everyone. This discrimination against a small population of very ill patients still persists and we as physicians must acknowledge our ethical and moral responsibility regarding this issue.

In our opinion, LDLT represent the improvement of no longer depending on the accessibility of deceased donor organs. Opponents of transplantation for acute alcoholic liver disease cannot argue that the procedure deprives another patient of an appropriate organ. Additionally, there are risks to the donor, and thus the procedure must only be carrying out when there is a chance of a good outcome. In case, of early post-transplant liver failure after LDLT, for example due to technical difficulties, patients must have "high urgency" legal access to deceased organ allocation system.

In summary, because of shortage of organs, the "self-inflicted disease" doctrine and the need for convincing abstinence from alcohol before and after liver transplantation, these patients have been given low priority for LT. However, the need for six-month abstinence before LT set by some centers is not valid in the SAAH setting. In addition, several studies have shown that LT is effective in well-selected patients with SAAH unresponsive to corticosteroids therapy by improving patient survival whilst alcohol relapse rates after LT remain relatively low. A comprehensive medical and psycho-social evaluation by a multidisciplinary team including an addiction specialist is absolutely necessary when selecting SAAH patients for LT.

The need for intensive post-transplant surveillance should not be underestimated and it's much more important than pre-transplant selection. Risk factors for relapse should be identified, alcohol rehabilitation, family counseling, social support and lifelong medical and psychological care are crucial factors to prevent relapse to alcohol and to achieve good long-term results.

CONCLUSION

In conclusion, we believe that patients benefit more from implementing effective and standardized post transplant care plans rather than general exclusion policies. In this context, SAAH should be considered a curable condition and LT should be offered as a treatment option for these patients.

Conflict of Interest

All authors declare having no conflict of interests or financial disclosures.

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