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REVIEW

Liver transplantation and alcoholic liver disease: History, controversies, and considerations

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Abstract

Alcohol consumption accounts for 3.8% of annual global mortality worldwide, and the majority of these deaths are due to alcoholic liver disease (ALD), mainly alcoholic cirrhosis. ALD is one of the most common indications for liver transplantation (LT). However, it remains a complicated topic on both medical and ethical grounds, as it is seen by many as a "self-inflicted disease". One of the strongest ethical arguments against LT for ALD is the probability of relapse. However, ALD remains a common indication for LT worldwide. For a patient to be placed on an LT waiting list, 6 mo of abstinence must have been achieved for most LT centers. However, this "6-mo rule" is an arbitrary threshold and has never been shown to affect survival, sobriety, or other outcomes. Recent studies have shown similar survival rates among individuals who undergo LT for ALD and those who undergo LT for other chronic causes of end-stage liver disease. There are specific factors that should be addressed when evaluating LT patients with ALD because these patients commonly have a high prevalence of multisystem alcohol-related changes. Risk factors for relapse include the presence of anxiety or depressive disorders, short pre-LT duration of

sobriety, and lack of social support. Identification of risk factors and strengthening of the social support system may decrease relapse among these patients. Family counseling for LT candidates is highly encouraged to prevent alcohol consumption relapse. Relapse has been associated with unique histopathological changes, graft damage, graft loss, and even decreased survival in some studies. Research has demonstrated the importance of a multidisciplinary evaluation of LT candidates. Complete abstinence should be attempted to overcome addiction issues and to allow spontaneous liver recovery. Abstinence is the cornerstone of ALD therapy. Psychotherapies, including 12-step facilitation therapy, cognitive-behavioral therapy, and motivational enhancement therapy, help support abstinence. Nutritional therapy helps to reverse muscle wasting, weight loss, vitamin deficiencies, and trace element deficiencies associated with ALD. For muscular recovery, supervised physical activity has been shown to lead to a gain in muscle mass and improvement of functional activity. Early LT for acute alcoholic hepatitis has been the subject of recent clinical studies, with encouraging results in highly selected patients. The survival rates after LT for ALD are comparable to those of patients who underwent LT for other indications. Patients that undergo LT for ALD and survive over 5 years have a higher risk of cardiorespiratory disease, cerebrovascular events, and *de novo* malignancy.

Key words: Alcoholic liver disease; Alcoholic hepatitis; Alcoholic cirrhosis; Alcoholism; Liver transplantation; Alcoholic recurrence; Controversies; Alcoholic abstinence; Relapse; Selection criteria

Core tip: Alcohol consumption accounts for 3.8% of annual global mortality worldwide. Cirrhosis is a common complication of alcoholic liver disease (ALD) and when end-stage liver disease is reached, the only chance of survival is liver transplantation (LT). There are controversies and ethical dilemmas associated with LT for ALD. This study reviews the history and controversies and considers the development of, indications for, and outcomes of LT in ALD, including severe acute alcoholic hepatitis. Relapse, therapeutic options, and outcomes are emphasized.

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INTRODUCTION

Liver transplantation (LT) is the treatment of choice for patients with liver failure in end-stage liver disease, and it is their only chance of survival. As patients on LT waiting lists outnumber the number of LTs performed, and due to the high waiting list mortality rate, prioritization of individuals who are most likely to die without LT is needed. Access based on who is most likely to benefit from organ donation requires a legal, fair and ethical basis for the allocation[1-3].

Alcohol consumption accounts for 3.8% of global mortality and 4.6% of disability-adjusted life-years (DALYs) lost due to premature death[4]. Among the various harmful effects of alcohol, alcoholic liver disease (ALD) induces a wide spectrum of liver abnormalities, including simple steatosis, alcoholic hepatitis (AH) or steatohepatitis, progressive fibrosis, and ultimately alcoholic cirrhosis (AC) and/or hepatocellular carcinoma (HCC)[5].

One of the common causes of chronic liver disease, for which LT is potentially lifesaving, is ALD. This has been highly controversial from the beginning. The ever-increasing shortage of organs has accentuated the low priority given to patients with ALD, which is considered a "self-inflicted" condition. However, by improving the long-term survival rates (thereby making them similar to those for LT patients with other indications) and recognizing that alcoholism is a primary disease, ALD has become one of the most common indications for LT in Europe and North America, a situation thought unfathomable 30 years ago. Unfortunately, there are still many issues with the use of LT for ALD.

LT for ALD used to be associated with many ethical dilemmas, but this has recently changed as alcoholism is now understood to be a chronic, recurrent neurological disease process with a clear biological basis. Alcoholism is no longer primarily viewed to be a result of moral weakness and self-destructive behavior, but an addiction and dependence that should be considered from other perspectives[5].

ALD progression is dependent on patient characteristics, as well as drinking patterns. Abstinence is fundamental to the treatment of all forms of ALD, and the alcohol consumption relapse rate is lower than that expected in alcoholics. The consequences of excessive drinking after LT range from asymptomatic biochemical and histological abnormalities to graft failure and death.

HISTORICAL PERSPECTIVE, CONTROVERSIES, AND CONSIDERATIONS

History

LT for ALD has been a controversial situation from the beginning because of the ever-increasing demand for donor organs and the inadequate rate of organ donation, combined with the concern that patients with alcoholism might relapse, thereby damaging the transplanted liver. There was an apprehension that the outcome of LT in these patients may not be the same as for LT patients with other indications.

Of the first ten patients who underwent LT, performed

by Starzl (before the advent of cyclosporine), nine did not survive the first 4 mo. This poor initial outcome was attributed to excessive alcohol consumption causing significant extrahepatic organ damage (such as pancreatitis, cardiomyopathy, cerebral dysfunction, and poor nutritional status). This was probably due to the selection of critically ill patients who were too sick to improve even with LT, and ALD was then considered a predictor of poor LT outcomes compared to other indications[6,7]. In 1984, Scharschmidt reported on the experience of four transplant centers that had performed 540 LTs in the United States and Western Europe. The 3-year survival rate for the 20 patients who underwent LT after 1980 was 20%; non-AC cirrhosis was associated with an impressive 42% survival rate[8].

In the United Kingdom, the University of Cambridge Department of Surgery at Addenbrooke's Hospital and the Liver Unit at King's College Hospital, London, started the Liver Transplant program in a joint collaborative endeavor in 1968[9], involving Roy Calne and Roger Williams. They have stated that patients with AC are seldom suitable for transplantation since they are often malnourished and particularly prone to precipitous clinical deterioration often provoked by infections, and there are often doubts as to their ability to control their drinking again after the transplant[9].

Between 1968 and 1987, 325 LTs were carried out, eight of which were for AC. Active alcoholism was a specific contraindication. All of them died before 25 wk, except for the last two, who died at 48 wk (around the time of publication of the report on the 325 patients); only one returned to drinking alcohol[10].

The United States National Institutes of Health (NIH) Consensus Conference on Liver Transplantation in 1983 concluded that ALD is an appropriate indication for LT, provided that the patient is judged likely to abstain from alcohol after LT[6]. Following this, there was an increase in the number of LTs being performed for ALD. However, the conference attendees still considered and predicted that ALD would be a marginal indication for LT.

The first positive data published on the survival rate of ALD patients after LT, in comparison to patients with other indications, were reported in 1988[11]. Starzl reported a 73% 1-year survival rate among 41 patients when cyclosporine was used as the main immunosuppressive drug[12], and only 3% of these patients had relapsed to alcoholism. This was a convincing argument in favor of LT for ALD.

In 1991, the US Health Care Financing Administration identified ALD as one of the seven conditions for which it approved payment for LT, but it recommended a "significant" period of abstinence before patients with alcoholism underwent the procedure, as well as the availability of a reasonable social support system. Beresford *et al*[12] proposed a selection method for identifying alcoholic patients who were suitable for LT. Furthermore, Lucey *et al*[13] reported on a multidisciplinary collaboration of transplant hepatologists, surgeons, and psychiatrists that identified psychosocial predictors of long-term sobriety and compliance after LT among patients with alcoholism.

The appropriateness of LT for ALD was confirmed in European and American centers in the early 90s, with 1-year survival rates being 66%-96%. There was increasing evidence that most ALD patients selected for LT have similar, if not better, survival rates compared to those who undergo LT for other indications (1-year survival rate of 86%)[14-18].The NIH workshop in 1996 on LT for ALD patients concluded that LT provides good outcomes for alcoholic patients and that relapse rates after LT were lower if the patients had successfully completed a conventional alcohol rehabilitation program prior to LT[7].

The European Liver Transplant Registry (ELTR)[19] accumulated information on LTs from 1968-2015 based on a progressive increase of cases. Among all the LT cases, the ELTR reported a rate of cases involving cirrhosis of 46%-55%, a rate of cases involving AC of 9%-44%, and a rate of cases involving AC + hepatitis C virus (HCV) infection of 2%-3%. In this period, viral cases increased from 8% to 27%, primary biliary cirrhosis cases decreased from 29% to 7%, and autoimmune hepatitis cases decreased from 10% to 5%[19]. There was a progressive increase in the number of indications for LT in the US after 2002, and the number of donors is much smaller than the number of patients who require LT.

Controversies

Patient selection for LT has always been a demanding responsibility for transplantation professionals. Less than 4% of AC patients were placed on an LT waiting list in the United States in 2007. In the United States, the majority of candidates with end-stage ALD who are eligible for referral for LT are not being referred. Kotlyar *et al*[20] analyzed data on alcohol abuse and dependence in the United States and found that the potential number of patients with ALD and decompensated AC who could be candidates for LT was 100000 patients/year. However, of these, only 10% (10000) were referred, and of these, 3673 were on the LT waiting list and 1200 underwent LT in 2018. Thus, every year, 4% of patients with decompensated AC were on the waiting list and 1.2% underwent LT. This pattern of referral may lead to as many as 12,000 deaths/year. There are multiple reasons for poor referral of these patients and these reasons occur at all levels[20].

LT for ALD still generates controversy because of both the perception that the patient's liver disease was self-inflicted and concerns related to relapse after LT. The general public, and even some practicing physicians outside the transplant community, view individuals with alcoholism as lower priorities for LT. Many specialists considered it unacceptable to "waste" grafts on individuals with alcoholism who were responsible for the harm caused to their liver, as they still consider alcoholism to be a bad habit, and there is a general reluctance to provide LT for these patients. Particularly in

the past, the naysayers believed that excessive alcohol consumption had multisystem organ consequences that precluded good surgery outcomes, that relapse-induced redevelopment of liver disease would occur, and that patients were unlikely to withstand the psychological issues caused by such a serious operation, resulting in poor compliance. However, neuroscience has shown that alcoholism is a chronic relapsing medical disease of the brain, and not a bad behavior. Ethical principles recommend active treatment of these patients, without discrimination[21-25].

LT provides the patients with a physiologically functioning liver and reverses the complications of end-stage liver disease, improving survival and quality of life, but it does not treat the underlying alcoholism and alcohol dependence, leading to the potential for relapse. The probability of long-term sobriety becomes robust only after 5 years of sustained abstinence[26-28].

Pre-LT alcohol abstinence represents one of the hottest and most controversial open questions on this topic. Many transplant centers use the criterion of 6 mo of abstinence to determine whether ALD patients should receive livers, known as the "6-mo rule". This rule has two purposes: to allow the patient's liver a chance to recover and to reduce the risk of alcohol consumption relapse. Six months is an arbitrary threshold and this period has never been shown to affect survival after LT, although there is a weak association between sobriety and LT outcome[29-32].

The rule was established in 1997, when the United Network for Organ Sharing (UNOS) had a meeting to discuss the criteria for placing adult ALD patients in need of a new liver on LT waiting lists. The recent guidelines of the American Association for the Study of Liver Diseases, European Association for the Study of the Liver, UNOS, and French Consensus Conference state that 6 mo of zero alcohol consumption before LT should no longer be an absolute rule or a defining factor to determine whether a patient is accepted as an LT candidate[29,33-36].

There is no firm consensus on the appropriate minimum duration of alcohol abstinence or on what constitutes good psychosocial criteria for placing patients on LT waiting lists. Physicians in the transplant community perceive selected patients with end-stage ALD as good candidates. An interval of sobriety prior to LT is very desirable from a medical point of view. Abstinence may markedly improve liver function[37].

ALD was the underlying etiology in the majority of patients who were removed from an LT waiting list following recompensation. There were only two independent predictors among ALD patients of recompensation/removal from the LT waiting list: A model for end-stage liver disease (MELD) score < 20 and serum albumin $\geqslant$ 32 g/L. The probability of recompensation was 70% when both factors were present when the patient was placed on the LT waiting list. Thus, it seems advisable for ALD patients to undergo a period of observation to check whether they have both favorable factors before embarking on living donor LT[38].

Patients with ALD were placed on an LT waiting list based on the Ohio Solid Organ Transplantation Consortium (OSOTC) exception criteria. These criteria allow patients with low to medium risk of relapse to undergo LT after only 1-3 mo of abstinence. The results showed that the LT rate and short- and long-term post-LT survival are comparable between these patients and the general population of United States patients with AC who underwent LT[39].

Considerations

Compared to the traditional criteria for assessing risk of relapse, a careful selection process with more flexibility to evaluate eligibility on a case-by-case basis can lead to similar survival rates after LT. With regard to alcoholism, a mandatory period of abstinence is a poor predictor of relapse. Pre-LT abstinence does not reliably predict post-LT abstinence or compliance[37].

When considering whether to add patients to an LT waiting list, 3 mo of alcohol abstinence may be better than 6 mo. Patients with a lack of social support, active smoking, psychotic or personality disorders, or a pattern of nonadherence should be added to the waiting list only with reservation. Those who have a diagnosis of alcohol abuse, as opposed to alcohol dependence, may make better LT candidates. Patients who have regular addiction treatment appointments with a psychiatrist or psychologist also seem to do more favorably[20].

Alcohol addiction is considered a big problem after LT, while moderate alcohol consumption is underestimated by both patients and their healthcare providers. Sometimes there is even a recommendation to carefully assess the alcohol consumption of patients on LT waiting lists who have non-AC cirrhosis[40,41].

Alcohol consumption can complicate a patient's health after LT, and moderate consumption is important because it can aggravate metabolic syndrome and non-alcoholic fatty liver disease, which often develop, irrespective of alcohol consumption, as the side effect of post-LT immunosuppressive agents. This immunosuppressive treatment can lead to a risk of de novo malignancy that is 2-7-fold higher than usual after adjusting for age and gender, and 5- and 10-year incidence rates are estimated to be 10%-14.6% and 20%-32%, respectively[42,43]. Moderate alcohol consumption can have a negative effect on LT as it increases the risk of liver fibrosis, mainly in women, even if alcohol consumption is < 12 g/d[40-43].

Medical law experts are repeatedly reminded, albeit from a different point of view than those associated with medical practice, that US constitutional law prohibits discrimination against subgroups and differentiating individuals as being either worthy or unworthy of life. The exclusion of non-sober ALD patients from LT waiting lists discriminates against them and violates this United States constitutional law[44].

The fact that patients with acute liver failure after ecstasy consumption and patients with acute hepatitis

B virus (HBV) infections due to careless sexual practices have full access to LT waiting lists raises the question as to why patients with severe acute AH or acute-on-chronic liver failure should be treated any differently[44]. The lack of pre-LT abstinence should not be considered as a justification for denying the legal right of patients with advanced ALD to have access to LT waiting lists[45]. The sidelining of patients with severe AC who, after complete evaluation, are otherwise considered to be candidates for LT must be avoided[46]. There are no moral or ethical arguments that could justify the exclusion of very ill patients with ALD from potentially lifesaving LT, as exclusion could be considered a death sentence for these patients[20,47].

ALD diagnoses are often made in the later stages of the disease because patients often remain in primary care for a long time, managing their alcoholism, and ALD diagnosis only occurs when hepatic manifestations belatedly raise clinical suspicion. Poor patient awareness, misinformation among the referring clinicians, delayed alcohol cessation intervention and counseling, premature and overconfident attribution of liver disease to another etiology (*e.g.*, HBV or HCV) are just some of the factors that limit effective management of AC[48,49].

In the end, alcoholism has to be accepted as a disease that, in some cases, has a genetic background[50]. As alcoholism is a life-long disease, it is to be expected that it should persist after LT[51].

LT FOR ALD

ALD is a worldwide health problem, resulting in high morbidity and mortality, not only due to the effects of alcohol on the liver, but because of the risk it poses to the health of other organs and the increased risk of accidents and violence-related deaths[52]. One type of ALD is AC, which is a leading indication for LT in the Unites States and Europe, accounting for approximately 15% and 20% of LT cases, respectively[53-55]. A recent analysis of three US databases (the National Health and Nutrition Examination Survey, HealthCore, and UNOS) showed that the proportion of patients on the LT waiting list or the proportion who have undergone LT due to cirrhosis secondary to HCV infection is declining, while the proportion on the list or who have undergone LT due to non-alcoholic fatty liver disease or ALD is increasing[56,57]. These findings are probably due to the advent of highly effective and well-tolerated treatments for HCV infection, which, up until now, was the main indication for LT[52].

PRE-LT EVALUATION OF PATIENTS WITH ALD

Comorbidities

In general, the indications and contraindications for LT in patients with AC are the same as those for patients with cirrhosis of any etiology[52]. There are, however, specific factors that should be addressed when evaluating AC patients for LT, given that they have a high prevalence of multisystemic alcohol-related changes. These comorbidities can be neurological (dementia, peripheral neuropathy, and vertigo), cardiological (cardiomyopathy, hypertension, and chronic renal disease), hematological (chronic anemia), gastrointestinal (chronic pancreatitis, diarrhea, and malnutrition), musculoskeletal (sarcopenia and osteoporosis), or psychiatric (including tobacco and illicit substance use)[57-61]. For example, malnutrition is present in about two-thirds of patients with cirrhosis on the LT waiting lists and negatively impacts survival, quality of life, and the patient's ability to cope with surgery or infections. When alcohol is an etiologic factor underlying cirrhosis, the prevalence of malnutrition is higher[62,63]. The incidence of comorbidities in AC has recently been reviewed, and a high comorbidity rate was found [hazard ratio (HR) for any comorbidity: 3.74; 95%CI: 3.56-3.94], including for non-cancer comorbidities (HR for any non-cancer comorbidity: 4.33; 95%CI: 4.06-4.62), but with the exception of acute myocardial infarction. The presence of these comorbidities must be carefully evaluated before LT, as they may negatively impact LT outcomes[57,64].

Alcohol consumption progresses over the years, and alcohol and its metabolites are toxic *per se*. However, there are other mechanisms of action regarding the negative health effects of alcohol consumption. By increasing gut permeability and exposing Kupffer cells to Gram-negative intestinal bacteria, alcohol induces cytokine production and a systemic inflammatory response[65].

An additional challenge of LT for AC is the need for lifelong post-LT follow-up, taking into consideration the comorbidities that may not be fully resolved or may return (along with alcohol consumption relapse) in the post-LT period. It is not surprising that cardiovascular illnesses and de novo malignancies are significantly overrepresented in AC patients who underwent LT[53]. With the recent advances in hepatitis C treatment and lack of HCV-related LTs, long-term follow-up of LT recipients will often entail more challenging circumstances involving patients who underwent LT for non-alcoholic steatohepatitis or ALD.

Neurological comorbidities

Chronic heavy intake of alcohol is a well-established cause of brain atrophy and dementia[54]. Patients may present with mild-to-moderate short- or long-term memory issues or more severe manifestations. There may be deficits in attention, concentration, learning, abstract reasoning, and motor skills. Hepatic encephalopathy can prevent a proper neurological evaluation of alcohol-induced brain damage prior to LT. These clinical manifestations may or may not be fully reversible after alcohol cessation. After LT, neurological improvement in AC patients with encephalopathy is not as good as for patients with cirrhosis of a different etiology[37].

Wernicke's encephalopathy is an alcohol-related syndrome characterized by ataxia, ophthalmoplegia, and

confusion, often with associated nystagmus, peripheral neuropathy, cerebellar signs, and hypotension. There is impaired short-term memory loss and emotional lability. Wernicke-Korsakoff's syndrome can develop after Wernicke's encephalopathy, characterized by anterograde and retrograde amnesia and confabulation. Wernicke-Korsakoff's syndrome is caused by a chronic thiamine deficiency, resulting in damage to the thalamic nuclei, mammillary bodies, brainstem, and cerebellar structures.

Alcohol can cause a polyneuropathy that can involve paresthesia, numbness, weakness, and chronic pain. Other neurologic conditions associated with chronic alcohol consumption are headache (cluster and migraine), neurocardiogenic (vasovagal and vasodepressor) syncope, compromised olfactory function, sleep disturbances, and peripheral vertigo. A small proportion of patients (< 1%) may develop midline cerebellar degeneration with ataxia. Seizures occur frequently upon alcohol withdrawal[66].

Cardiovascular comorbidities

The most common complications of ALD are cardiomyopathy, hypertension, and supraventricular arrhythmias. Alcoholic cardiomyopathy is the most common type of non-ischemic cardiomyopathy in Western countries (approximately 45% of cases). When being evaluated for surgery, many patients with ALD are found to have asymptomatic cardiac involvement, and are at risk of adverse short- and long-term outcomes. These findings may be confused with the findings associated with cirrhotic cardiomyopathy[53]. The clinical manifestations of ALD are similar to other causes of cardiac failure.

Abstinence can result in improvement in some cases. There are findings of beneficial cardiovascular effects with moderate alcohol consumption, but, when alcohol consumption is excessive, it results in hypertension. It has been shown that reducing alcohol dose-dependently decreases blood pressure, especially in heavy drinkers, and hypertension disappears with ⩽ 2 doses/d[37]. Chronic alcoholism is associated with a higher risk of cardiovascular mortality due to its epidemiological associations with known risk factors (smoking, age > 50 years, dyslipidemia, obesity, and hypertension).

The most common arrhythmias related to alcohol consumption are atrial fibrillation and supraventricular tachycardia, which commonly occur during acute intoxication and withdrawal. Cardiomyopathy can also induce ventricular arrhythmias.

Gastrointestinal comorbidities

Acute and chronic alcohol consumption cause mucosal inflammation, impairment of gut motility, sphincteric dysfunction, increased acid output, and damage to the small intestinal mucosa; these issues can occur directly due to a toxic effect or indirectly due to bacterial overgrowth and an impaired immune response[67].

Disregarding cirrhosis-related varices, Mallory-Weiss tears are a major cause of gastrointestinal bleeding, and a history of alcohol use can be found in > 40% of cases[68]. Diffuse esophageal spasm is also more frequent in individuals with alcoholism.

Alcoholic gastropathy (submucosal hemorrhages) typically involves abdominal pain, nausea, and vomiting.

Alcoholism accounts for about one-third of all cases of pancreatitis. The risk of pancreatitis in patients with alcohol dependence is approximately 4-fold higher than that in the general population, and it increases according to dose. Chronic pancreatitis develops in 10% of alcohol addicts after 6-12 years of 80 g daily alcohol intake[69]. Individuals with recurrent acute episodes of pancreatitis may develop chronic pancreatitis that can aggravate malnutrition.

Hematopoietic system comorbidities

The anemia that is commonly seen in patients with chronic alcohol problems can be multifactorial. Blood loss can cause anemia due to iron deficiency, which can occur due to the gastrointestinal diseases mentioned above. Dietary folate deficiency can cause megaloblastic anemia. Alcohol also has a direct toxic effect on the bone marrow, which can lead to sideroblastic anemia that resolves after abstinence. Alcohol also suppresses megakaryocyte production causing thrombocytopenia, which rapidly resolves about a week after cessation of alcohol intake. Lastly, alcohol interferes with platelet and white blood cell function, increasing the risks of bleeding and particular infections[66].

Malignancies

Previous alcohol abuse was shown to be associated with a 3-fold increased risk of post-LT *de novo* tumors. The mean duration until diagnosis has been reported to range between 3 and 5 years after LT[37]. Chronic alcohol use increases the risk of head and neck cancer, squamous cell carcinoma of the esophagus, and breast, prostate, pancreas, cervix, lung, and colon cancer. The risk is further potentiated by concomitant smoking and remains elevated despite alcohol abstinence, so screening should be considered after LT[66].

Infectious diseases

It has been demonstrated that both chronic alcohol consumption and moderate acute drinking can modulate the function of cells of the innate immune system, such as monocytes, macrophages, and dendritic cells. Alcohol is associated with increased intestinal permeability to endotoxins, altered proportions of monocyte population subsets, and altered cytokine profiles. These changes subside after 14 d of abstinence[70]. Alcoholism is associated with increased frequency and severity of infections, such as epidural abscesses, tuberculosis, meningitis, pneumonia, tick-borne fever, and others.

Psychiatric comorbidities

Psychiatric illnesses are commonly associated with alcoholism. The psychiatric and social issues associated with alcoholism can be more severe than the direct

medical effects. Anxiety and other mood disorders are found in at least a third of patients with alcoholism and multiple drug use is also prevalent. This is considered to be a bidirectional relationship. Alcohol may be used as a "medication" to relieve symptoms and, on the other hand, chronic use may lead to the development and/or worsening of these symptoms, either by compromising social skills or through the direct effect of alcohol on the brain[71]. Alcohol-related behavioral issues can cause other health issues, including domestic abuse injuries, other violence-related trauma, motor vehicle accidents, and burns.

Other diseases

There are many other conditions associated with alcohol consumption, including rhabdomyolysis, osteonecrosis (avascular necrosis), IgA nephropathy, and porphyria cutanea tarda.

ALD, HCC, AND SURVEILLANCE

In AC patients, mainly in those who were drinking > 80 g of alcohol daily, there was a positive association between the amount of alcohol intake and the risk of HCC (HR: 4.5), and this increased by 22% for those who drank 6 alcoholic units/day. In countries where there is heavy alcohol consumption, the cumulative risk of HCC is increased by 5-7-fold[72-74]. Several recent studies have established that the underlying etiology of liver disease determines the cumulative risk of HCC, and patients with viral, fatty liver, or autoimmune cirrhosis have a higher risk than those with AC[75-77].

The HCC surveillance recommendations for AC patients are similar to those for other cirrhotic patients (*i.e.*, periodic 6-mo ultrasound screening), with no specific recommendations. In alcoholic patients, the risk factors are age, metabolic syndrome, and the severity of the underlying liver disease[78]. In a surveillance study of 450 AC patients [Child-Turcotte-Pugh (CTP) classes A and B], Mancebo *et al*[79] found that 62 patients developed HCC, with an annual incidence of 2.6%. The risk was independently associated with age (> 55 years) and platelet count (< 125000/mm^3). The annual incidence was 0.3% in patients without risk factors, 2.6% in patients with one risk factor, and 4.8% in patients with two risk factors (P < 0.0001). Genomic analysis of alcohol-related HCC has demonstrated the presence of mutations in genes that modulate the HCC pathway, which helps to better define the risk classes and to adapt strategies for HCC surveillance.

NUTRITIONAL EVALUATION IN ALD

Poor nutritional status in patients with liver diseases is common, occurring in 20%-90% of cases. The main outcome is loss of muscle mass and fat, which is associated with the etiology of liver disease[80-83]. In ALD, there is marked loss of weight and muscle mass, with deficiencies of macronutrients and micronutrients, which can adversely affect the body composition of AC patients[84,85].

High daily alcohol intake can end up ensuring caloric maintenance, despite the fact that excessive alcohol consumption can inhibit hunger and compromise the palate, stimulating the search for ultra-processed foods, which also compromise the body composition of this population[86].

The change in muscle mass in quantity and/or function characterizes a clinical condition called sarcopenia. In some cases, no weight loss is observed. However, a discrepancy between the percentages of lean and fat mass may occur, which determines the diagnosis of sarcopenic obesity[86]. In sarcopenic obesity, there are mitochondrial and bioenergetic dysfunctions. The neurological consequences of alcohol that generate fatigue and asthenia make it difficult to determine whether changes in the skeletal muscles are the direct effects of ethanol and/or ALD.

After LT, some of the complications of cirrhosis disappear, but this does not occur easily with sarcopenia; on the contrary, the complications may be aggravated by the use of post-LT immunosuppressants[87,88]. Clinical improvement is not directly proportional to muscle function and muscle turnover but, in ALD, sarcopenia worsens the prognosis. The mechanisms involved are still unclear[89].

Nutritional assessment in patients with liver diseases has limitations due to difficulties with reproducibility and the lack of a gold standard. The current most accurate assessment involves the use of several methods that may be complementary[90]. The classic anthropometric assessment involving the assessment of body mass index (BMI), arm circumference, arm muscle circumference (BMC), and tricipital skinfold is a low-cost, universally used nutritional assessment. However, it has poor reproducibility (regarding inter- and intra-observer assessment) and it does not accurately measure muscle and fat mass in cases of cirrhosis involving ascites and edema[91].

The Subjective Global Assessment (SGA) is a low-cost, easy to apply method. However, it has flaws in implementation. It is based on body weight and subjective assessment and involves data that are self-reported by the participant (or guardian), with no accurate quantification of muscle mass[92-96]. The Patient-Generated Subjective Global Assessment (PG-SGA) is being used routinely, with early nutritional risk being identified more accurately, taking into account the disease staging and the patient's drug regimen; however, this method has only been validated for cancer patients[97].

The determination of the function of cirrhotic muscle mass using dynamometry is low cost and reproducible. However, it may not reflect the patient's actual nutritional status, especially in ALD patients, as it is based on the principle of muscular contractility and the use of alcohol

(depending on the amount of alcohol and duration of abstinence) may compromise these results. In AC patients with encephalopathy, it is not possible to apply this method because it is based on the principle of hand-grip strength[90,97-99].

Methods for quantifying lean mass, such as bioelectrical impedance analysis (BIA), dual energy X-ray absorptiometry (DEXA), and impedance plethysmography, are reproducible and objective. However, BIA and plethysmography may be inaccurate in cases of "body asymmetry" (*e.g.*, involving ascites and edema) and DEXA is a potential radiation-related risk factor (especially if it is routinely used) and is expensive, making it difficult to use in clinical practice[100-102].

Imaging methods, such as computed tomography (CT) and magnetic resonance imaging (MRI), can be used to quantify skeletal muscle mass, but they are high-cost methods[103,104]. The skeletal muscle area determined from a single CT or MRI section involving the third or fourth lumbar vertebra has been shown to reflect the muscle mass of the entire body[103]. Using these methods, patients with cirrhosis have lower muscle and fat mass compared to controls[87,105]. AC patients have been included in several studies but etiology-specific data have not yet been reported. Ultrasound assessments of lean muscle mass exhibit variability across observers, and analyzing body portions only provides an estimate of whole-body measurements and does not allow assessment of muscle functionality[87,104,105].

The above-mentioned methods all have limitations because they are based on the body composition model, valuing only lean muscle and fat mass. In 2000, Ellis proposed the use of a cellular composite multicompartment model of body composition[106]. This evaluates cellular functionality and can aid in an objective, reproducible, and serial way in the determination of cellular composition and functionality based on the use of the BIA phase angle (PA). PA is based on measurement of electrical resistance (R) and reactance (Xc) and it reflects the structure and functionality of the cell membrane[107].

Studies involving different populations have identified PA cutoff points that differentiate the pathophysiology in question from a lack of the pathophysiological condition. ALD patients have different cellular characteristics than patients with other conditions. This is because ethanol induces autophagic mechanisms (adaptive cellular responses to eliminate damaged organelles) and the production of cytotoxic cellular proteins (due to changes in homeostasis, protein synthesis, and autophagic proteolysis) that result in the loss of skeletal muscle[108]. Factors that contribute to cellular damage in ALD patients include hyperammonemia (due to cirrhosis), endocrine abnormalities (such as hypogonadism), and intestinal dysbiosis.

PA assessment of cirrhosis prognosis has a sensitivity of 68.9% and a specificity of 70.0%, indicating that it is a good prognostic marker. Assessing PA to investigate different cirrhosis stages is useful, as a lower PA indicates a worse disease stage[90,109-112]. In the follow-up of pre- and post-LT patients, Deutrich *et al*[113] observed that changes in PA were the only measurable changes that correlated with the improvement in the clinical condition. Two studies evaluating cirrhotic patients identified the same cutoff point for PA (5.4°), where those who were below this value had a poor prognosis[90,114]. Recently, a pilot study of cirrhotic patients identified a cutoff of 4.9°[115], which is different from the previous study findings. This demonstrates the need for cohort studies with greater robustness in order to determine a reliable cutoff point that can indicate the prognosis/clinical condition of cirrhotic patients.

For Baumgartner *et al*[116], the PA is an indicator for the diagnosis of metabolic, physiological, nutritional, and hydration disorders that could be applied to any living creature. In an experimental study of rats with carbon tetrachloride (CCl_4)-induced cirrhosis, PA was determined before and after induction of cirrhosis, being reduced in cirrhotic animals. It was also observed that a decrease in fatty acids (FA) accompanied the worsening of the cirrhosis, measured by cellular damage using the thiobarbituric acid reactive substances (TBARS) technique, compared to controls[117].

In different liver diseases, PA can provide different relevant information. For example, in chronically infected HCV patients, PA is a good predictor of advanced fibrosis; each degree of decrease in FA increases the risk of advanced fibrosis 4-fold. In HCV patients undergoing antiviral treatment, the reduction in PA is associated with an increase in the adverse effects of the therapy[118,119].

PA also serves as a basis for bioelectrical impedance vector analysis (BIVA), a slightly more complex evaluation, which provides information on the body composition (cellularity) and cell hydration state, independently of the alteration in body composition. BIVA is of great importance in cases of edema and ascites that make identifying nutritional compromise difficult[120,121].

There have been no studies of PA and/or BIVA in patients with ALD alone. There is a need to develop this research area further to understand cellular functioning in ALD patients in order to develop preventive and curative strategies regarding nutritional and other clinical issues, improving quality of life and post-LT outcomes.

FUNCTIONAL LIMITATIONS IN CIRRHOTIC PATIENTS

Cirrhosis leads to systemic and metabolic alterations that compromise pulmonary, renal, encephalic, cardiac, and metabolic functions, and complications such as ascites, encephalopathy, jaundice, and sarcopenia, which increase morbidity and mortality and compromise quality of life[122,123].

Metabolic changes associated with cirrhotic malnutrition are frequent, negatively affect the musculoskeletal system, and directly interfere with physical fitness[124,125]. The deficiency in protein synthesis leads to persistent cachexia, which limits the physiological integrity of the

Table 1 Liver transplantation survival rates reported by the European Liver Transplant Registry

n	Etiology	1 yr	5 yr	10 yr
		%		
15019	AC	86	73	59
1790	AC + HCV	85	69	54
6507	Acute liver failure	70	64	58
10753	HCV	80	65	53
4187	HBV	83	74	68
9122	Cirrhosis + HCC	83	62	49
9114	Cholestasis	87	78	70
1892	AIH	85	76	67
468	Hemochromatosis	76	66	53

AC: Alcoholic cirrhosis; HCV: Hepatitis C virus; HBV: Hepatitis B virus; HCC: Hepatocellular carcinoma; AIH: Autoimmune hepatitis.

muscular system and impairs its functioning, with loss of muscle strength and worsening of quality of life. Protein filaments of actin and myosin undergo adaptive processes and lose their contractile components, with muscular hypotrophy. Concomitantly, there is a change in lipid metabolism that influences the biochemical composition of lipoproteins. In cirrhotic patients, there is insufficient glycogen due to limitations in hepatic synthesis, which increases the use of amino acids as an energy source and causes an acceleration in the decomposition of skeletal muscle to release amino acids, which results in a loss of muscle mass. These changes limit muscle functioning and negatively affect the performance of daily activities[126].

A possible explanation for the reduction in function may be related to the loss of muscle mass in this population, but it may also be due to a decrease in the mitochondrial oxidative capacity and/or number of mitochondria in the muscle tissue. The adenosine triphosphate (ATP), phosphocreatine, and total magnesium (Mg^{2+}) levels are decreased in cirrhotic skeletal muscle. This concept was demonstrated by Jacobsen *et al*[127], who found higher rates of mRNA and mitochondrial ATP in patients with CTP cirrhosis compared to those with CTP-B and CTP-C scores (Table 1).

Sarcopenia is associated with age, but it is also present in chronic neoplastic diseases and leads to a decrease in functional capacity and an increased risk of mortality[128]. Severe muscle depletion or sarcopenia is defined as a decrease in muscle mass, strength, and function. Sarcopenic dysfunctions are predictors of morbidity and mortality in cirrhotic patients[129].

Abdominal cross-sectional studies [involving lumbar segments 3 and 4 (L3-L4)], including those that involve CT or MRI, represent the gold standard for quantifying skeletal muscle mass. They involve detailed objective assessment for the identification of sarcopenia and assist in improving the nutritional/metabolic outcomes of patients with cirrhosis[130]. Muscle tissue loss may be an important factor for muscle dysfunction and worsening of quality of life. However, it is necessary to specifically measure muscle dysfunction with precise methods, such as isokinetic dynamometry, palmar grip dynamometry, and manovacuometry (which measures respiratory muscle strength)[131].

Montano-Loza *et al*[130], using measurements based on abdominal L3-L4 CT images, evaluated the impact of sarcopenia on cirrhosis in patients on a waiting list for LT. They found a 6-mo survival rate of 71% in sarcopenic patients and 90% in non-sarcopenic patients. The frequency of sepsis and death was significantly higher in the sarcopenic patients[130].

Regarding functional evaluation, the 6-min walk test (6MWT) is an accessible, easy, cheap, and reproducible assessment. In cirrhotic patients, 6MWT performance < 400 m is an independent predictor of mortality. Based on a receiver operating characteristic (ROC) curve analysis, 6MWT had a greater sensitivity and specificity for mortality compared to maximal oxygen consumption and respiratory muscle strength[132].

The muscular dysfunctions in patients with cirrhosis may be influenced by the etiology of the disease. Patients with AC may present with alcoholic myopathy. Galant *et al*[133] showed that AC patients had lower muscle strength and poorer 6MWT performance and quality of life compared to cirrhosis patients with HBV or HCV. Physical fitness is a marker of mortality due to cirrhosis in AC patients, with patients with a peak oxygen uptake (VO_2) < 14 mL/kg having a lower survival rate over 3 years compared to those with superior results.

A multidisciplinary intervention for muscular recovery in patients with cirrhosis, involving nutritional supplementation and supervised physical activity, led to a gain in muscular mass and improvement in functional activity, directly impacting quality of life and preparation for LT (Figure 1)[134].

MANAGEMENT OF ALCOHOL ADDICTION BEFORE LT

The patient's history of alcohol and other substance use, such as tobacco, opioids and illicit/recreational drugs must be thoroughly evaluated[52]. Psychiatrists, psychologists, social workers and dependency specialists are essential in the evaluation of these patients. The information collected will help the multidisciplinary team to determine whether a transplant should be performed in these patients, as well as to establish a therapeutic plan before and after the procedure[52,135,136]. There is evidence that the work of such teams in transplant centers reduces the rates of recurring alcoholism and mortality after LT compared to patients referred for outpatient treatment[55,60]. Simple standardized questionnaires, such as CAGE and Alcohol Use Disorders Identification Test (AUDIT), can be used in clinical practice to track the chronic and excessive use of alcohol in transplant patients, including those with cirrhosis of other etiologies[52,137,138]. An additional tool for the psychosocial assessment of transplant candidates is the Stanford Integrated Psychosocial Assessment for Transplantation. Its strengths include standardization

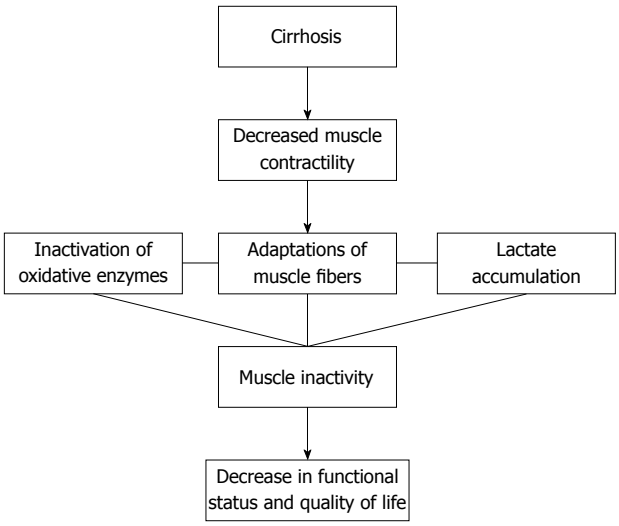

Figure 1 Flow chart demonstrating the consequences of cirrhosis regarding muscular adaptation and functional repercussions[134].

of the evaluation process and the ability to identify individuals at risk of negative psychosocial events after transplantation in order to develop interventions aimed at improving the patient's pre-LT conditions. This instrument also allows evaluation of the psychosocial factors that best predict patient compliance and graft survival. Eighteen risk factors are divided into four domains, including patient readiness, social support, psychological stability and substance use. Based on an index composed of all the domains, patients are classified as excellent, good, minimally acceptable, high risk or poor transplant candidates[52,139].

A constant concern of health professionals is the patient's possible return to alcohol use after LT or the relapse of an ALD patient before transplantation[40]. To date, however, no standardized definition of recurrence has been formulated. Consequently, the rates found in the literature vary widely, due both to the different definitions of the term and different follow-up times. A 2015 review[17] indicated rates from 3% (ingestion > 60 g/d) to 43.70% (any consumption). It seems important, then, to distinguish between patients who occasionally drink small amounts of alcohol from those who regularly drink moderate amounts from those who continuously drink large amounts. Thus, recurrence can be distinguished from alcoholism[136]. Nevertheless, it requires emphasis that patients who underwent LT for ALD are obligated to stay abstinent. Unfortunately, this is an extremely difficult goal to achieve consistently.

Predictive factors of recurrence

In 1997, an American consensus suggested that patients with AC should have a minimum abstinence period of 6 mo before being included on the LT waiting list, the so-called "6-mo rule." The rationale of this recommendation was to evaluate the improvement of liver function, commonly observed after three to 6 mo of sobriety[140,141]. This abstinence period also serves as a predictor of post-transplant recurrence. As a result, major guidelines recommend this rule[55,135]. The logic is that the longer the period of sobriety, the lower the risk of returning to alcohol use. However, rules based on specific sobriety times, particularly those of short duration, are not consistent with what is known about the evolution of alcohol use disorder or predictions of future abstinence[142,143]. Although each month of sobriety increases the likelihood that the patient will not resume drinking, patients abstinent for 6 mo have only a slightly better risk reduction than those with 4 or 5 mo of sobriety[60]. Therefore, rigid adherence to the "6-mo rule" could result in unnecessary delays in listing patients who would otherwise be good candidates for transplantation, especially if we consider that this abstinence period is a weak predictor of post-transplant alcohol consumption[52]. For this reason, other predictors of recurrence after LT should be identified besides a specific period of sobriety. A 2015 review[21] highlighted an association between the following factors and recurrence: psychiatric co-morbidity, poor social support, multiple treatment failures, illicit drug use, a family history of alcoholism, medical non-compliance and the continued use of alcohol despite its consequences. It is up to the multidisciplinary team to investigate the presence of these factors and, if appropriate, adopt the best strategies for circumventing them. However, other factors suggest a lower risk of recurrence, such as: the patient's recognition that alcoholism is a disease, family support, employment, having a permanent residence, the ability to perform activities that replace daily drinking, and participation in rehabilitation programs[21,52].

LT SURGICAL ISSUES IN ALD

At present, there is no evidence for the association between ALD and increased incidence of portal vein or arterial thrombosis pre- or post-LT. The type of LT technique used is based on the experience of the transplant center, and there are no recommendations based on cirrhosis etiology. The techniques include the piggyback technique (preservation of the vena cava with lateral-lateral cava-cava anastomosis or suprahepatic cava-hepatic veins terminal-terminal anastomosis) and conventional vena cava-cava terminal-terminal anastomosis (without preservation of the recipient's vena cava).

NEED FOR SURGERY AFTER LT

Causal associations have been established between alcohol consumption and cancers of the oral cavity, pharynx, larynx, esophagus, liver, colon, rectum, and, in women, breast; associations are also suspected for cancers of the pancreas and lung[26,37,136,144,145]. Evidence suggests that the effect of alcohol is modulated by polymorphisms in genes encoding enzymes for ethanol metabolism, folate metabolism, and DNA repair. The mechanisms by which alcohol consumption exerts a

carcinogenic effect have not been completely defined[145].

The higher risk of malignancies for patients with AC should be considered in the routine assessment of these patients[37]. Surveillance protocols for earlier detection of *de novo* malignancy are needed to improve long-term post-LT outcomes[144]. Appropriate surgical treatment is the best option for curing solid organ malignant neoplasms, such as skin, esophageal, lung, digestive, or head and neck cancer. Proper resection of these lesions can contribute to increased survival when the disease is diagnosed in the early stages. Radiotherapy, chemotherapy, or immunotherapy are indicated for palliative care in the advanced stages of each specific neoplastic disease.

ACUTE AH

Background

AH is a distinct severe form of steatohepatitis that occurs in patients with alcoholism. It can present as acute or chronic liver failure associated with a rapid decline in liver synthetic function, and a consequent increase in mortality[146,147]. The mortality rate in patients with severe AH is 30%-50% at 3 mo, often despite supportive medical care. The amount of alcohol intake that puts an individual at risk of AH is not known, but generally, most AH patients have a history of heavy alcohol use (> 100 g/d) for decades[35,146-149].

The pathogenic pathways that lead to the development of AH are complex and involve oxidative stress, gut dysbiosis, and dysregulation of the innate and adaptive immune system, with injury to parenchymal cells and activation of hepatic stellate cells[146].

Incidence

The annual incidence of AH remains largely unknown. Concerning its prevalence, a large study of systematic biopsies in 1604 alcoholic patients, symptomatic or not, showed the prevalence of AH to be 20%[149]. In symptomatic patients, including those with decompensated liver disease, the prevalence of AH is not well known, partly because most centers rely on clinical criteria and do not consider transjugular liver biopsy as a routine practice in the management of patients with decompensated ALD[35].

History

Patients with AH are often aged 40-50 years, with most patients presenting before the age of 60 years. Patients with AH typically have a history of daily heavy alcohol use (> 100 g/d) for > 20 years[150].

Clinical features and diagnosis

The characteristic clinical features of AH are malaise, anorexia, fever, jaundice, tender hepatomegaly, signs of malnutrition, and complications such as ascites or variceal bleeding[146,151]. Progressive jaundice is the main presenting feature of symptomatic cases. Patients with severe AH and/or underlying AC may exhibit signs of hepatic encephalopathy, may develop hepatorenal syndrome, and are prone to developing bacterial infections[147]. Serum aminotransferases are moderately elevated (typically < 300 IU/L and rarely > 500 IU/L), with aspartate transaminase (AST) > alanine transaminase (ALT) and often > 2:1, which is rarely seen in other forms of liver disease[152-154]. Patients with AH typically have elevated serum bilirubin and γ-glutamyltransferase (GGT) and leukocytosis with a predominance of neutrophils. Depending upon the severity, serum albumin may be decreased, and the international normalized ratio (INR) may be elevated[35].

Imaging tests and liver biopsy

Abdominal imaging (ultrasound, CT, and MRI scans) in patients with AH may suggest fatty changes in the liver, evidence of underlying AC, or ascites. Transjugular liver biopsy is recommended, as about 30% of patients diagnosed with AH can be misdiagnosed when the diagnosis is based only on clinical parameters[155]. Histologic findings in liver biopsies from patients with AH include steatosis (typically micro- or macrovesicular steatosis, but in some cases alcoholic foamy degeneration is seen); hepatocellular ballooning with cytoplasmic rarefaction, Mallory-Denk bodies; neutrophil or lymphocyte infiltration; cholestasis and bile duct proliferation; and fibrosis with a perivenular, perisinusoidal, and/or pericellular distribution[156,157].

Determining disease severity

Several models have been proposed to determine the severity of AH and predict early death 1-2 mo after hospitalization[35]. The Maddrey discriminant function (DF) and the MELD score are the most commonly used scores to help identify patients who are more likely to benefit from pharmacotherapy. Other validated scores include the Glasgow Alcoholic Hepatitis score, ABIC score (which includes Age, serum Bilirubin, International Normalized Ratio, and serum Creatinine), and Lille score (which is used to determine whether a patient is responding to treatment)[35,158,159].

Maddrey DF: The Maddrey DF (also known as the Maddrey score) was the first score to be developed and remains the most widely used. It is calculated as follows[160,161]:

DF = {4.6 × [prothrombin time (s) - control prothrombin time (s)]} + [serum bilirubin (mg/dL)]

In the absence of treatment, the 1-mo spontaneous survival of patients with a DF ⩾ 32 has fluctuated between 50% and 65%[162,163]. Those with lower scores have low short-term mortality rates and do not appear to benefit from glucocorticoids[164].

MELD score: The MELD score is a statistical model developed to predict survival in patients with cirrhosis that has also been used to predict mortality in patients

hospitalized for AH[165,166]. The score ranges from 6 to 40 and is based on serum bilirubin, creatinine, and INR.

In one report, a MELD score > 11 performed as well as the DF in predicting 30-d mortality[165]. The sensitivity and specificity of MELD for predicting 30-d mortality was 86% and 81%, respectively, and 86% and 48%, respectively, for the DF. In a second study, a MELD score ⩾ 21 had a sensitivity of 75% and a specificity of 75% for predicting 90-day mortality[167]. In addition, an increase in the MELD score ⩾ 2 points in the first week of hospitalization may independently predict in-hospital mortality[166].

Lille score: The Lille score is a method to determine whether patients with AH are responding to glucocorticoid therapy. It combines six variables: age, renal insufficiency (creatinine > 1.3 mg/dL or creatinine clearance < 40 mL/min), albumin, prothrombin time, bilirubin, and change in bilirubin at day 7 (bilirubin at day 7 - bilirubin at day 0)[165]. The Lille model guides treatment decisions, with a score > 0.45 suggesting that a patient is not responding to glucocorticoids and predicting a mortality rate of 75% at 6 mo[158]. Based on the Lille score, corticosteroid treatment can be stopped in those with no improvement after a week of therapy[168].

General management

Patients with AH require general supportive care, including support for alcohol abstinence, prevention and treatment of alcohol withdrawal symptoms, fluid management, nutritional support (enteral feeding is preferred over intravenous nutrition), correction of nutritional deficiencies, infection surveillance, prophylaxis against gastric mucosal bleeding, and discontinuation of nonselective beta blockers in patients with severe AH (in addition, beta blockers, if indicated, should not be started in patients with AH until after they have recovered)[164,168,169].

Infections are frequent and difficult to diagnose in AH patients as they often fulfil the criteria for systemic inflammatory response syndrome (SIRS) at admission, which reflects either the inflammatory state associated with the AH episode or an ongoing bacterial infection. Systematic body fluid sampling and close clinical monitoring are advised for early detection of infection. In the absence of scientific evidence, criteria for initiating empirical antibiotic administration, although widely used, remain debated. In patients with severe AH, infection screening at admission is particularly warranted because a quarter of them have infections at admission[170].

Mild to moderate AH

Patients with mild to moderate AH (Maddrey DF < 32) and without corticosteroid treatment have only a 10% mortality rate at 28 d. Supportive management is therefore adequate for such patients[171]. The mainstay of treatment for patients with mild to moderate AH is abstinence from alcohol. In addition, general supportive care (*e.g.*, nutritional support and hydration) should be provided, but pharmacological treatment with glucocorticoids is not recommended as it does not appear to be beneficial in patients with mild to moderate AH. Pentoxifylline has only been studied in patients with severe AH and not in patients with mild to moderate AH[164].

Severe AH

In addition to general supportive care, pharmacological treatment is indicated for patients with severe HA (Maddrey DF ⩾ 32). Most guidelines recommend treating patients with severe AH with prednisolone at 40 mg/d for 4 wk (then tapering the dose over 2-4 wk, or stopping prednisolone treatment, depending on the clinical situation), provided there are no contraindications for its use (*e.g.*, active bacterial or fungal infection or chronic hepatitis C or B)[35,172]. Steroids have a potent immunosuppressant effect, suppressing two pro-inflammatory transcription factors: nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and activator protein 1 (AP-1). This results in lower levels of tumor necrosis factor (TNF)-α and interleukin (IL)-8. In a randomized trial [STeroids Or Pentoxifylline for Alcoholic Hepatitis (STOPAH)] involving 1103 patients with severe AH, prednisolone showed a trend toward improving survival (odds ratio: 0.72; 95%CI: 0.52-1.01)[173].

Pentoxifylline is an oral phosphodiesterase inhibitor that also inhibits the production of TNFα, which is increased in patients with AH, among other cytokines. The role of pentoxifylline in the treatment of AH remains uncertain because questions remain regarding its efficacy[173-175]. Pentoxifylline may be an alternative in patients who are at risk of sepsis or failing to follow up after discharge (thereby making tapering off prednisolone unlikely, which could result in serious adverse effects). Pentoxifylline is given as a 400 mg dose three times/day (or 400 mg once/day in patients with a creatinine clearance < 30 mL/min)[164]. The largest meta-analysis published on this topic supports the observation that pentoxifylline decreases the risk of acute kidney injury and suggests that pentoxifylline improves the mortality rate compared with placebo but not compared to glucocorticoids[174]. The American Association for the Study of Liver Diseases and the European Association for the Study of the Liver recommend pentoxifylline for patients who cannot receive glucocorticoids[35,172].

A multicenter randomized placebo-controlled trial of prednisolone, pentoxifylline, and combination therapy has been completed. It showed that 4-week treatment with combination therapy compared with prednisolone alone did not improve the 6-mo survival rate[176].

Prognosis

Mortality rates among patients who do not receive pharmacological therapy (*e.g.*, prednisolone) for AH are variable. In patients with severe AH, short-term mortality rates are high (approximately 25%-45% at 1 mo)[160,177-179], whereas patients with mild to moderate

AH have lower short-term mortality rates (< 10% at 1-3 mo)[180,181]. Multiple risk factors for increased mortality in patients with AH have been identified and some have been incorporated into prognostic models. These include older age, acute kidney injury, elevated bilirubin levels, elevated INR, leukocytosis, alcohol consumption > 120 g/d, infection (sepsis, spontaneous bacterial peritonitis, pneumonia, and other infections), hepatic encephalopathy, upper gastrointestinal bleeding, bilirubin to GGT ratio of > 1, and meeting the criteria for SIRS[164].

Long-term outcomes after initial hospitalization for AH

An important determinant of the outcome among patients with AH is whether they continue to drink alcohol. In a case series involving 87 patients with AH who survived their index hospitalization, the overall estimated 5-year survival rate was 32%. However, among those who abstained from alcohol, the estimated survival rate was 75%, whereas for those who relapsed and continued to consume alcohol it was 27% and 21%, respectively[182].

LT IN AH

AH is a clinical syndrome associated with hepatic impairment and systemic inflammatory response that is observed in alcoholic patients (most of them cirrhotic). It is characterized by progressive jaundice, mild to moderate elevation of liver enzymes, coagulopathy and hepatic encephalopathy[52,155]. In its severe form, mortality is 30% to 50% at 3 mo and up to 70% at 6 mo, especially when associated with renal impairment[147,176]. Most transplant centers adopt the "6-mo rule" before listing patients with ALD. However, patients with AH that do not respond to clinical treatments cannot wait 6 mo to be placed on an LT waiting list, considering the short-term mortality rate, which can be as high as 50%[183]. Thus, the lack of salvage treatment for these patients is the basis for considering immediate LT.

In a case-control study, Mathurin *et al*[184] selected 26 severe AH patients who had a favorable psychosocial profile and did not respond to standard treatment for early transplantation. This group of patients was compared to a matched group of 26 patients with severe AH who received standard treatment. The cumulative 6-mo survival rate of early transplant recipients was dramatically higher than controls (77% *vs* 23%, $P < 0.001$). The greatest benefits were observed within the first month after transplantation and were maintained during two years of follow-up (HR: 6.08; $P = 0.004$). Recurrence was reported in 12% of the cases. Singal *et al*[185] analyzed the UNOS database and identified 59 patients between 2004-2010 who underwent LT due to an AH diagnosis. The survival of grafts and AH transplant patients was compared with matched AC LT patients. Five-year graft and patient survival of AH and AC patients were 75% and 73% ($P = 0.97$) and 80% and 78% ($P = 0.90$), respectively. At New York's Mount Sinai Hospital, 94 patients with severe AH who did not respond to medical therapy were evaluated for early LT. Overall, nine (9.6%) candidates with favorable psychosocial profiles underwent early LT, comprising 3% of all adult LT during the study period. The 6-mo survival rate was higher among those receiving early LT than matched controls (89% *vs* 11%, $P < 0.001$). Eight recipients were still alive at a median of 735 d, with one alcohol relapse[186]. Most recently, the John Hopkins Hospital group published their trial of early LT in severe AH[187]. Seventeen patients with severe AH who were transplanted early were compared with 26 AC patients with ⩾ 6 mo of abstinence who were transplanted during the same period. The 6-mo survival was 100% and 89% for AH and alcoholic liver cirrhosis patients, respectively ($P = 0.27$). Alcohol relapse was similar in both groups: 23.5% and 29.2%, respectively ($P > 0.99$). Harmful drinking was higher among AH than cirrhotic patients, despite a lack of statistical significance (23.5% *vs* 11.5%, respectively; $P = 0.42$). A systematic review of 11 studies[188] concluded that survival and recurrence rates are similar in early-transplanted severe AH patients and AC transplant patients. Thus, despite the evidence that transplantation in patients with severe AH is feasible and presents good results in a well selected subgroup of patients, there is still a long way to go before considering this type of treatment as standard for this population[189,190].

POST-LT OUTCOMES IN ALD PATIENTS

Relapse

LT can cure liver disease, but not the underlying alcohol use disorder[135]. Therefore, the transplantation team should be alert to possible alcohol consumption relapse after LT. Although self-reported alcohol use is commonly of little value, biomarkers can be a helpful replacement. For instance, metabolites of alcohol, such as ethyl glucuronide, can reveal alcohol use up to 3-4 d after the last drink[191]. However, due to its high sensitivity, it can yield false-positive results when medications that contain alcohol or hand sanitizers that contain small amounts of ethanol are used[192]. Measuring ethyl glucuronide in hair samples can detect longer-term alcohol use[193].

A prospective study[146] following 208 ALD LT patients for up to 9 years found that 113 (54%) did not relapse. Among those who did ($n = 95$), four alcohol consumption patterns were identified: 1) the majority ($n = 55$; 28.6%) consumed small amounts infrequently; 2) others ($n = 13$; 6.4%) began by drinking moderate amounts early on, but reduced consumption over time; 3) some ($n = 15$; 7.9%) began drinking later and in increasing amounts; and 4) a minority ($n = 12$; 5.8%) resumed drinking shortly after LT and in increasing amounts. Patients in groups 2 and 4 (who started drinking early) were more likely to present with steatohepatitis (according to hepatic biopsy) and LT rejection, and all of those who died from ALD recurrence were in these groups. The researchers identified several pre-LT factors associated with relapse: An established diagnosis of alcohol dependence, a short sobriety period, a family history of alco-

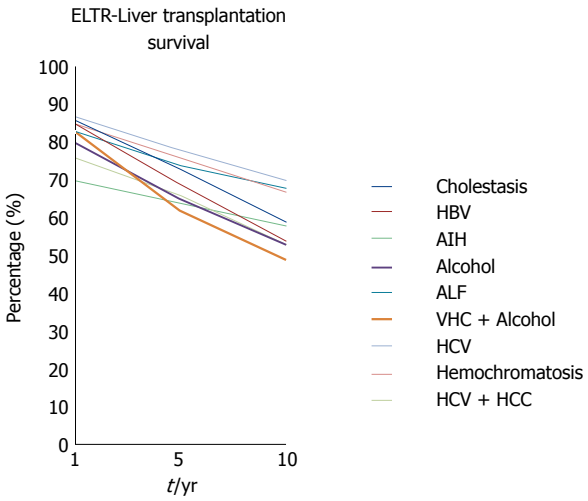

Figure 2 Survival of liver transplantation patients in Europe: 1, 5, and 10 years after liver transplantation. ELTR: European Liver Transplant Registry; HBV: Hepatitis B virus; AIH: Autoimmune hepatitis; ALF: Acute liver failure; HCV: Hepatitis C virus; HCC: Hepatocellular carcinoma.

holism, and the use of other substances[194].

A French multicenter retrospective study[147] analyzed the outcomes of 712 AC LT patients over approximately 9 years of follow up. At the end of the study, 128 patients (18%) had severe relapse (defined as a mean daily alcohol consumption > 20 g in women and > 30 g in men) for at least 6 mo. Of these, 41 (32%) developed AC on average 5 years after LT and 4 years after drinking again. A higher risk of relapse was observed in younger patients and those with a shorter sobriety period. Lastly, survival was lower in each time period in patients who developed recurrent AC compared to those who did not[195].

The results of these studies emphasize the importance of assessing alcohol use after LT and, if identified, taking measures to avoid the negative consequences.

Survival

Patient survival rates after LT for AC based on data from different parts of the world have been reported to be 81%-92%, 78%-86%, and 73%-86% at 1, 3, and 5 years, respectively[144].There are slight differences with the survival rates of ALD LT patients: 93.1%, 87.4%, and 82% at 1, 3, and 5 years, respectively; these results were mostly obtained from small case series in localized geographic regions and regions with particular ethnic characteristics, such as Australia[196].

Survival rates after LT for ALD are comparable to those for patients who underwent LT for other causes[190]. The ELTR evaluated 121,546 patients who underwent LT in 1968-2015 in Europe, and the study found that the survival rates for AC patients (n = 22648) at 1, 5 and 10 years after LT were 86%, 73%, and 59%, respectively. These rates were greater than those observed for patients with HCV (80%, 65%, and 53%), HCC (83%, 62%, and 49%), acute liver failure (70%, 64%, and 58%), and hemochromatosis (76%, 66%, and 53%); similar to those observed for patients with AC plus HCV or HBV (85%, 69%, and 54%); and a little lower than those observed for patients with cholestasis (87%, 78%, and 70%), autoimmune hepatitis (85%, 76%, and 67%), and HBV (83%, 74%, and 68%) (Figure 2)[197,198].

However, this somewhat equivalent survival among AC LT patients compared to other LT patient did not persist beyond 5 years due to the increased risk among AC LT patients of cardiorespiratory disease, cerebrovascular events, and *de novo* malignancy. Although all LT recipients are at greater risk of *de novo* malignancy, the incidence rate is significantly higher in patients with ALD, particularly regarding oropharyngeal and lung cancers, which may be related to substance abuse and smoking history[197]. Nearly 40% of ALD LT recipients resume smoking soon after LT[26]. Therefore, pre- and post-LT follow-up efforts regarding ALD patients should be focused not only on alcohol consumption relapse, but also on treating and avoiding other modifiable risk factors such as tobacco smoking. Pre-LT psychiatric and psychosocial evaluation and post-LT follow-up with physicians, psychiatrists, and addiction specialists are important for dealing with these problems[26].

Recent studies have indicated that resumption of alcohol abuse following LT leads to significantly reduced survival rates. Patients who resumed heavy drinking have been reported to have 5- and 10-year survival rates of 69.5% and 20.1%, respectively, compared to 90.3% and 81.5%, respectively, in abstinent patients[7,190,199].

In Australia, 16% of patients who underwent LT for ALD fulfilled criteria for harmful relapse and 21% experienced any form of alcohol consumption relapse. Harmful relapse was associated with increased mortality. Based on a multivariate analysis, only two factors were independently associated with harmful relapse: Lack of prior participation in an alcohol rehabilitation program and single versus married status[196]. Younger women dependent on alcohol shortly before LT are at greatest risk of relapse[199].

Among patients who underwent LT for AC, there is improvement in the quality of life, mood, and cognitive functioning, with no difference compared to patients who underwent LT for non-AC etiologies. LT patients were able to return to society and lead active and prolific lives, irrespective of the indication for LT[190].

The key factor determining the outcome of LT for AC is intensive lifelong medical and psychological care. Post-LT surveillance might be much more important than pre-LT selection[37].

CONCLUSION

Alcohol is largely consumed worldwide, causing many diseases in several organs and systems. For patients with ALD, when end-stage liver disease is reached, the only chance of survival is LT. There are controversies and ethical dilemmas associated with the indication of LT for ALD. Accurate stratification of potential LT candidates should be performed to identify those most likely to

remain abstinent after LT. The survival of patients who underwent LT for AC is comparable to that of patients who underwent LT for other non-AC etiologies. Psychiatrists, psychologists, social workers and dependency specialists, along with the transplantation team, are essential in the post-LT follow-up of these patients. AC patients who underwent LT are most likely to develop cardiovascular illnesses and malignancies 5 years after LT; it is also imperative that these patients stop smoking.

The two most important words related to ALD are addiction and abstinence. The first represents hell in the life of the alcoholic and refers to the most difficult pathways of degradation and death. It can be circumvented in a complex and time-consuming process, often with relatively little success that, when obtained, should be preserved with the greatest possible effort of the patient and the surrounding supporters, in a constant struggle. The second represents redemption, achieved with much effort and persistence, and it must be preserved at all costs, constantly and permanently, always glimpsing the future of physical and emotional recovery. The sequelae may disappear and recovery, when possible, may be complete. Abstinence is the solid foundation on which recovery is based. However, it is fragile as well, and requires constant vigilance from the patient and the supporters, not to return to hell.

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