

Perceptions of post-transplant recidivism in liver transplantation for alcoholic liver disease

Yoshikuni Kawaguchi, Yasuhiko Sugawara, Nobuhisa Akamatsu, Junichi Kaneko, Tomohiro Tanaka, Sumihito Tamura, Taku Aoki, Yoshihiro Sakamoto, Kiyoshi Hasegawa, Norihiro Kokudo

Yoshikuni Kawaguchi, Yasuhiko Sugawara, Nobuhisa Akamatsu, Junichi Kaneko, Sumihito Tamura, Taku Aoki, Yoshihiro Sakamoto, Kiyoshi Hasegawa, Norihiro Kokudo, Artificial Organ and Transplantation Surgery Division, Department of Surgery, Graduate School of Medicine, University of Tokyo, Tokyo 113-0033, Japan

Tomohiro Tanaka, Organ Transplantation Service, University of Tokyo, Tokyo 113-0033, Japan

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Correspondence to: Yasuhiko Sugawara, MD, Artificial Organ and Transplantation Surgery Division, Department of Surgery, Graduate School of Medicine, University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan. yasusugatky@yahoo.co.jp

Telephone: +81-3-38155411 Fax: +81-3-56843989

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Abstract

Although alcoholic liver disease (ALD) is regarded as a common indication for liver transplantation (LT), debatable issues exist on the requirement for preceding alcoholic abstinence, appropriate indication criteria, predictive factors for alcoholic recidivism, and outcomes following living-donor LT. In most institutions, an abstinence period of six months before LT has been adopted as a mandatory selection criterion. Data indicating that pre-transplant abstinence is an associated predictive factor for alcoholic recidivism supports the reasoning behind this. However, conclusive evidence about the benefit of adopting an abstinence period is yet to be established. On the other hand, a limited number of reports available on living-donor LT experiences for ALD patients suggest that organ donations from rela-

tives have no suppressive effect on alcoholic recidivism. Prevention of alcoholic recidivism has proved to be the most important treatment after LT based on the resultant inferior long-term outcome of patients. Further evaluations are still needed to establish strategies before and after LT for ALD.

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Key words: Abstinence; Alcoholic liver disease; Liver transplantation; Six-month rule

Core tip: Prevention of alcoholic recidivism has proved to be the most important treatment after liver transplantation based on inferior long-term outcome of patients. Further evaluations, however, are still needed to establish strategies before and after liver transplantation with alcoholic liver diseases.

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INTRODUCTION

Alcoholic liver disease (ALD) is regarded as a common indication for liver transplantation (LT), and accounts for approximately 40% of all primary transplants in Europe^[1] and 25% in the United States^[2]. One of the reasons making LT for ALD a complicated topic of issue is that alcohol abuse is the primary cause for end-stage liver disease development. Patients themselves are viewed as being responsible for their illness as compared to other diseases including cholestatic liver diseases and viral cir-

rhosis. Thus, controversy may exist over organ allocation to ALD patients in deceased-donor liver transplantation (DDLT). Organ allocation to patients with self-inflicted disease is less acceptable to society^[3-5], and post-transplant alcoholic recidivism may raise questions on sharing organs as a public resource. By contrast, living-donor liver transplantation (LDLT), which remains the mainstream approach in Asia including Japan, does not conflict with the above-mentioned issues on organ allocation. However, requiring an abstinence period of at least six months (the so-called six-month rule^[6]) to soften the controversy may also be debatable because the benefit of such pre-transplant abstinence remains unclear. Nevertheless, prevention of alcoholic recidivism is inevitably the most important factor to enhance medical benefits of LT and to gain more public acceptance as well. In the present article, we review the current status of LT for ALD mainly derived from DDLT cases, and focus on controversies involved in LDLT with the aim to explore the future direction of LT for ALD.

LT FOR ALD

Selection criteria

Selection criteria of LT for ALD, such as pre-transplant abstinence period, participation in rehabilitation program, and consultation with a psychiatrist, have been used in most institutions in addition to common criteria for other original diseases^[7-13]. This is presumably because the criteria allow observations needed to determine the recovery odds from potential liver failure^[7,14,15] and prevent post-transplant alcoholic recidivism^[16-20]. In addition, there is a preponderance of evidence supporting that a pre-transplant abstinence period of six months has become a mandatory selection criterion^[8,11-13,19-21], as its benefit was reported by Bird *et al*^[6] in 1990. However, there are also reports indicating that an abstinence period of more than six months is not a significant predictive factor for alcoholic recidivism^[22-24], along with those demonstrating that LT candidates with ALD barely survive for six months even with no alcohol intake^[15,23]. A solid validation for requiring pre-transplant abstinence, as well as optimal duration of abstinence, if necessary, has yet to be established.

Alcoholic recidivism

Alcoholic recidivism has been considered to negatively impact postoperative compliance and long-term outcomes of recipients^[21,24-30]. This perception may have encouraged LT professionals to evaluate predictive factors for alcoholic recidivism and therefore, to require specific criteria for ALD patients to prevent alcoholic recidivism in addition to commonly applied criteria. Rates and predictive factors of alcoholic recidivism are summarized according to the previous reports in Table 1^[11,19-22,24,31,32]. The rates of alcoholic recidivism ranged widely from 10% to 42% as a result of inconsistent definitions on alcoholic recidivism and follow-up time. In fact, DiMartini *et al*^[33] classified post-transplant alcohol consumption patterns into five categories based on time until relapse,

three of which are harmful to the patients: no alcohol use, infrequent/low level of consumption, early onset/moderate and decreased consumption, later onset/harmful level of consumption, and early onset/heavy/increasing consumption. According to this classification, 46% of patients developed alcohol recidivism, with harmful use of alcohol accounting for 19%. In addition to inconsistent definitions on alcoholic recidivism, the fact that its detection is mainly based on statements from patients and/or reports from relatives makes evaluation difficult^[11,19-22,24,31,32,34,35]. Random conducting of blood alcohol tests is useful for surveillance of ALD patients^[19] as indicated through the resulting reduced rate of pre-transplant recidivism. With respect to predictive factors for alcohol recidivism, the following factors have been indicated in previous reports: abstinence period, presence of psychiatric comorbidity, poor compliance, family history of alcoholism, high-risk alcoholism relapse score (4-6)^[36], poor social support, presence of young children, female sex, age < 50 years. An abstinence period before LT has been demonstrated as the predictive factor in most^[11,19-21,31], but not all^[22,24,32], publications.

Patient outcomes

The long-term survival rates of patients who underwent LT for ALD are reportedly 82%-92% at one year, and 72%-83% at 5 years^[1,11,21,37,38]. These results are comparable to those of patients including all etiologies from different parts of the world (79%-83% at one year and 67%-77% at five years)^[28,37,39]. Alcohol recidivism has been reported to impair long-term outcome^[24,26,27,29-31], presumably due to its negative influence on the recipients, including alcohol toxicity, poor compliance, development of post-transplantation malignancies and occurrence of cardiovascular diseases. Rates of graft loss due to alcoholic recidivism range between 0% and 50%^[21,27,30,40,41], and significant association of ALD patients with increased development of post-transplantation malignancy and occurrence of cardiovascular diseases were suggested^[1,42].

Concerns on LT for acute alcoholic hepatitis without an abstinence period

Alcoholic hepatitis is a distinct clinical syndrome associated with recent or ongoing alcohol consumption, and its severity leads to high mortality exceeding 50%^[35,43-46]. Medical treatment including the use of corticosteroids and/or pentoxifylline reduces the mortality rate to approximately 20%-30%^[43,47]. Non-responsive patients suffer high mortality, and thus LT for alcohol hepatitis has been proposed in select patients^[35,47,48]. However, alcoholic hepatitis is a controversial indication, or even a contraindication, for LT in most institutions^[49,50] due to the high potential for alcohol recidivism, and conceivably due to the lack of pre-transplant abstinence period. A recent prospective multicenter study showed clear improvement on the odds of survival among patients unresponsive to medical therapy and followed with LT for severe alcoholic hepatitis^[55]. The six-month and two-year survival rates among LT patients were significantly higher among

Table 1 Predictive factors for alcoholic recidivism

Ref.	Year	Alcoholic recidivism	Predictive factors
Gish <i>et al</i> ^[32]	2001	20%	Poor compliance and personality disorder
Jauhar <i>et al</i> ^[22]	2004	15%	Family history of alcoholism
DiMartini <i>et al</i> ^[19]	2006	42%	Alcohol dependence and an abstinence period
De Gottardi <i>et al</i> ^[11]	2007	12%	HRAR high score (4-6), presence of psychiatric comorbidity, and an abstinence period (≤ 6 mo)
Pfutzmann <i>et al</i> ^[21]	2007	19%	An abstinence period (< 6 mo), poor social support, presence of young children, and a poor psychosomatic prognosis
Tandon <i>et al</i> ^[31]	2009	24%	Pre-transplant abstinence
Karim <i>et al</i> ^[20]	2010	10%	An abstinence period (< 6 mo), female sex, presence of psychiatric comorbidity, age < 50 yr
Egawa <i>et al</i> ^[24]	2014	23%	Presence of psychiatric comorbidity

HRAR: High-risk alcoholism relapse.

non-LT patients (six months: $77\% \pm 8\%$ *vs* $23\% \pm 8\%$, $P < 0.001$; two years: $71\% \pm 9\%$ *vs* $23\% \pm 8\%$, $P < 0.001$). The survival rate of patients who underwent LT was comparable to that of patients who responded to medical therapy ($77\% \pm 8\%$ *vs* $85\% \pm 4\%$). The overall recidivism rate with relapse was 12%, with no case of alcoholic relapse within the initial six-month follow-up period after LT. Similar survival rates were reported in a retrospective study comparing LT outcomes for patients with alcoholic hepatitis to those with alcoholic cirrhosis (one year: 93% *vs* 88% ; two years: 91% *vs* 84% ; five years: 80% *vs* 78%)^[48]. However, both studies mentioned an observable difference in society's readiness towards transplants for ALD and other self-inflicted liver diseases, despite their comparable mortality. In fact, criticism from the public is not present in response to LT for patients with fulminant hepatic failure stemming from voluntary acetaminophen poisoning, nor intravenous-drug users with acute hepatitis B virus infection^[35,48]. In order to gain public acceptance, some sensitive issues surrounding LT for alcoholic hepatitis need to be addressed even though the medical benefits of LT have been proposed for strictly selected patients.

CONSIDERATIONS ON LDLT FOR ALD

Although there are many reports on DDLT for patients with ALD, there are few concerning LDLT. This is most likely because ALD is not a major primary disease for LT in the regions where LDLT is common, and DDLT is not practical due to the shortage of deceased donors. For instance, ALD accounts for only 2% of all primary transplantations in Japan, where 98% of LT has been performed through LDLT according to the registry by the Japanese Liver Transplantation Society^[37]. Nevertheless, ALD is an important indication for LT following an annual increase of ALD recipients in Japan^[37]. There are only two published reports on LDLT for ALD patients; one is a single-center study from our own institution^[13], and the other is a multi-center questionnaire-based study in Japan^[24].

Single-center study

Although the number of patients with ALD was limited in our single-center study, the results indicated a relatively

low recidivism rate (8%) after LDLT for ALD patients selected based on a strict criteria that required the six-month rule, participation in Alcoholics Anonymous or equivalent rehabilitation program, consultation with a psychiatrist, and signed agreement declaring an intention of lifetime abstinence^[13]. In addition, the study implied that pre-transplant abstinence was useful to observe possible recovery from liver failure as well as to identify patients who would not abstain from alcohol before and/or after LT. From this, we assumed that the role of abstinence before LDLT is to ensure positive effects on preventing post-transplant alcoholic recidivism even if results are not established and to recompense the potential risks the donor carried.

Multi-center study

In contrast, the rate of post-transplantation relapse in the multi-center study involving 38 institutions in Japan, with selection criteria for ALD patients determined at each institution, ranged from 7% to 95%^[24]. The study noted the possibility that relatives who donated their organs, notwithstanding operation risks, may have allowed recipients' alcohol consumption after LT. In fact, recidivism rates of patients whose parents or siblings were donors ranged from 28% to 50%, slightly higher than those whose donors were spouses (13%) or relatives (23%). Considering the relatively high alcoholic relapse rate after LDLT, the study suggested that DDLT may be more suitable for patients with ALD.

Patient outcomes

The long-term survival rate of patients who underwent LDLT for ALD was comparable with that of DDLT^[1,11,21,37,38]; 100% at one year and 91% at five years in the single-center study^[13], and 81% at one year and 76% at five years from data in the registry of the Japanese Liver Transplantation Society^[37]. Similar to DDLT^[21,26,27,29,30], the long-term survival rate for relapsing patients was significantly lower than that for abstinent patients (one year: 100% *vs* 100%; three years: 95% *vs* 99%; five years: 90% *vs* 96%, $P = 0.01$)^[24].

Public and ethical perspectives on LDLT for ALD

LDLT for ALD may seem to be generally accepted by

society from a public point of view because, unlike with DDLT, it does not conflict with organ allocation issues. Nevertheless, ethical issues remain. First, liver transplantation professionals are confronted with difficult situations caused by the dilemma between strong willingness displayed by the family to donate and compliance with pre-transplant abstinence rule. For instance, professionals working in most institutions feel obliged to inform patients who may have prospective living donors and their family members that the requirement for a six-month abstinence period is still applicable, even when some of the patients are not expected to survive more than six months. Second, recidivism is not readily accepted by society even if the organ is donated by a family member because LT is supported by national- and/or social- welfare systems in general. LDLT for ALD, inseparable from the public opinion, becomes a complicated topic that requires a viewpoint slightly different from DDLT for ALD when addressing their issues.

The extremely limited number of reports on LDLT for ALD led to difficulty in achieving consensus on optimal selection criteria for ALD patients as well as on strategies for preventing alcoholic recidivism after LT. To improve current status of LDLT for ALD and support liver transplantation professionals involved in the treatment for ALD, a significant increase in the number of reports on this topic are essential, not to mention a well-designed prospective study.

CONCLUSION

Alcoholic liver disease remains a commonly recognized indication for LT in Europe and the United States, with an increasing presence in Asia as well. ALD is a self-inflicted disease in which patients may possibly relapse to alcohol consumption after transplantation. These facts still raise questions on sharing organs as a public resource for DDLT. LDLT, unlike DDLT, may not necessarily link to organ allocation issues, but it is nonetheless inseparable from the public eye as an ethical standpoint. Considerable efforts to improve post-transplant outcome are required to recompense the potential risks to living donors.

Prevention of alcoholic recidivism is regarded as the most important post-transplant treatment because alcohol impairs long-term outcome of ALD patients. Although not conclusive, an abstinence period and presence of psychiatric comorbidity are potential predictive factors for post-transplantation recidivism. Organ donations from relatives do not suppress alcoholic recidivism as the recipient's alcohol consumption tends to be tolerated by the donors themselves. Incidentally, recent studies promote the medical benefits of LT for patients with alcoholic hepatitis whose medical therapy was ineffective, but recidivism is anticipated in these patients who likely continue to consume large volumes of alcohol. LT for alcoholic hepatitis is still a highly controversial issue from the public point of view, and needs to be resolved.

Well-designed prospective studies on DDLT/LDLT

are essential to resolve the debatable issues on LT for ALD. Establishment of accurate predictive factors for alcoholic recidivism, benefits and optimal duration of pre-transplant abstinence, and appropriate indication criteria of LT for ALD are among high priority issues. Further evaluations on these issues will help to more effectively control alcoholic recidivism and improve, not only the outcome of LT for ALD patients, but also acceptance from society.

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