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**Post-transplant recidivism in liver transplantation for alcoholic liver disease and its medical, public, and ethical perception**

Kawaguchi Y *et al.* Liver transplantation for alcoholic liver disease

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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 of alcoholic abstinence prior to LT, appropriate indication criteria of LT for ALD, predictive factors for alcoholic recidivism, and outcomes following living-donor liver transplantation (LDLT) for patients with ALD. In most institutions, an abstinence period of mostly 6 months before LT has been adopted as a mandatory selection criterion. Study indicating pre-transplant abstinence as 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 LDLT experiences for ALD patients suggest that organ donations from relatives have no suppressive effect on alcoholic recidivism. Prevention of alcoholic recidivism has proved to be the most important treatment after LT based on inferior long-term outcome of patients with post-transplantation recidivism. Further evaluations are still needed to establish strategies before and after LT for ALD.

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**Key words:** Liver transplantation; Alcoholic liver disease; 6-month rule; Abstinence

**Core tip:** Prevention of alcoholic recidivism has proved to be the most important treatment after liver transplantaion based on inferior long-term outcome of patients with post-transplantation recidivism. Further evaluations, however, are still needed to establish strategies before and after liver transplantaion with alcholic 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](#_ENREF_1)] and 25% in the United States[[2](#_ENREF_2)]. One of the reasons which make LT for ALD a complicated topic of issue is that alcoholic 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 cirrhosis. 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](#_ENREF_3)], 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 6 mo (the so-called 6-month rule[[6](#_ENREF_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.

**LIVER TRANSPLANTATION FOR ALCOHOLIC LIVER DISEASE**

***Selection criteria of LT for ALD***

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](#_ENREF_7)]. This is presumably because the criteria allow observations needed to determine the recovery odds from potential liver failure[[7](#_ENREF_7),[14](#_ENREF_14),[15](#_ENREF_15)] and prevent post-transplant alcoholic recidivism[[16-20](#_ENREF_16)]. In addition, there is a preponderance of evidence supporting that a pre-transplant abstinence period of 6 months has become a mandatory selection criterion[[8](#_ENREF_8),[11-13](#_ENREF_11),[19-21](#_ENREF_19)] since its benefit was reported by Bird *et al*[[6](#_ENREF_6)] in 1990. However, there are also reports indicating that an abstinence period of more than 6 months is not a significant predictive factor for alcoholic recidivism[[22-24](#_ENREF_22)], along with those demonstrating that LT candidates with ALD barely survive for 6 months even with no alcohol intake[[15](#_ENREF_15),[23](#_ENREF_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](#_ENREF_21),[24-30](#_ENREF_24)]. This perception may have encouraged liver transplantation professionals to evaluate predictive factors for alcoholic recidivism and therefore, to require specific criteria for ALD patients to prevent alcoholic recidivism in addition to common criteria applied to other original diseases. Rates and predictive factors of alcoholic recidivism are summarized according to the previous reports and shown in Table 1[[11](#_ENREF_11),[19-22](#_ENREF_19),[24](#_ENREF_24),[31](#_ENREF_31),[32](#_ENREF_32" \o "Gish, 2001 #79355)]. 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](#_ENREF_33)] classified post-transplant alcohol consumption patterns into five based on time, of which three are harmful to the patients. The classification is based on time until relapse and is as follows: 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[[33](#_ENREF_33)]. 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 of alcoholic recidivism difficult[[11](#_ENREF_11),[19-22](#_ENREF_19),[24](#_ENREF_24),[31](#_ENREF_31),[32](#_ENREF_32),[34](#_ENREF_34),[35](#_ENREF_35)]. Random conducting of blood alcohol test is useful for surveillance of ALD patients[[19](#_ENREF_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 (Table 1): abstinence period, presence of psychiatric comorbidity, poor compliance, family history of alcoholism, high-risk alcoholism relapse score[[36](#_ENREF_36)] (4-6), 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](#_ENREF_11),[19-21](#_ENREF_19),[31](#_ENREF_31)] but not all publications[[22](#_ENREF_22),[24](#_ENREF_24),[32](#_ENREF_32)].

***Outcomes of patients who underwent LT for ALD***

The long-term survival rates of patients who underwent LT for ALD are reported to be 82%-92% at 1 year and 72%-83% at 5 years[[1](#_ENREF_1),[11](#_ENREF_11),[21](#_ENREF_21),[37](#_ENREF_37),[38](#_ENREF_38)]. These results are comparable to those of patients including all etiologies from different parts of the world, recording 79%-83% at 1 year and 67%-77% at 5 years[[28](#_ENREF_28),[37](#_ENREF_37),[39](#_ENREF_39)]. Alcohol recidivism has been reported to impair long-term outcome of patients[[24](#_ENREF_24),[26](#_ENREF_26),[27](#_ENREF_27),[29-31](#_ENREF_29)], presumably due to 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 were reported between a relatively wide range of 0% to 50%[[21](#_ENREF_21),[27](#_ENREF_27),[30](#_ENREF_30),[40](#_ENREF_40),[41](#_ENREF_41)] and significant association of ALD patients with increased development of post-transplantation malignancy and occurrence of cardiovascular diseases were suggested[[1](#_ENREF_1),[42](#_ENREF_42)].

***Concerns on LT for acute alcoholic hepatitis without 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](#_ENREF_35),[43-46](#_ENREF_43)]. Medical treatment including the use of corticosteroids and/or pentoxifylline reduces the mortality rate to approximately 20%-30%[[43](#_ENREF_43),[47](#_ENREF_47)]. Non-responsive patients suffer high mortality, and thus LT for alcohol hepatitis has been proposed in select patients[[35](#_ENREF_35),[47](#_ENREF_47),[48](#_ENREF_48)]. However, alcoholic hepatitis is a controversial indication or even a contraindication for LT in most institutions[[49](#_ENREF_49),[50](#_ENREF_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[[35](#_ENREF_35)]. The 6-month and the 2-year survival rates among LT patients were significantly higher than those among non-LT patients (6 months; 77% ± 8% *vs* 23% ± 8%, *P* < 0.001, 2 years; 71% ± 9% *vs* 23% ± 8%, *P* < 0.001). The survival rate of patients who underwent LT was comparable to that of patients who responded to medical therapy. (77% ± 8% *vs* 85% ± 4%, *P* = 0.33). The overall recidivism rate with relapse was 12%, with no case of alcoholic relapse within the initial 6-mo follow-up period after LT. Similar survival rate was reported in a retrospective study comparing LT outcomes for alcoholic hepatitis to those of alcoholic cirrhosis[[48](#_ENREF_48)]. The survival rate after LT for patients with alcoholic hepatitis showed no significant difference compared to those with alcoholic cirrhosis (1 year; 93% *vs* 88%, *P* = 0.33, 2 years; 91% *vs* 84%, *P* = 0.24, 5 years; 80% *vs* 78%, *P* = 0.91). However, both studies mentioned visible 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](#_ENREF_35),[48](#_ENREF_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 LIVING-DONOR LIVER TRANSPLANTATION FOR ALD**

While there have been many reports on DDLT for patients with ALD, LDLT experiences have been rarely reported. 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 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](#_ENREF_37)]. Nevertheless, ALD is an important indication for LT following annual increase of ALD recipients in Japan[[37](#_ENREF_37)]. There are only two published reports on LDLT for ALD patients; one is a single-center study in authors’ institution[[13](#_ENREF_13)] and the other is a multicenter questionnaire-based study in Japan[[24](#_ENREF_24)].

***Single-center study***

Although the number of patients with ALD was limited in the single-center study, our previous study indicated a relatively low recidivism rate (8%) after LDLT for ALD patients selected based on a strict criteria which required 6-month rule, participation in Alcoholic Anonymous or equivalent rehabilitation program, consultation with a psychiatrist, and signed agreement declaring intention of lifetime abstinence[[13](#_ENREF_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 potential risks the donor carried as well.

***Multi-center study***

By contrast, the rate of post-transplantation relapse ranged from 7% to 95% at 38 institutions in Japan according to multicenter study, with selection criteria for ALD patients determined at each institution[[24](#_ENREF_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 were 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.

***Outcomes of patients who underwent LDLT for ALD***

The long-term survival rate of patients who underwent LDLT for ALD was comparable with that of DDLT[[1](#_ENREF_1),[11](#_ENREF_11),[21](#_ENREF_21),[37](#_ENREF_37),[38](#_ENREF_38)]; it was reported to be 100% at 1 year and 91% at 5 years in the single-center study[[13](#_ENREF_13)], and to be 81% at 1 year and 76% at 5 years from the data in registry by the Japanese Liver Transplantation Society[[37](#_ENREF_37)]. Similar to DDLT[[21](#_ENREF_21),[26](#_ENREF_26),[27](#_ENREF_27),[29](#_ENREF_29),[30](#_ENREF_30)], the long-term survival rate for relapsing patients was reported to be significantly lower than that for abstinent patients (1 year; 100% *vs* 100%, 3 years; 95% *vs* 99%, 5 years; 90% *vs* 96%, *P* = 0.01)[[24](#_ENREF_24)].

***Public and ethical perspective on LDLT for ALD***

LDLT for ALD may seem to be generally accepted by society from a public point of view because it does not conflict with organs allocation issues as DDLT for ALD does. Nevertheless, ethical issues remain. First, liver transplantation professionals are confronted with difficult situations caused by the dilemma between strong willingness displayed by family to donate and compliance with pre-transplant abstinence rule. For instance, those professionals working in most institutions feel obliged to inform patients and their family member who may have prospective living donors that the requirement of 6-month abstinence period is still applicable, even when some of them are not be expected to survive more than 6 months. Secondly, 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 significantly increasing number of reports on LDLT for ALD are essential for the achievement, not to mention a well-designed prospective study.

**CONCLUSION**

Alcoholic liver disease remains to be a commonly recognized indication for LT in Europe and the United States, increasing presence in Asia as well. ALD is a self-inflicted disease in which patients may possibly relapse in 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 in an ethical standpoint. Considerable efforts to improve post-transplant outcome are required to recompense the potential risks run by living donors.

Prevention of alcoholic recidivism is regarded as the most important post-transplant treatment because alcohol impairs long-term outcome of ALD patients. An abstinence period and presence of psychiatric comorbidity have been indicated as predictive factors for post-transplantation recidivism in most previous reports. However, no conclusive evidence is available. One study also suggests that organ donations from relatives have no suppressive effect on alcoholic recidivism because recipients’ alcohol consumption tends to be tolerated by the donors themselves. Incidentally, recent studies encourage medical benefits of LT for alcoholic hepatitis whose medical therapy was ineffective, but such patients are likely to have consumed a certain high volume of alcohol recently or on an ongoing basis, with high potential of recidivism anticipated. 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 for DDLT/LDLT for ALD, along with a significant number of reports on LDLT for ALD, 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 are anticipated to control alcoholic recidivism more effectively to improve not only the outcome of LT for ALD patients but acceptance from society as well.

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| --- | --- | --- | --- |
| **Table 1 Predictive factors for alcoholic recidivism reported in literatures.** | | | |
| Ref. | Year | Alcoholic  recidivism, % | Predictive factors |
| Gish *et al*[[32](#_ENREF_32)]  Jauhar *et al*[[22](#_ENREF_22)]  DiMartini *et al*[[19](#_ENREF_19)]  De Gottardi *et al*[[11](#_ENREF_11)]  Pfitzmann *et al*[[21](#_ENREF_21)]  Tandon *et al*[[31](#_ENREF_31)]  Karim *et al*[[20](#_ENREF_20)]  Egawa *et al*[[24](#_ENREF_24)] | 2001  2004  2006  2007  2007  2009  2010  2014 | 20  15  42  12  19  24  10  23 | Poor compliance and personality disorder  A family history of alcoholism  Alcohol dependence and an abstinence period  HRAR1 high score (4-6), presence of psychiatric comorbidity, and an abstinence period (≤ 6 mo)  An abstinence period (< 6 mo), poor social support, presence of young children, and a poor psychosomatic prognosis  A pre-transplant abstinence  An abstinence period (< 6 mo), female sex, presence of psychiatric comorbidity, Age < 50 yr  Presence of psychiatric comorbidity |
| 1HRAR score, a high-risk alcoholism relapse score[[36](#_ENREF_36)]. | | | |