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

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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 relatives 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.

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 continues 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\textsuperscript{[3,4]}, 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\textsuperscript{[8]}) 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\textsuperscript{[7-13], [22-24, 35, 47, 48]}. This is presumably because the criteria allow observations needed to determine the recovery odds from potential liver failure\textsuperscript{[16-20]} and prevent post-transplant alcoholic recidivism\textsuperscript{[7-13]}. In addition, there is a preponderance of evidence supporting that a pre-transplant abstinence period of six months has become a mandatory selection criterion\textsuperscript{[6-11, 13-15, 22-24, 32, 33, 35, 47, 48]}, as its benefit was reported by Bird et al\textsuperscript{[22-24]} 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\textsuperscript{[22-24]}, along with those demonstrating that LT candidates with ALD barely survive for six months even with no alcohol intake\textsuperscript{[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\textsuperscript{[22-24, 32]}. 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\textsuperscript{[11, 19, 22-24, 30-32]}. 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\textsuperscript{[32]} 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\textsuperscript{[11, 19, 22-24, 31, 32, 34, 35]}. Random conducting of blood alcohol tests is useful for surveillance of ALD patients\textsuperscript{[32]} 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)\textsuperscript{[15]}; 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\textsuperscript{[11, 19, 21, 31]}, but not all\textsuperscript{[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\textsuperscript{[11, 19, 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)\textsuperscript{[38, 39-41]}. Alcoholic recidivism has been reported to impair long-term outcome\textsuperscript{[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%\textsuperscript{[21, 22, 27, 30, 40-42]}, and significant association of ALD patients with increased development of post-transplantation malignancy and occurrence of cardiovascular diseases were suggested\textsuperscript{[6, 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%\textsuperscript{[33, 43, 46]}. Medical treatment including the use of corticosteroids and/or pentoxifylline reduces the mortality rate to approximately 20%-30%\textsuperscript{[33, 47]}. Non-responsive patients suffer high mortality, and thus LT for alcoholic hepatitis has been proposed in select patients\textsuperscript{[33, 43, 46]}. However, alcoholic hepatitis is a controversial indication, or even a contraindication, for LT in most institutions\textsuperscript{[33, 46]} 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\textsuperscript{[33]}. The six-month and two-year survival rates among LT patients were significantly higher among...
non-LT patients (six months: 77% ± 8% vs 23% ± 8%, P < 0.001; two 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%). 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%) [31]. 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 [3], and the other is a multi-center questionnaire-based study in Japan [21,26,27,29,30].

**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 unrelated (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 [21,26,27,29,30], 100% at one year and 91% at five years in the single-center study [3], 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, 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. DDLT 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.

REFERENCES

1. Burra P, Senzolo M, Adam R, Delwart V, Karam V, Germani G, Neuberger J. Liver transplantation for alcoholic liver disease in Europe: a study from the ELTR (European Liver Transplant Registry). Am J Transplant 2010; 10: 138-148 [PMID: 19951276 DOI: 10.1111/j.1660-6143.2009.02869.x]
2. Singal AK, Guturu P, Hmoud B, Kuo YF, Salameh H, Wiesner RH. Evolving frequency and outcomes of liver transplantation based on etiology of liver disease. Transplantation 2013; 95: 785-760 [PMID: 23537070 DOI: 10.1097/TP.0b013e31827fa8a3]
3. Cohen C, Benjamin M. Alcohols and liver transplantation. The Ethics and Social Impact Committee of the Transplant and Health Policy Center. JAMA 1991; 265: 1299-1301 [PMID: 1995978 DOI: 10.1001/jama.265.10.1299]
4. McMaster P. Transplantation for alcoholic liver disease in an era of organ shortage. Lancet 2000; 355: 424-425 [PMID: 10841118 DOI: 10.1016/S0140-6736(99)03128-4]
5. Perut V, Conti F, Scatton O, Soubrane O, Calmus Y, Vidal-Trecan C. Might physicians be restricting access to liver transplantation for patients with alcoholic disease? J Hepatol 2009; 51: 707-714 [PMID: 19665248 DOI: 10.1016/j.jhep.2009.04.018]
6. Bird GL, O’Grady JG, Harvey FA, Calne RY, Williams R. Liver transplantation in patients with alcoholic cirrhosis: selection criteria and rates of survival and relapse. BMJ 1990; 301: 15-17 [PMID: 2383700 DOI: 10.1136/bmj.301.6742.15]
7. Foster PF, Fabrega F, Karademir S, Sankary HN, Mital D, Williams JW. Prediction of abstinence from ethanol in alcoholic recipients following liver transplantation. Hepatology 1997; 25: 1469-1477 [PMID: 9185770 DOI: 10.1002/hep.102505627]
8. Bravata DM, Keefe EB. Quality of life and employment after liver transplantation. Liver Transpl 2001; 7: S119-S123 [PMID: 11689784 DOI: 10.1033/201.2001.28520]
9. Miguet M, Monnet E, Vanlemmens C, Gache P, Messner M, Hruskovsky S, Perarranz JM, Pageaux GP, Duvox C, Minello A, Hillon P, Bresson-Hadni S, Manton G, Miguet JP. Predictive factors of alcohol relapse after orthotopic liver transplantation for alcoholic liver disease. Gastroenterol Clin Biol 2004; 28: 845-851 [PMID: 15523219 DOI: 10.1016/S0334-3020(04)95146-9]
10. Dew MA, DiMartini AF, Steel J, De Vito Dabbas A, Myasakovsky L, Unruh M, Greenhouse J. Meta-analysis of risk for relapse to substance use after transplantation of the liver or other solid organs. Liver Transpl 2008; 14: 159-172 [PMID: 18226389 DOI: 10.1002/lt.21279]
11. De Gottiardi A, Spahr L, Gelez P, Morard I, Menth G, Guillod O, Majno P, Morel P, Hadengeue A, Paliard P, Scoazec JY, Boillot O, Girotra E, Dumortier J. A simple score for predicting alcohol relapse after liver transplantation. Hepatology 2009; 49: 755-760 [PMID: 23370710 DOI: 10.1002/hep.22379]
Liver transplantation for alcoholic liver disease.

S, Aoki T, Sakamoto Y, Hasegawa K, Nojiri K, Kokudo N. Role of 6-month abstinence rule in living donor liver transplantation for patients with alcoholic liver disease. *Hepatol Res* 2013; 43: 1169-1174 [PMID: 23874810 DOI: 10.1111/hepr.12065]

Lucey MR, Brown KA, Everson GT, Fung J, Gish R, Keeffe EB, Kneteman NM, Lake JR, Martin P, Rakela J, Shiffman ML, So S, Wiesner RH. Minimal criteria for placement of adults on the liver transplant waiting list: a report of a national conference organized by the American Society of Transplant Physicians and the American Association for the Study of Liver Diseases. *Transplantation* 1998; 66: 956-962 [PMID: 9785717 DOI: 10.1097/00007890-199808110-00034]

Veldt BJ, Laine F, Guilligymard’C, Launiv L, Boudjema K, Messner M, Brissot P, Deugnyer M, Moirand R. Indication of liver transplantation in severe alcoholic cirrhosis: quantitative evaluation and optimal timing. *J Hepatol* 2002; 36: 93-98 [PMID: 11804670 DOI: 10.1016/S0168-8278(01)00228-8]

Pageaux GP, Michel J, Coste V, Perney P, Possoz P, Perrigault FF, Navarro F, Fabre JM, Domerge J, Blanc P, Larrey D. Alcoholic cirrhosis is a good indication for liver transplantation, even for cases of recidivism. *Gut* 1999; 45: 421-426 [PMID: 10446113 DOI: 10.1136/gut.45.3.421]

Osorio RW, Ascher NL, Avery M, Bacchetti P, Roberts JP, Lake JR. Predicting recidivism after orthotopic liver transplantation for alcoholic liver disease. *Hepatology* 1994; 20: 105-110 [PMID: 8020879 DOI: 10.1002/hep.1840200117]

Platz KP, Mueller AR, Spree E, Schumacher G, Nüssler NC, Rayes N, Glanemann M, Bechtstein WO, Neuhaus P. Liver transplantation for alcoholic cirrhosis. *Transplant Int* 2000; 13 Suppl 1: S127-S130 [PMID: 11111978 DOI: 10.1010/s00470505297]

DiMartini A, Day N, Dew MA, Javed L, Fitzgerald MG, Jain A, Fung J, Fontes P. Alcohol consumption patterns and predictors of use following liver transplantation for alcoholic liver disease. *Liver Transplant* 2006; 12: 813-820 [PMID: 16528710 DOI: 10.1097/01.IT.0000212688]

Karim Z, Intaraprasong P, Sudomare CH, Erb SR, Soos JG, Cheung E, Cooper P, Buzckowski AK, Chung SW, Steinbrecher UP, Yoshida EM. Predictors of relapse to significant alcohol dependence or alcohol abuse after liver transplantation. *Can J Gastroenterol* 2010; 24: 245-250 [PMID: 20431813]

Pfitzmann R, Schwenzer J, Rayes N, Seeboher D, Neuhaus R, Nüssler NC. Long-term survival and predictors of relapse after orthotopic liver transplantation for alcoholic liver disease. *Liver Transplant* 2007; 13: 197-205 [PMID: 17205656 DOI: 10.1002/lt.20934]

Jauhar S, Bellamy CO, Meeberg G, Bergsten D, Carbonneau M, Bain VG. A shorter duration of pre-transplant abstinence predicts problem drinking after liver transplantation. *Am J Gastroenterol* 2009; 104: 1708-1706 [PMID: 19471255 DOI: 10.1038/ajg.2009.226]

Gish RG, Lee A, Brooks L, Leung J, Lau JY, Moore DH. Long-term follow-up of patients diagnosed with alcohol dependence or alcohol abuse who were evaluated for liver transplantation. *Liver Transplant* 2001; 7: 581-587 [PMID: 11460224 DOI: 10.1053/jlt.2001.25455]

Mathurin P, Moreno C, Samuel D, Dumortier J, Salleron J, Durand F, Castel H, Duhamel A, Pageaux GP, Leroy V, Dharnacy S, Louvet A, Boleslawski E, Lucidi V, Gustot T, Francoz C, Letoublon C, Castaing D, Dubochet J, Donchain V, Pruvot FR, Duclos-Vallée JC. Early liver transplantation for severe alcoholic hepatitis. *N Engl J Med* 2011; 365: 1790-1800 [PMID: 22070476 DOI: 10.1056/NEJMoa1104753]

Weinrieb RM, Van Horn DH, McLe llan AT, Lucey MR. Interpreting the significance of drinking by alcohol-dependent liver transplant patients: fostering candor is the key to recovery. *Liver Transplant* 2000; 6: 769-776 [PMID: 11084066 DOI: 10.1053/jlt.2000.18497]

Yates WR, Booth BM, Reed DA, Brown K, Masterson B. Descriptive and predictive validity of a high-risk alcoholism relapse model. *J Stud Alcohol* 1993; 54: 645-651 [PMID: 8271799]

Japane se Liver Transplantation Society. Liver transplantation in Japan: registry by the Japanese Liver Transplantation Society. *Jap J Transplant* 2010; 46: 524-536. Available from: URL: http://www.jstage.jst.go.jp/article/jst/49/2-3/49_261/_article

Bellamy CO, DiMartini AM, Ruppert K, Jain A, Dodson F, Torbenson M, Starzl TE, Fung J, Demetris AJ. Liver transplantation for alcoholic cirrhosis: long-term follow-up and impact of disease recurrence. *Transplantation* 2001; 72: 619-626 [PMID: 11544420 DOI: 10.1097/00007890-200108270-00010]

Hendriks HG, van der Meer J, de Wolf JF, Peeters PM, Porte RJ, de Jong K, Lip H, Post WJ, Slooff MJ. Intraoperative blood transfusion requirement is the main determinant of early surgical re-intervention after orthotopic liver transplantation. *Transplant Int* 2005; 18: 673-679 [PMID: 15717214 DOI: 10.1111/j.1432-2277.2004.tb00493.x]

Conjevaram HS, Hart J, Lissoos TW, Sciano TD, Dasgupta
K, Befeler AS, Millis JM, Baker AL. Rapidly progressive liver injury and fatal alcoholic hepatitis occurring after liver transplantation in alcoholic patients. *Transplantation* 1999; 67: 1562-1568 [PMID: 10401763 DOI: 10.1097/00007890-19990627-0-00010]

41 Lucey MR, Carr K, Beresford TP, Fisher LR, Shieck V, Brown KA, Campbell DA, Appelman HD. Alcohol use after liver transplantation in alcoholics: a clinical cohort follow-up study. *Hepatology* 1997; 25: 1223-1227 [PMID: 9141441 DOI: 10.1002/hep.510250526]

42 Singal AK, Hmoud BS, Guturu P, Kuo YF. Outcome after liver transplantation for cirrhosis due to alcohol and hepatitis C. Comparison to alcoholic cirrhosis and hepatitis C cirrhosis. *J Clin Gastroenterol* 2013; 47: 727-733 [PMID: 23751845 DOI: 10.1097/MCG.0b013e318294148d]

43 Akrividias E, Botla R, Briggs W, Han S, Reynolds T, Shakil O. Pentoxifylline improves short-term survival in severe acute alcoholic hepatitis: a double-blind, placebo-controlled trial. *Gastroenterology* 2000; 119: 1637-1648 [PMID: 11113085 DOI: 10.1053/gast.2000.20189]

44 Mathurin P, O’Grady J, Carithers RL, Phillips M, Louvet A, Mendenhall CL, Ramond MJ, Naveau S, Maddrey WC, Morgan TR. Corticosteroids improve short-term survival in patients with severe alcoholic hepatitis: meta-analysis of individual patient data. *Gut* 2011; 60: 255-260 [PMID: 20940288 DOI: 10.1136/gut.2010.224097]

45 Louvet A, Naveau S, Abdelnour M, Ramond MJ, Diaz E, Fartoux L, Dharancy S, Texier F, Hollebecque A, Serfati L, Boleslawski E, Deltenre P, Canva V, Pruvot FR, Mathurin P. The Lille model: a new tool for therapeutic strategy in patients with severe alcoholic hepatitis treated with steroids. *Hepatology* 2007; 45: 1348-1354 [PMID: 17518367 DOI: 10.1002/hep.21607]

46 Dureja P, Lucey MR. The place of liver transplantation in the treatment of severe alcoholic hepatitis. *J Hepatol* 2010; 52: 759-764 [PMID: 20347501 DOI: 10.1016/j.jhep.2009.12.021]

47 Lucey MR, Mathurin P, Morgan TR. Alcoholic hepatitis. *N Engl J Med* 2009; 360: 2758-2769 [PMID: 19553649 DOI: 10.1056/NEJMra0805786]

48 Singal AK, Bashar H, Anand BS, Jampana SC, Singal V, Kuo YF. Outcomes after liver transplantation for alcoholic hepatitis are similar to alcoholic cirrhosis: exploratory analysis from the UNOS database. *Hepatology* 2012; 55: 1398-1405 [PMID: 22213344 DOI: 10.1002/hep.25544]

49 Sorrell MF, Zetterman RK, Donovan JP. Alcoholic hepatitis and liver transplantation: the controversy continues. *Alcohol Clin Exp Res* 1994; 18: 222-223 [PMID: 8048716 DOI: 10.1111/j.1530-0277.1994.tb00003.x]

50 Miller C, Kamean J, Berk PD. Liver transplantation for alcoholic hepatitis? An unanswered question. *Alcohol Clin Exp Res* 1994; 18: 224-227 [PMID: 8048717 DOI: 10.1111/j.1530-0277.1994.tb00004.x]
