症 例

Bevacizumab高用量の再投与にて長期生存を得た結腸癌大動脈周囲リンパ節転移の1例

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Long-Term Survival of a Patient with Advanced Colon Cancer and Para-Aortic Lymph Node Metastases Treated with Re-Administration of High-Dose Molecular Targeted Agent Bevacizumab: Yoshiaki Ebisawa[*1], Naoyuki Chisato[*1], Taishi Okayama[*1], Chikayoshi Tani[*1], Toru Kono[*2], Masahiko Taniguchi[*1] and Hiroyuki Furukawa[*1] ([*1]*Division of Gastroenterologic and General Surgery, Asahikawa Medical University*, [*2]*Dept. of Surgery, Sapporo Higashi Tokushukai Hospital*)

Summary

A 49-year-old woman was admitted to our hospital because of epigastralgia and abdominal distension. She was diagnosed as advanced colon cancer with para-aortic and common iliac lymph node metastases, without liver and lung metastasis. Extended right hemicolectomy was performed to remove symptoms of stenosis. Bevacizumab (BV) (5 mg/kg)+mFOLFOX6 was performed as the initial postoperative chemotherapy. The tumor marker CEA, CA19-9 decreased, and reduction in the size of distant lymph node metastasis was confirmed, which obtained PR. In July 2009, computed tomography revealed the right pulmonary hilar lymph node metastases and progressive disease was confirmed; therefore, cetuximab and FOLFIRI combination therapy was initiated. However, in October 2009, bilateral inguinal lymph node metastases was seen; therefore we changed chemotherapy to BV (10 mg/kg) and FOLFIRI. Although the abdominal lymph node was decreased slightly after 2 months, chemotherapy was changed to BV (10 mg/kg) and mFOLFOX6 since the inguinal lymph node had enlarged. Skin metastases appeared, and there was no change in the inguinal lymph node and abdominal lymph node. She was deceased due to peritonitis carcinomatosis; however, her survival time exceeded 30 months. There was a possibility that long-term survival could be obtained by increasing the quantity of BV and re-administering it in second-line chemotherapy after PD in BV+FOLFOX first-line chemotherapy. **Key words**: Colon cancer, Para-aortic lymph nodes, High-dose bevacizumab (*Received Nov. 2, 2012/Accepted Feb. 19, 2013*)

要旨 症例は49歳，女性。上腹部不快感，腹満を主訴に当科を受診し，上行-横行結腸癌，大動脈周囲リンパ節～総腸骨リンパ節転移の診断がなされた。肝・肺転移なし。狭窄症状を認めたため，2007年10月下旬に拡大右半結腸切除術を施行。術後約1か月後に全身化学療法の一次治療としてベバシズマブ（bevacizumab: BV 5 mg/kg）+mFOLFOX6を開始。腫瘍マーカーは減少，遠隔リンパ節転移も縮小しPRを得た。2009年7月に右肺門部リンパ節転移が出現しPDとなり，cetuximab+FOLFIRIに変更するも，3か月後に両側鼠径リンパ節転移出現を認めBV（10 mg/kg）+FOLFIRIに変更。2か月半後に腹部リンパ節はわずかに縮小したが，鼠径リンパ節が増大したためBVを10 mg/kgに増量したBV+mFOLFOX6に変更した。その2か月後に皮膚転移が出現するも，鼠径リンパ節，腹部リンパ節には変化を認めなかった。その後，癌性腹膜炎などを生じ死亡したが，30か月を超える生存期間が得られた。一次治療でPDとなったBV+FOLFOX療法でも，二次治療以降でBVを増量し再投与することで，長期生存が得られる可能性が示唆された。

はじめに

治癒切除不能大腸癌の一次治療としてベバシズマブ[bevacizumab (BV)]併用療法がなされており，二次治療以降でのBV再投与およびその用量についてのエビデンスも確立されてきている。今回われわれは，一次治療

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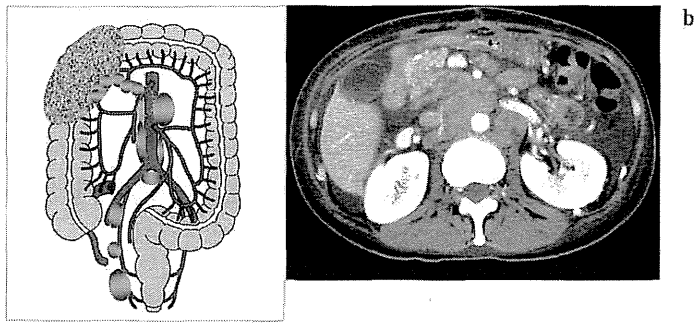

Fig. 1 a: Schema of primary tumor and lymph node metastasis. : Primary tumor, : Lymph node metastasis
b: Abdominal CT scan shows para-aortic lymph node metastasis.

で5 mg/kg，二次治療以降で10 mg/kgのBV併用療法により長期生存を得た症例を経験したので報告する。

Ⅰ．症　例

患者: 49歳，女性。

主訴: 上腹部不快感，腹満，食欲不振。

現病歴: 2007年8月下旬より，上腹部不快感，腹満，食欲不振出現。10月初旬に近医を受診し，大腸内視鏡検査にて全周性狭窄を伴う上行～横行結腸癌，CTにて大動脈周囲リンパ節～総腸骨リンパ節腫大を認め（Fig. 1a, b），手術を勧められ当科紹介となった。

既往歴: 特記すべきことなし。

家族歴: 特記すべきことなし。

臨床経過: 狭窄症状を有する転移性大腸癌であることから，手術を先行し2007年10月に拡大右半結腸切除術（D2）を施行した。肝・肺転移は認めず。術中所見として，腹膜播種を認めなかったが，傍大動脈周囲から側方リンパ節にかけて連続する著明なリンパ節腫大を認めた。病理組織学的に大腸癌は，粘液癌（muc＞tub2），pSS, ly3, v1, pN2［#211（4/4），#221（9/9），#201（0/3），#202（0/3）］，M1［#216（1/1），#206（1/1）］，pStage Ⅳであった。できる限り積極的な治療と仕事を続けたいという患者の意向に沿い，12月より一次治療としてBV（5 mg/kg, day 1, q2w）＋mFOLFOX6（L-OHP 85 mg/m^2 day 1, *l*-LV 200 mg/m^2 day 1, 5-FU 400 mg/m^{2}急速静注，5-FU 2,400 mg/m^{2}持続静注，q2w）を開始。腫瘍マーカーは減少，遠隔リンパ節転移も2サイクル後にPR in し（Fig. 2），PS 0で良好なQOLを維持しつつ，計19サイクル投与継続。有害事象は好中球減少grade（G）3，しびれG2であった。2009年7月に右肺門部リンパ節転移巣が出現し，CA19-9の上昇もみられPDとなり，K-ras遺伝子野生型を確認後，二次治療としてcetuximab（初回は400 mg/m^2，2回目以降は250 mg/m^{2}で毎週投与）＋FOLFIRI（CPT-11 150 mg/m^2 day 1, *l*-LV

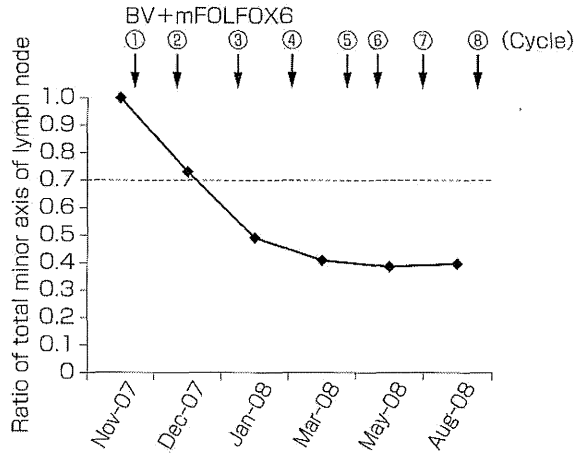

Fig. 2 Response rate in RECIST criteria
PR was achieved after 2 cycles.

200 mg/m^2 day 1, 5-FU 400 mg/m^{2}急速静注，5-FU 2,400 mg/m^{2}持続静注，q2w）に変更し6サイクル施行，有害事象は好中球減少G3，皮診G2，食欲不振G2であった。3か月後にCTにて両側鼠径リンパ節転移出現を認め，三次治療としてBV（10 mg/kg）＋FOLFIRIに変更し5サイクル施行，有害事象は好中球減少G3，蛋白尿G1，下痢G1であった。2か月半後に腹部リンパ節はわずかに縮小した（Fig. 3）が，鼠径リンパ節が増大したためBV（10 mg/kg）＋mFOLFOX6に変更，5サイクル施行し（Fig. 4）有害事象は蛋白尿G1であった。その2か月後に皮膚転移が出現するも，CT画像上，鼠径リンパ節，腹部リンパ節には変化なく（Fig. 5），皮膚転移，鼠径リンパ節転移に対して放射線治療（40 Gy/20 Fr）を施行した。その1か月後に右大腿部の疼痛，会陰部の帯状疱疹が出現し，抗ウイルス剤を投与した。その6か月後には腹腔内リンパ節転移増大による腸閉塞が認められ，best supportive careを施行し，術後31か月で永眠された。なお，皮膚転移，鼠径リンパ節転移に対し放射線治療を行うまで休薬などは行わず，化学療法が遂行可能であった。

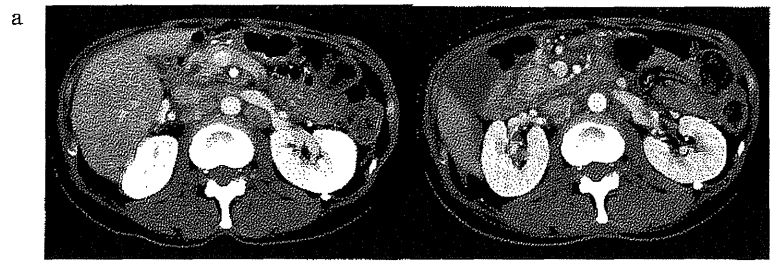

Fig. 3 Para-aortic lymph node metastasis was decreased slightly after chemotherapy.
a: Before chemotherapy [BV (10 mg/kg)+FOLFIRI].
b: After chemotherapy [BV (10 mg/kg)+FOLFIRI)].

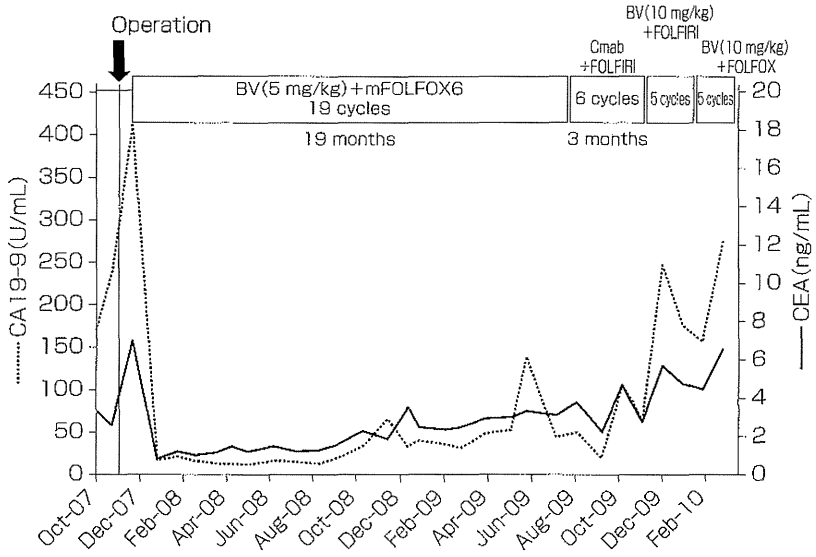

Fig. 4 Therapeutic course and CEA and CA19-9 level after operation

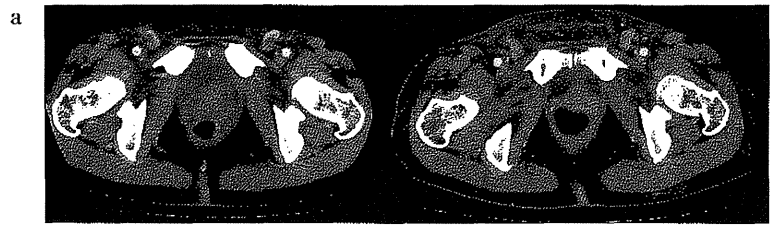

Fig. 5 Bilateral inguinal lymph node metastasis was no change after chemotherapy.
a: Before chemotherapy [BV (10 mg/kg)+FOLFOX].
b: After chemotherapy [BV (10 mg/kg)+FOLFOX].

Ⅱ. 考　察

大腸癌における遠隔リンパ節は領域外リンパ節に相当し，その転移は大腸癌取扱い規約（第7版）ではM1と定義される。遠隔リンパ節転移の頻度（1998年）は3.5%（190例/5,364例）[1]と比較的まれであり，CTV，MRI，PET/CTなどにて診断される。1997年の第44回大腸癌研究会アンケート調査によると#216転移率はS状結腸癌2.1%，直腸癌1.9%であり，それらの症例の臨床的特徴としては壁深達度が深く，低分化型腺癌・粘液癌・印環細胞癌の頻度が高く，高度脈管侵襲やリンパ節転移個数も多く認められ，さらに肝転移31%，腹膜播種は21%に認められ，57%が根治度Cであった。このことから#216郭清効果の意義はほとんどないと考えられ，化学療法を中心とした集学的治療が有効であると考えられるが，それを結論付けるためには症例の集積，RCTが必要である[2]。進行・再発大腸癌に対する化学療法は5-FU，L-OHP，CPT-11をkey drugとし，この3剤を使うこ

とにより20か月以上のMSTが得られるとされ[3]，これに分子標的薬を組み合わせることにより，さらに長い25か月以上のMSTが得られることが報告されている。BV併用療法は一次治療[4]，二次治療[5]としてOS延長が確認され，本邦の大腸癌治療ガイドライン2010年版[6]においても推奨されており，最近ではML18147試験で一次治療PD後の二次治療継続投与によりOSおよびPFSの有意な延長が確認された[7]。一方，二次治療以降でのBV再投与の際の用量増量についてのエビデンスは現在のところ確立しておらず，本邦においてL-OHP，BV既治療進行再発大腸癌に対する二次治療BV併用FOLFIRI療法におけるBV至適投与量の第Ⅲ相ランダム化比較試験（EAGLE study）が行われており，その結果が待たれるところである。本症例は結腸癌大動脈周囲リンパ節転移という遠隔リンパ節のみに転移が認められた，予後不良の比較的まれな症例であるが，一次治療でPDとなったBV+FOLFOX療法でもBVを増量し再投与することで，31か月という長期生存を得た。これは一次治療が19か月継続できたこと，またその後も腫瘍血管形成における促進因子であるVEGFを継続的に阻害したことが寄与したと考えられる。二次治療以降のBV増量投与による重篤な副作用（高血圧，蛋白尿，出血，消化管穿孔，血栓など）の発現を認めなかったことから，二次治療以降でもBV増量による再投与は検討される治療法の一つになると考えられる。本症例では腫瘍のK-ras遺伝子が野生型であったことから，二次治療として抗EGFR抗体薬を選択したが，今後はML18147試験の結果を踏まえて，K-ras遺伝子変異の有無にかかわらずBVの一次，二次継続治療も考慮される。皮膚転移は血行性，リンパ行性に生じる末期癌の一症状であるが，最後まで仕事を続けたいという患者の希望がかなえられ，終末期でも治療ができた貴重な症例と考えられた。

本論文の要旨は第48回日本癌治療学会総会（2010年10月，京都市）にて報告した。

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LIVER TRANSPLANTATION 20:298-310, 2014

ORIGINAL ARTICLE

Risk Factors for Alcohol Relapse After Liver Transplantation for Alcoholic Cirrhosis in Japan

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Alcoholic liver cirrhosis (ALC) is an established indication for liver transplantation (LT). Most LT procedures in Japan are living donor liver transplantation (LDLT) because of an extreme shortage of deceased donors. Social circumstances enabling LDLT could be favorable for preventing relapse. The aims of this retrospective study were to analyze the outcomes of LDLT for ALC and to evaluate risk factors for relapse in this cohort. One hundred ninety-five subjects underwent LT [LDLT (n = 187), deceased donor LT (n = 5), or domino LT (n = 3)] for ALC in Japan from November 1997 to December 2011. Risk factors for alcohol relapse and the impact of relapse on outcomes were analyzed for 140 patients after the exclusion of 26 patients who died in the hospital and 29 patients without information about alcohol relapse. The incidence of alcohol consumption after LT was 22.9%. The risk factors for patient survival were a donor age $\geq$ 50 years ($P < 0.01$) and a Model for End-Stage Liver Disease score $\geq$ 19 ($P = 0.03$). The 10-year patient survival rates were 21.9% and 73.8% for patients who had relapsed and patients who had not relapsed 18 months after LT, respectively ($P = 0.01$). The relapse rates were 50.0%, 34.5%, 13.3%, 19.7%, and 14.3% for patients who had received livers from parents, siblings, spouses, sons/daughters, and deceased or domino donors, respectively. A history of treatment for psychological diseases other than alcoholism before LT was a significant indicator for the risk of recidivism ($P = 0.02$), and noncompliance with clinic visits after LT and smoking after transplantation were promising indicators for the risk of recidivism ($P = 0.06$, and $P = 0.05$, respectively). Preoperative alcohol consumption was not a risk factor. In conclusion, rather than selecting patients on the basis of preoperative alcohol use, we should provide sociomedical support to improve adherence after LT for ALC in Japan. ***Liver Transpl 20:298-310, 2014.*** © **2013 AASLD.**

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Alcoholic liver cirrhosis (ALC) is the second most common indication for deceased donor liver transplantation (DDLT) for chronic liver disease in the Western world. In Japan, following cholestatic liver diseases and viral cirrhosis, ALC is the third most common indication.[1] Most liver transplantation (LT) in Japan involves living donors because of an extreme shortage of deceased donors.

Medical professionals have made considerable efforts to prevent graft loss secondary to the recurrence of the original disease; for example, they provide antiviral therapies to patients with hepatitis B or

Abbreviations: ABO-I AMR, ABO blood type incompatibility–related antibody-mediated rejection; ALC, alcoholic liver cirrhosis; CI, confidence interval; CTP, Child-Turcotte-Pugh; DIC, disseminated intravascular coagulation; DDLT, deceased donor liver transplantation; GRWR, graft/recipient weight ratio; HRAR, high-risk alcohol relapse; LDLT, living donor liver transplantation; LT, liver transplantation; MELD, Model for End-Stage Liver Disease; SLVR, standard liver volume ratio.

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hepatitis C, and they modify patient selection and organ distribution for patients with hepatocellular carcinoma. A patient with ALC may return to a pattern of alcohol consumption, which potentially can damage the transplanted liver and affect compliance with the immunosuppressive regimen and follow-up appointments; this may put the graft at risk.[2] Hence, selection criteria for predicting alcohol relapse from preoperative data and postoperative education and support to keep patients away from recidivism have been strengthened.[2-12]

In 1990, Bird et al.[3] reported the usefulness of an abstinence period of at least 6 months. Since then, the 6-month rule has been the most widely used criterion.[4-8] However, the length of abstinence before transplantation has not predicted alcohol relapse in some studies.[2,9,10] DiMartini et al.[11] found that each additional month of pretransplant sobriety lowered the risk of posttransplant drinking by 33%; however, they could not identify a specific length of pretransplant sobriety that predicted abstinence. Tandon et al.[12] obtained similar results in 2009.

De Gottardi et al.[13] applied a high-risk alcohol relapse (HRAR) scale,[14] which was originally designed to predict recidivism in nontransplant patients after alcohol rehabilitation, to the prediction of alcohol relapse after transplantation, and they found that an HRAR score > 3 was associated with harmful relapse. However, the independent predictive ability of the HRAR score for posttransplant recidivism remains controversial.[15] Familial and social support has also been reported to be important for preventing alcohol relapse.[10,16]

In DDLT, organs are considered to be a public resource that should be shared fairly and effectively. Hence, alcohol relapse could be considered a reason for transplant units and public opinion to deny transplantation. In living donor liver transplantation (LDLT), healthy relatives donate their organs to the patients. The conditions for alcohol relapse may be different after LDLT versus DDLT. For example, the relapse rate might be lower when patients are being watched by relatives, including donors; in such cases, LDLT might be favorable. The only report on LDLT for ALC came from a single-center study that showed a low recidivism rate for 13 patients selected according to very strict criteria.[7] No studies of recidivism after LDLT have been performed with a large cohort.

The aims of this study were (1) to analyze the outcomes of LDLT for ALC, (2) to find risk factors for patient survival, and (3) to evaluate risk factors for alcohol relapse in this cohort.

PATIENTS AND METHODS

LT for ALC was performed for 197 patients at 38 institutions according to the registry of the Japanese Liver Transplantation Society. These 38 institutions were sent questionnaires that asked about institutional policies for patient selection, patient characteristics, the preoperative alcohol consumption status of patients, treatments, postoperative living conditions, and clinical courses after transplantation for patients who underwent LT for ALC. Patient characteristics included the following: disease, age, sex, and blood types of the recipient and donor; relationship between the recipient and the donor; Model for End-Stage Liver Disease (MELD) score[17]; Child-Turcotte-Pugh (CTP) score[18]; hepatitis C, hepatitis B, and hepatocellular carcinoma status; smoking status; living or not living with the family or donor; occupational status; and marital status. The alcohol consumption status before transplantation included the duration of drinking, the amount of ethanol per day, the number of inpatient treatments for alcoholism, a history of psychiatric problems other than alcoholism, and the length of abstinence before transplantation. Treatment data included the graft/recipient weight ratio (GRWR), the standard liver volume ratio (SLVR), and follow-up by psychiatrists. Postoperative living conditions included the smoking status, living with family, living with the donor, and occupational status. The clinical course included alcohol relapse as well as rejection, surgical and infectious complications, renal dysfunction, malignancies, noncompliance with clinic visits (3 absences without notice), and follow-up by psychiatrists. Liver biopsy was performed on demand. Histological findings of liver biopsy specimens were collected from medical records. Data on mortality and causes of death were also collected. This retrospective, multicenter study was approved by the human ethics review board of Tokyo Women's Medical University (2417 on February 29, 2012) as the place of data collection and analysis in accordance with the Declaration of Helsinki (as revised in Seoul, Korea in October 2008).

Selection Criteria for LT for ALC

The indication for LT for ALC was based on a patient's history of alcohol consumption and clinical and laboratory findings determined before LT at each institution. At all institutions, psychiatrists interviewed the patients and their families and confirmed the absence of substance abuse, including alcohol abuse and dependence, and the presence of an agreement indicating the intention of lifetime abstinence after LT. Since 1997, the Assessment Committee of Indication for Transplantation has assessed patients and determined their priority on the waiting list for DDLT in Japan. Currently, this committee accepts only patients with ALC for DDLT who score 2 or lower on the HRAR scale.[14]

Pretransplant Alcohol Use and Other Psychosocial Variables

A history of alcohol intake was also obtained, and this included the duration of drinking, types and amounts of alcohol consumed, and previous treatment history. The HRAR score was calculated. This score consists of 3 variables: the duration of heavy drinking, the number of drinks per day, and the number of earlier inpatient treatments for alcoholism.[14] Other demographic and psychosocial information collected during the

pretransplant evaluation included the current or prior use of other substances, the diagnosis of substance use disorders and depressive or anxiety disorders, and treatment for psychiatric disorders. Pretransplant abstinence was defined as the time between the last consumption of alcohol and the date of the transplant.

Posttransplant Alcohol Use Outcomes

The diagnosis of alcohol relapse was based on patient self-reports, reports by the patient's relatives and friends, comments by the primary care physician, and relevant laboratory or histological findings, and relapse was divided into 2 stages: recidivism and harmful relapse. Recidivism was defined as any alcohol intake after transplantation, and the onset time was reported. Harmful relapse was defined as declared alcohol consumption associated with the presence of alcohol-related damage, either physical (including histological features of alcohol liver injury on liver biopsy specimens and abnormal values on biochemical examinations for which etiologies other than ethanol were ruled out) or mental.[13] The diagnosis of harmful relapse was made at the last follow-up during this study, and the onset time was not available.

Three alcohol relapse patterns were defined [adapted from a study by DiMartini et al.[11]]: (1) relapse within 6 months of transplantation, (2) frequent use (4 drinking days per week), and (3) binge use (72 g of ethanol or more for men and 48 g of ethanol for women per day).

Statistical Analysis

Survival curves were constructed with the Kaplan-Meier method. In univariate and multivariate analyses, the log-rank test and Cox proportional hazards regression analysis were used to evaluate the association between patient characteristics and overall survival. Receiver operating characteristic curves were plotted, and areas under the curve were calculated to assess the optimal cutoff values for the MELD score, GRWR, and SLVR in the analysis of prognostic factors for patient survival.

The log-rank test and Cox proportional hazards regression analysis were also used to evaluate the association between patient characteristics and the incidence of recidivism in univariate and multivariate analyses. The incidence of harmful relapse was compared by means of the chi-square test, and multivariate logistic regression analysis was used to evaluate the association between patient characteristics and harmful relapse.

JMP 10.0 (SAS Institute, Inc., Cary, NC) was used for the statistical analysis.

RESULTS

Patients

Clinical and laboratory data were available for 195 patients who underwent LT at 36 of 38 institutions between November 1997 and December 2011. Among the 195 patients, 26 patients died before discharge after transplantation. Among the 169 patients who were discharged, information about alcohol relapse was available for 140 patients, and information about harmful relapse was available for 139 patients. The length of the follow-up period ranged from 3 to 4962 days with a median of 1319 days.

An analysis of prognostic factors for survival was performed for 195 patients. An analysis of risk factors for recidivism and the impact of recidivism on patient survival was performed for 140 patients, and an analysis of risk factors for harmful relapse and the impact of harmful relapse on patient survival was performed for 139 patients (Fig. 1).

Demographic data for the 195 patients are shown in Table 1. The MELD score ranged from 6 to 48 with a median value of 20. For most patients, the CTP score was C. The recipients' ages ranged from 25 to 69 years with a median age of 35 years. The donors' ages ranged from 17 to 65 years with a median age of 52 years. The blood type combination was identical for 127 patients, compatible for 49 patients, incompatible for 17 patients, and unknown for 2 patients. Six patients had a hepatitis C infection, 4 patients were positive for hepatitis B DNA, and 47 had hepatocellular carcinoma. GRWR ranged from 0.44% to 2.4% with a median value of 0.88%. SLVR ranged from 23.6% to 126% with a median value of 46.0%. Sixty-nine patients were male, and 195 patients were female. One hundred eighty-seven patients underwent LDLT, 5 patients underwent DDLT, and 3 patients had domino LT.

Institutional Policy of Patient Selection for LT for ALC in the Setting of LDLT

A period of abstinence of at least 6 months before LT was absolutely mandated at 21 institutions, was not required at all at 4 institutions, and was preferred but ignored in life-threatening cases at 11 institutions. The HRAR score was used for patient selection for LDLT at 13 institutions and was not used at 23 institutions.

Analysis of Prognostic Factors for Patient Survival

In univariate analyses, prognostic factors that were significantly and favorably associated with patient survival were a low MELD score (<19 versus ≥ 19) and a low donor age (<50 years versus ≥ 50 years). Both the MELD score and the donor age were also significant factors in the multivariate analysis (Tables 1 and 2).

Morbidity and Mortality

Postoperative comorbidities are shown in Table 3. The major complications were biliary complications ($n = 41$), cytomegalovirus infections ($n = 38$), bacterial infections ($n = 37$), acute cellular rejection ($n = 34$), and intra-abdominal hemorrhaging ($n = 26$). The causes of deaths before discharge for 26 patients are shown in Table 4. The most common causes were

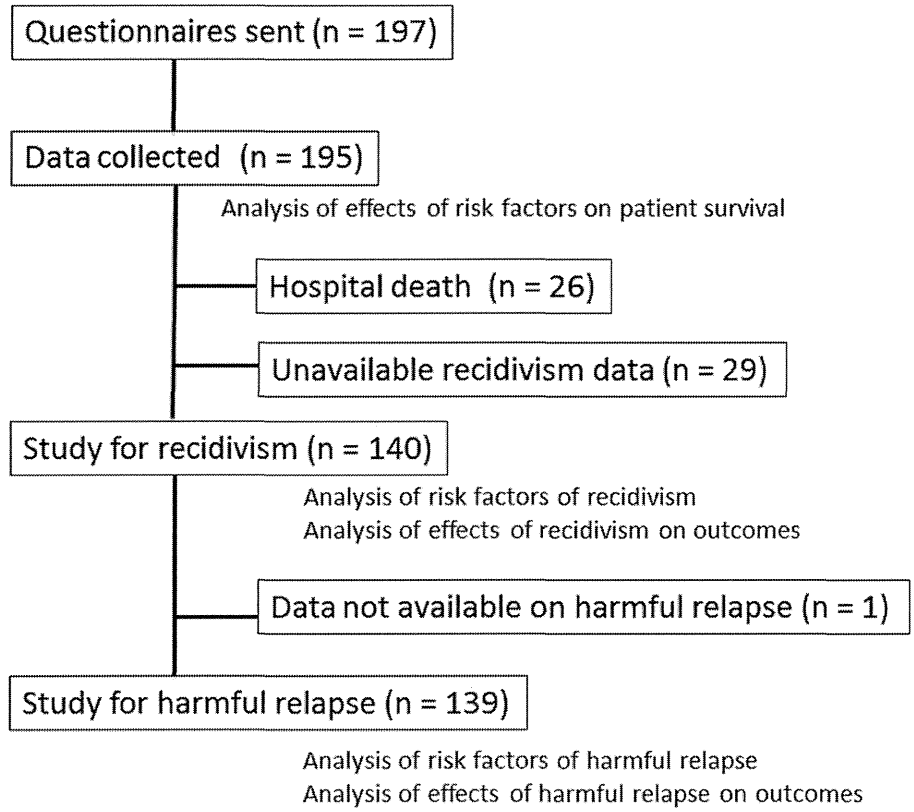


Figure 1. Patient enrollment and inclusion in our analysis. Questionnaires were sent to 38 centers for 197 patients. Clinical data were collected for 195 patients from 36 centers, and risk factors for patient survival were analyzed for these patients. Risk factors for recidivism and the impact of recidivism on patient survival were analyzed for 140 patients after 55 patients were excluded (26 who died in the hospital and 29 without data about recidivism). Data on harmful relapse were obtained and analyzed for 139 patients.

infectious complications (n = 10), small-for-size syndrome (n = 3), acute cellular rejection (n = 3), and hepatic artery thrombosis (n = 2).

The causes of death after discharge for 23 patients and their survival periods are shown in Table 5. Six patients died because of infectious complications; 7 died because of malignancies, including recurrent hepatocellular carcinoma; 2 died because of cerebral or myocardial vascular complications; and 1 died because of chronic rejection. Two patients died because of ALC on postoperative days 2526 and 4641.

There were 5 de novo tumors, including 2 gastric cancers and 3 squamous cell cancers. All 5 patients with these malignancies were abstinent and did not smoke after transplantation. Interestingly, however, all 5 patients had smoked before transplantation and quit after LT. The incidence of de novo malignancies increased as the quantity of daily drinking before transplantation increased on the HRAR scale [2.4% (1/41) with 108 g of ethanol or less each day, 6.1% (2/33) with >108 g-<204 g of ethanol each day, and 9.1% (2/22) with 204 g of ethanol or more each day], although there was no significant relationship ($P = 0.50$).

Risk Factors for Alcohol Relapse

The significant risk factors for recidivism were a positive history of treatment for psychological diseases other than alcoholism before transplantation, an absence of a marital history, noncompliance with clinic visits after transplantation, and smoking after transplantation according to univariate analyses adjusted by the time of onset (Table 6). The significant risk factors for harmful relapse were living alone before LT, no marital history before LT, and noncompliance with clinic visits after LT (Table 6). The HRAR score had no relationship with the incidence of recidivism or harmful relapse. Six months of abstinence before LT had no significant impact. Abstinence for 24 months or longer decreased the incidence of harmful relapse (to 3.3%), but this difference was not significant. The occupational status had no impact on the incidence.

Risk factors for recidivism and harmful relapse that were significant ($P < 0.05$) in the univariate

TABLE 1. Influence of Pretransplant Risk Factors on Patient Survival in 195 Patients With ALC: A Log-Rank Analysis

Characteristic	Patients (n)	Patient Survival (%) 1 Year	3 Years	5 Years	10 Years	Log-Rank *P* Value
Entire cohort	195	82.5	78.4	74.5	50.4	
MELD score						0.04*
≥19	103	76.5	72.0	72.0	40.1	
<19	84	89.2	86.7	82.6	49.5	
Unknown	8	—	—	—	—	
CTP score						0.17
A	5	80.0	80.0	53.3	—	
B	43	83.7	83.7	79.0	67.7	
C	141	82.2	77.4	76.2	40.5	
Unknown	6	—	—	—	—	
Recipient age						0.96
≥50 years	117	82.0	77.1	75.7	66.0	
<50 years	78	81.9	80.3	78.3	39.5	
Donor age						0.01*
≥50 years	44	81.5	72.8	67.9	—	
<50 years	151	83.0	80.0	78.0	64.0	
Blood type combination						0.17
Identical	127	83.4	79.6	76.6	46.3	
Compatible	49	83.6	79.3	76.5	41.2	
Incompatible	17	68.2	64.2	64.2	—	
Unknown	2	—	—	—	—	
Hepatitis C						0.65
Yes	6	83.3	83.3	—	—	
No	186	81.6	77.9	75.2	52.3	
Unknown	3	—	—	—	—	
Hepatitis B DNA–positive						0.65
Yes	4	100.0	100.0	100.0	—	
No	190	81.4	77.8	75.1	51.4	
Unknown	1	—	—	—	—	
Hepatocellular carcinoma						0.97
Yes	47	87.1	77.7	74.1	60.5	
No	148	81.0	78.6	76.2	49.2	
GRWR						0.16
≥0.7%	156	84.5	80.4	77.6	5.4	
<0.7%	34	70.6	67.4	67.4	—	
Unknown	5	—	—	—	—	
SLVR						0.08
≥30%	179	82.6	78.8	75.9	50.2	
<30%	7	57.1	57.1	57.1	—	
Unknown	9	—	—	—	—	

*$P < 0.05$.

TABLE 2. Multivariate Analysis of Pretransplant Risk Factors for Patient Survival in 195 Patients With ALC: A Proportional Hazards Analysis

Risk Factor	Risk Ratio	95% CI	*P* Value
Donor age ≥ 50 years	2.33	1.28-4.13	<0.01*
MELD score ≥ 19	1.91	1.07-3.55	0.03

*$P < 0.05$.

analysis were chosen for the multivariate analysis. A history of treatment for psychological diseases other than alcoholism before transplantation was a significant indicator of the risk of recidivism, and noncompliance with clinic visits after transplantation and smoking after transplantation were promising indicators of the risk of recidivism ($P = 0.06$ and $P = 0.05$, respectively; Table 7). Noncompliance with clinic visits was a significant indicator of the risk of harmful relapse.

The rates of recidivism were similar for patients living with donors (22.9% before LT and 27.9% after LT) and patients not living with donors (26.4% before LT and 25.9% after LT). Recidivism was high when the donors were parents (50.0%) or siblings (34.5%), but it was much lower when the donors were children (19.7%), spouses (13.3%), or nonrelatives (14.3%), although the difference was not

significant (Table 6). Similarly, the incidence of harmful relapse was much higher, but not significantly so, when the donors were parents or siblings versus when the donors had other relationships with the recipients (Table 6).

TABLE 3. Comorbidities After Transplantation in 195 Patients

Comorbidities	Patients (n)
Biliary complications	41
Cytomegalovirus diseases	38
Bacterial infection	37
Acute cellular rejection	34
Intra-abdominal hemorrhage	26
Malignancies*	13
Vascular complications	12
Fungal infection	12
Permanent dialysis	8
Steroid-resistant acute cellular rejection	5
Chronic rejection	2

*Recurrence of hepatocellular carcinoma (n = 8), gastric cancer (n = 2), lung squamous cell cancer (n = 1), tongue squamous cell cancer (n = 1), and frontal sinus squamous cell cancer (n = 1).

TABLE 4. Causes of Hospital Deaths

Cause of Death	Patients (n)
Infection	10
Small-for-size syndrome	3
Acute cellular rejection	3
Chronic rejection	1
Hepatic artery thrombosis	2
Portal vein flow insufficiency	1
Cerebral hemorrhage	1
ABO-I AMR	1
Graft-versus-host disease	1
Multiorgan failure	1
Biliary stenosis	1
Graft injury	1

Impact of Alcohol Consumption After LT on Patient Survival

The survival rates were compared for recidivist patients and abstinent patients 18 months after LT. Five patients for whom the time of relapse was not obtained and 10 patients who had died within 18 months of LT were excluded from this analysis. The survival rates were 100.0%, 94.7%, 89.5%, 65.7%, and 21.9% at 1, 3, 5, 7, and 10 years, respectively, for recidivist patients and 100.0%, 98.6%, 96.4%, 92.7%, and 73.8% at 1, 3, 5, 7, and 10 years, respectively, for abstinent patients. There was a significant difference in survival ($P = 0.01$; Fig. 2).

Impact of Alcohol Consumption Status on Harmful Relapse

The impact of an early onset of drinking, frequent drinking, and the consumption of large amounts of alcohol after LT on the incidence of harmful relapse was analyzed in 32 recidivist patients. The incidence of harmful relapse was higher for patients who consumed alcohol 4 days or more per week (88.9%) versus patients who drank less frequently (35.7%, $P = 0.008$; Table 8), and it was higher for patients who binged (100%) versus patients who drank less (25%, $P = 0.002$; Table 8). One patient showed all 3 patterns of harmful drinking, and 5 patients showed 2 of the 3 patterns.

Histological Changes in the Liver After LT

Liver biopsy was performed for 20 recidivist patients and 53 abstinent patients. Results from biopsy samples obtained before hospital discharge were included. The incidence of fatty changes was greater in the recidivism group (45.0%) versus the abstinent group (13.2%; Table 9). In contrast, the incidence of rejection was greater in the abstinent group (30.6%) versus

TABLE 5. Causes of Death After Discharge

Cause of Death	Patients (n)	Survival Period (Days)
Infection	6	3802, 2256, 662, 517, 328, 295
Hepatocellular carcinoma recurrence	5	2588, 2057, 422, 357, 300
Gastric cancer	1	2309
Lung cancer	1	195
Cholangitis	2	3302, 1414
Alcoholic cirrhosis	2	2526, 4641
Arachnoid hemorrhage	1	246
Myocardial infarction	1	2983
DIC/lung edema	1	1990
Chronic rejection	1	528
Accident	1	3361
Intra-abdominal hemorrhage	1	373

TABLE 6. Univariate Analysis of Risk Factors for Recidivism and Harmful Relapse After Transplantation

Risk Factor	Patients (n)	Recidivism: Log-Rank Test [n/N (%)]*	*P* Value	Patients (n)	Harmful Relapse: Chi-Square Test [n/N (%)]†	*P* Value
Before transplantation						
HRAR score			0.48			0.24
0	8	1/8 (12.5)		8	1/8 (12.5)	
1	25	8/25 (32.0)		25	6/25 (24.0)	
2	40	8/40 (20.0)		40	4/40 (10.0)	
3	16	4/16 (25.0)		15	3/15 (20.0)	
4	9	1/9 (11.1)		9	0/9 (0.0)	
Unknown	42	—		42	—	
Duration of heavy drinking			0.41			0.50
≥25 years	41	9/41 (22.0)		41	4/41 (9.8)	
<11->25 years	32	7/32 (21.9)		31	6/31 (19.4)	
≤11 years	31	9/31 (29.0)		31	7/31 (22.6)	
Unknown	36	—		36	—	
Daily alcohol consumption‡			0.96			0.47
≤9 g	43	11/43 (25.6)		43	9/43 (20.9)	
<9->17 g	36	8/36 (22.2)		36	4/36 (11.1)	
≥17 g	23	5/23 (21.7)		22	3/22 (13.6)	
Unknown	38	—		38	—	
Pretransplant abstinence			0.39			0.68
≥6 months	100	19/100 (19.0)		99	13/99 (13.1)	
<6 months	31	9/31 (29.0)		31	5/31 (16.1)	
Unknown	9	—		9	—	
Pretransplant abstinence			0.77			0.19
≥24 months	31	5/31 (16.1)		30	1/30 (3.3)	
12-24 months	20	3/20 (15.0)		20	3/20 (15.0)	
6-12 months	49	11/49 (22.4)		49	9/49 (18.4)	
<6 months	31	9/31 (29.0)		31	5/31 (16.1)	
Unknown	9	—		9	—	
History of treatment for psychiatric diseases other than alcoholism			<0.01‡			0.17
Yes	9	5/9 (55.6)		9	3/9 (33.3)	
No	125	27/125 (21.6)		125	18/125 (14.4)	
Unknown	6	—		5	—	
Recipient sex			0.16			0.73
Male	88	23/88 (26.1)		88	14/88 (15.9)	
Female	52	9/52 (17.3)		51	7/51 (13.7)	
Smoking			0.12			0.43
Smoking	46	15/46 (32.6)		46	10/46 (21.7)	
No history	24	5/24 (20.8)		24	3/24 (12.5)	
Quit	59	8/59 (13.6)		58	6/58 (10.3)	
Unknown	11	—		11	—	
Living			0.08			0.03‡
With family	122	27/122 (22.1)		121	16/121 (13.2)	
Alone	9	4/9 (44.4)		9	4/9 (44.4)	
Unknown	9	—		9	—	
Marital status			0.04‡			0.04‡
Stable partner	106	24/106 (22.6)		105	15/105 (14.3)	
Widowed/divorced	10	1/10 (10.0)		10	1/10 (10.0)	
No marital history	13	6/13 (46.2)		13	5/13 (38.5)	
Unknown	11	—		11	—	
Living with donor			0.99			0.28
Yes	70	16/70 (22.9)		69	8/69 (11.6)	
No	53	14/53 (26.4)		53	11/53 (20.8)	
Unknown	17	—		17	—	
Occupational status			0.41			0.85
No	42	9/42 (21.4)		41	7/41 (17.1)	
Part time	13	2/13 (15.4)		13	1/13 (7.7)	
Full time	64	16/64 (25.0)		64	10/64 (15.6)	
Unknown	21	—		21	—	

TABLE 6. *Continued*

Risk Factor	Patients (n)	Recidivism: Log-Rank Test [n/N (%)]*	*P* Value	Patients (n)	Harmful Relapse: Chi-Square Test [n/N (%)]†	*P* Value
After transplantation						
Noncompliance with clinic visits			<0.01‡			0.03§
Yes	8	4/8 (50.0)		7	4/7 (57.1)	
No	131	8/131 (6.1)		131	17/131 (13.0)	
Unknown	1	—		1	—	
Followed by psychiatrists			0.78			0.78
Yes	29	7/29 (24.1)		29	5/29 (17.2)	
No	108	25/108 (23.1)		107	16/107 (15.0)	
Unknown	3	—		3	—	
Smoking			<0.01‡			0.09
Yes	24	11/24 (45.8)		24	7/24 (29.2)	
No	73	12/73 (16.4)		72	7/72 (9.7)	
Unknown	43	—		43	—	
Living			0.25			0.07
With family	107	25/107 (23.4)		107	17/107 (15.9)	
Alone	8	4/8 (50.0)		8	3/8 (37.5)	
Unknown	25	—		24	—	
Living with donor			0.46			0.07
Yes	43	12/43 (27.9)		43	7/43 (16.3)	
No	58	15/58 (25.9)		57	12/57 (21.1)	
Unknown	39	—		39	—	
Occupational status			0.18			0.34
No	51	14/51 (27.5)		50	8/50 (16.0)	
Part time	14	4/14 (28.6)		14	4/14 (28.6)	
Full time	38	9/38 (23.7)		38	6/38 (15.8)	
Unknown	37	—		37	—	
Donors			0.07			0.07
Parent	6	3/6 (50.0)		6	3/6 (50.0)	
Sibling	29	10/29 (34.5)		29	8/29 (27.6)	
Son/daughter	61	12/61 (19.7)		61	4/61 (6.6)	
Nonrelative	7	1/7 (14.3)		7	1/7 (14.3)	
Spouse	30	4/30 (13.3)		29	3/29 (10.3)	
Nephew	3	1/3 (33.3)		3	1/3 (33.3)	
Cousin	1	0/1 (0.0)		1	0/1 (0.0)	
Brother-in-law	2	1/2 (50.0)		2	1/2 (50.0)	
Nephew-in-law	1	0/1 (0.0)		1	0/1 (0.0)	

*32/140 (22.9%).
†21/139 (15.1%).
One drink = 12 g of ethanol.
‡$P < 0.05$ (chi-square test)

the recidivism group (25.0%; Table 9). Alcoholic damage was found in 3 patients with recidivism.

Information on the presence or absence of acute cellular rejection after discharge was obtained from 130 patients. The incidence of rejection was 6.9% (2/29) for recidivist patients and 5.0% (5/101) for patients who were abstinent.

Patients for Whom Information on Alcohol Relapse Was Not Available

Twenty-nine patients for whom information on alcohol relapse was not available were excluded from the statistical analysis of alcohol relapse. To understand the impact of this exclusion on the results, we analyzed the overall survival and frequency of risks for recidivism for the 29 patients. There was no significant difference in overall survival between abstinent patients, relapsing patients, and patients of an unknown status (data not shown; $P = 0.09$, log-rank test). For abstinent patients, relapsing patients, and patients of an unknown status, the frequency of noncompliance with clinic visits was 3.7%, 12.5%, and 15.4%, respectively ($P = 0.03$); the frequency of smoking after LT was 17.5%, 47.8%, and 100.0%, respectively ($P < 0.001$); the frequency of no marital history was 7.1%, 19.3%,

TABLE 7. Multivariate Analysis of Risk Factors for Recidivism and Harmful Relapse

	Proportional Hazards Analysis		
Risk Factors for Recidivism	Risk Ratio	95% CI	*P* Value
History of treatment for psychiatric diseases other than alcoholism: yes versus no	5.15	1.26-17.78	0.02*
Marital status			
Stable partner	1.00	—	
Widowed/divorced	0.45	0.02-2.46	0.41
No marital history	1.24	0.34-4.99	0.75
Noncompliance with clinic visits: yes versus no	4.36	0.92-15.43	0.06
Posttransplant smoking: yes versus no	2.67	0.97-7.00	0.05

	Logistic Regression Analysis		
Risk Factors for Harmful Relapse	Odds Ratio	95% CI	*P* Value
History of treatment for psychiatric diseases other than alcoholism: yes versus no	5.15	1.26-17.78	0.02*
Marital status			
Stable partner	1.00	—	
Widowed/divorced	0.45	0.02-2.46	0.41
No marital history	1.24	0.34-4.99	0.75
Noncompliance with clinic visits: yes versus no	4.36	0.92-15.43	0.06
Posttransplant smoking: yes versus no	2.67	0.97-7.00	0.05
Pretransplant living: alone versus family	3.21	0.43-23.46	0.25
Pretransplant marital status			
Stable partner	1.00	—	
Widowed/divorced	0.31	0.01-2.32	0.28
No marital history	2.41	0.38-11.76	0.32
Noncompliance with clinic visits: yes versus no	16.32	2.56-149.34	0.004*

*$P < 0.05$.

and 4.2%, respectively ($P = 0.14$); and the frequency of a history of treatment for psychiatric diseases other than alcoholism was 3.9%, 15.6%, and 6.9%, respectively ($P < 0.001$). Although these 29 patients were less compliant with clinic visits than abstinent patients, 21 of the 29 patients visited the clinic regularly, 4 patients fell into noncompliance, 1 patient died, 1 patient changed hospitals, and the data for 2 patients were unknown. However, for 28 of the 29 patients (including 1 deceased patient), data for smoking as well as relapse data were not available.

Interactions Between Recipients Who Returned to Harmful Drinking and Related Donors

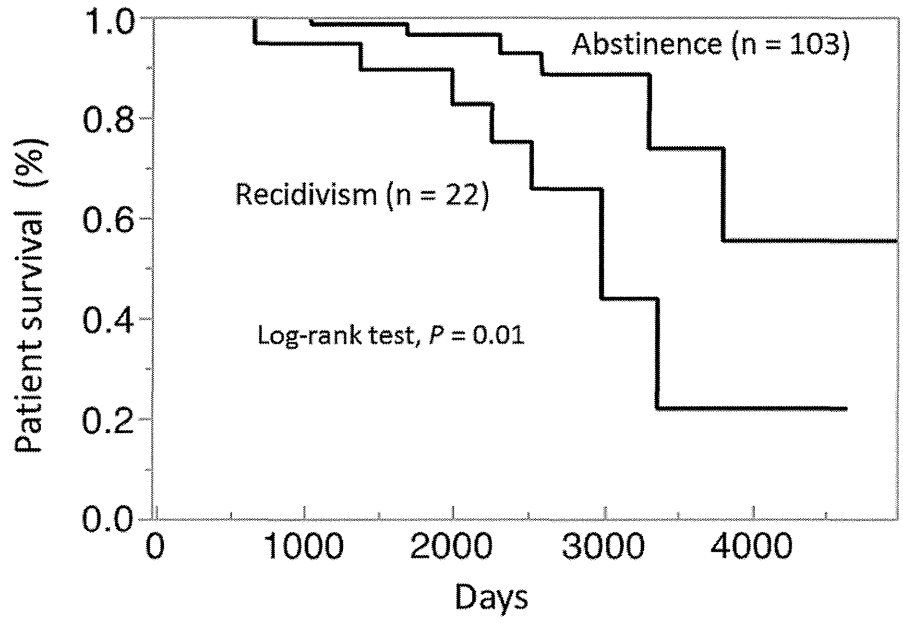
We hypothesized that interactions between a recipient who returns to harmful drinking and the family member who donated the liver might affect outcomes. Although we were not able to examine this directly, we compared the survival rates between recipients living with their donors and recipients who lived separately from their donors. The survival rates were 95.2%, 86.4%, 86.4%, 71.2%, and 63.3% at 1, 3, 5, 7, and 10 years, respectively, for recipients living with donors and 100.0%, 98.2%, 92.0%, 83.5%, and 41.8% at 1, 3, 5, 7, and 10 years, respectively, for recipients living without donors ($P = 0.66$). Although this result does not address the existence or absence of a change in the relationship after the onset of harmful drinking, if such changes do occur, they do not affect survival.

DISCUSSION

Patients undergoing LT for ALC must pledge to remain sober in order to protect the transplanted liver. However, not all recipients are able to maintain sobriety. Alcohol relapse can have a number of negative impacts, including (1) liver dysfunction secondary to alcohol toxicity, (2) noncompliance with medications or clinic visits, (3) rejection secondary to noncompliance, (4) graft failure secondary to rejection or alcohol toxicity, and (5) malignancies and cardiovascular diseases possibly related to smoking (which is highly associated with alcohol relapse). The perception that recipients will relapse may also decrease the willingness of others to donate organs.

Harmful Drinking and Impact

Reports have differed in both the definitions used for harmful drinking and its effects after LT. Schmeding



Numbers at risk	0 years	1 year	3 years	5 years	7 years	10 years
Recidivism	22	22	19	14	7	2
Abstinence	103	103	70	42	25	5

Figure 2. Impact of alcohol relapse on patient survival: comparison of recidivism and abstinence 18 months after transplantation. There was a significant difference in survival between the groups (log-rank test, $P = 0.01$).

TABLE 8. Impact of the Alcohol Consumption Status on Harmful Relapse in 32 Patients With Recidivism

	Patients (n)	Harmful Relapse [n/N (%)]	*P* Value
Recidivism within 6 months			0.91
Yes	12	8/12 (66.7)	
No	16	11/16 (68.8)	
Unknown	4	—	
Frequent use*			0.008†
Yes	9	8/9 (88.9)	
No	14	5/14 (35.7)	
Unknown	9	—	
Binge use‡			0.002†
Yes	6	6/6 (100.0)	
No	8	2/8 (25.0)	
Unknown	18	—	

*Four drinking days per week.
†$P < 0.05$ (chi-square test).
‡Seventy-two grams of ethanol or more for men and 48 g of ethanol or more for women.

et al.[15] found significantly lower 10-year patient survival for patients with alcohol consumption of 80 g/day or more for men or 20 g/day or more for women, and Cuadrado et al.[16] found significantly lower 10-year patient survival for patients with alcohol consumption of 30 g/day or more. In contrast, Tandon et al.[12] defined problem drinking as either any drinking to the point of intoxication or drinking above the

TABLE 9. Histological Changes in Liver Biopsy Samples Throughout the Study

Histological Findings	Recidivism (n = 20)	Abstinence (n = 53)
Minimal or normal changes	2 (10.0)	10 (18.9)
Fatty changes	9 (45.0)	7 (13.2)
Alcoholic damage	3 (15)	0
Cholestatic changes	0	4 (7.5)
Hepatitis	1 (5.0)	6 (11.3)
Rejection	5 (25.0)	21 (39.6)
Fibrosis	0	2 (3.8)
Hepatocellular carcinoma	0	1 (1.9)
Other changes	0	2 (3.8)

NOTE: The data are presented as numbers and percentages. $P = 0.01$ (chi-square test).

toxic threshold (>20 g/day for women and >40 g/day for men) on at least 2 separate occasions, and they found no effect of problem drinking on posttransplant mortality in a North American cohort. Frequent use and binge use contributed to harmful relapse, but early relapse did not. Harmful relapse was significantly related to noncompliance with clinic visits, although our study did not reveal whether noncompliance caused harmful relapse or vice versa because we did not have access to the timing of these elements.

Noncompliance and Rejection

Webb et al.[17] noted that the resumption of problem drinking can lead to noncompliance with the transplant follow-up program, which can, in turn, lead to rejection. In our study, the incidence of noncompliance with clinic visits was significantly greater for patients who had resumed drinking, but the rates of acute cellular rejection confirmed by liver biopsy were similar for the groups. The only patient who died because of chronic rejection was abstinent.

Malignancies and Cardiovascular Diseases

Alcohol use can contribute to the mortality of transplant recipients because of a variety of proximal causes. Burra et al.[18] reported that de novo tumors, cardiovascular events, and social causes (including noncompliance with immunosuppressive therapy, suicide, and trauma) were causes of death or graft failure for a higher percentage of those with alcohol disease in comparison with patients with other etiologies in a large cohort from the European Liver Transplant Registry.[18] Cuadrado et al.[16] reported significantly lower patient survival for patients with alcohol relapse and suggested that alcohol consumption and tobacco use may have contributed to cancer and cardiovascular events, which were frequent causes of death; however, they did not compare the incidences of these diseases between patients who relapsed into alcohol use or smoked and patients who did not. In our study, overexposure to the toxicity of alcohol and nicotine before transplantation might have been a risk factor for postoperative extrahepatic malignancies under immunosuppression therapy. Careful follow-up focusing on malignancies is recommended after LT for ALC whether or not the patient relapses.

Relapse Rates in DDLT and LDLT

In DDLT, organs are considered to be a public resource that should be shared fairly and effectively. Hence, alcohol relapse may result in public opposition to transplantation for ALC. In a study that defined relapse as any alcohol use, the rate of posttransplant alcohol consumption appeared to be quite high: approximately 50% of patients (range = 7%-95%) at a follow-up visit 21 to 83 months after transplantation.[19] We had hypothesized that recidivism might be lower among patients in Japan who had received transplants from family members, but our findings were more complicated. The incidence of recidivism for patients who had received donations from unrelated persons, including brain-dead donors and domino donors, was 14.3%, and the incidence for those who had received donations from spouses was 13.3%, whereas the incidence of recidivism for patients who had received donations from relatives other than spouses was higher (23.3%). The rates of recidivism and harmful relapse were quite high (27.6%-50.0%) when the donors were parents or siblings. Thus, contradicting our hypothesis, the relapse rate is not ubiquitously low for LDLT patients; instead, it is high, especially when a parent is the donor. As for interactions between related donors and relapsing patients, there were no episodes such as divorce or disownment due to recidivism after LT in this cohort as far as personal communications show. The related donors who accepted their own risks before LT might have forgiven the recipients who had relapsed after LT because of their voluntary donation on behalf of love.

We feel that DDLT is suitable for LT for ALC from the point of view of the relapse rate, but efforts are required to decrease the rate even further to ensure that public opinion about organ donation for ALC is favorable.

Limitations

The findings of this retrospective, multicenter study are limited by several factors inherent to this type of study, including variability in documentation, differences in selection criteria and data collection, and missing data. To minimize variability, we sent a standardized collection form containing 150 questions to the transplant centers. The answers either were to be chosen from several options or involved providing a name or a specific value. However, the quality of the pretransplant interviews, from which the baseline data were derived, and the quality of the posttransplant follow-up data across the 36 centers may have varied. The HRAR, CTP, and MELD scores were calculated by H.E. and S.T. The results could have been affected by missing data if the patients who were lost to follow-up were lost because of their drinking, but we cannot know if this is the case. Finally, the element of time should be taken into account in the statistical analyses because the subjects had different lengths of follow-up. Although we had data for the onset of recidivism, we did not have data for the onset of harmful relapse and noncompliance. To solve these limitations, a well-designed prospective study will be necessary.

How Can We Decrease Relapse?

The significantly lower survival rate for relapsing patients shown in this study indicates that preventing relapse is the central strategy for LT for ALC. In order to develop good protocols to decrease relapse, it is important to identify the major (and treatable) risks. Tandon et al.[12] reported that the duration of pretransplant abstinence was a strong predictor of posttransplant problem drinking in a North American cohort of patients undergoing transplantation for alcohol-related liver disease, but they failed to show the optimal period of abstinence. De Gottardi et al.[13] reported the utility of the HRAR score for predicting relapse after transplantation. Gish et al.[20] reported that noncompliance and personality disorders independently predicted recidivism. Kelly et al.[10] identified the following 6 potential predictors of harmful relapse: mental illness, the lack of a stable partner, grams of alcohol consumed per day at the time of assessment, reliance on family or friends for posttransplant support, tobacco consumption at the time of assessment, and lack of insight into alcohol as the cause of the liver disease.[10] Our current study showed that a history of treatment for psychological diseases other than alcoholism before transplantation was a significant indicator of the risk of recidivism, and noncompliance with clinic visits after transplantation and smoking after transplantation were promising (but not statistically significant) indicators. Noncompliance with clinic visits was a significant indicator of the risk of harmful relapse. Notably, we did not find that the HRAR score predicted recidivism or harmful relapse. Because of severe organ shortages, the Japanese Assessment Committee of Indication for Transplantation has used an HRAR score ≤ 2 as a selection criterion for DDLT for ALC in accordance with De Gottardi et al. However, on the basis of our findings, the Japanese Assessment Committee of Indication for Transplantation recently removed the HRAR score restriction.

Although the use of LDLT for ALC is increasing, alcohol relapse after transplantation is not yet widely recognized in Japanese society, and this is the first report on the risk factors for and frequency of relapse in patients undergoing LDLT for ALC in Japan. What Japanese society requests from clinical specialists is not punishment but rescue. To decrease the relapse rate, we have 2 options: we can restrict the patients who receive transplants on the basis of pretransplant indicators, or we can use professional personnel, such as psychiatrists, addiction specialists, and well-trained recipient coordinators, to provide systematic support to high-risk patients. We believe that improving compliance through systematic professional support is necessary for patients undergoing LT for ALC in Japan.

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Reply

We thank Dr Li and colleagues for their interest in our study.

There are data[1] supporting race as a risk factor for stroke and mortality after carotid endarterectomy, the risk being higher in persons of black race compared with white. The risk of complications for other races is unclear. Although it may be premature to generalise these findings to a mixed vascular surgery population and cardiac complications, it would have been interesting to assess the association between race and cardiac outcome. Unfortunately, data regarding race are not available in the study population.

Preoperative anaemia and blood loss are well-accepted risk factors for cardiac events after vascular surgery[2]. We adjusted for preoperative anaemia in multivariable analysis. However, blood loss is an intraoperative event and is therefore impossible to incorporate in preoperative cardiac risk stratification, which is the focus of our study. Furthermore, the amount of perioperative blood loss is unlikely to be influenced by the presence or absence of diabetes mellitus, making it unlikely as a confounding factor.

As pointed out by Li et al, intraoperative hypotension and tachycardia are undoubtedly influential on the risk of ischaemic myocardial injury. However, as stated above, preoperative cardiac risk assessment will have to rely on data available preoperatively. Therefore we chose not to include data on intraoperative haemodynamics.

Routine troponin measurements were performed three times a week during admission (or whenever clinically indicated). We agree with Li et al that this may have led to an underestimation of the risk of cardiac events. However, this effect is likely to be equally present in diabetics and non-diabetics and is therefore unlikely to limit the validity of the study.

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APRV in patients with atelectasis after liver transplantation

Atelectasis frequently occurs after living donor liver transplantation (LDLT)[1] and it is a risk factor for hypoxaemia and pneumonia. Airway pressure release ventilation (APRV), a mode providing two levels of airway pressure (P_{high} and P_{low}) during two set time periods (T_{high} and T_{low}), is one method that can be used to treat atelectasis. As far as we know, no studies have evaluated the impact of APRV on atelectasis and the hepatic blood-flow after LDLT.

After obtaining institutional ethics approval (013-0199), we compared the outcomes of patients who were ventilated with APRV after LDLT between January and December 2008. During this study period, APRV was used in patients who were more than 12 years old, with atelectasis confirmed on a chest X-ray within two days of LDLT. For each APRV patient we chose a similar historical control patient who was ventilated by synchronised intermittent mandatory ventilation (SIMV) after LDLT between October 2003 and December 2007. The ventilator settings and level of sedation were adjusted so that the PaO_2 was >100 mmHg, the $PaCO_2$ was 40±5 mmHg and the Richmond Agitation Sedation Scale was between -3 and 0, during either SIMV or APRV ventilation. The exclusion criteria included: 1) reoperation, 2) bilateral thoracentesis and 3) intolerance to APRV for at least 12 hours.

The weaning method consisted of continuous positive airway pressure or continuous positive airway pressure with pressure support in both groups, and the endotracheal tube was removed when the patients met all the following criteria: 1) stable liver function, 2) no haemodynamic instability, 3) PaO_2 to FiO_2 ratio of >200, 4) positive end-expiratory pressure of <5 cmH_2O and 5) pressure support of <5 cmH_2O.

During the study period, nine patients were treated with APRV (mean age=46.0 ± standard deviation 13, 4 male/5 female, body mass index=25.9±3.5, Model for End-Stage Liver Disease score=18.7±11.9 and duration of surgery=949.1±156.1 minutes) and they were compared to 27 historical controls subjects who had similar characteristics. The average APRV settings were P_{high} of 14.1±3.6 cmH_2O, P_{low} of 2.1± 2.7 cmH_2O, T_{high} of 5.2±2.9 seconds, T_{low} of 1.1±0.3 seconds, with a mean airway pressure (MAP) of 13.6±4.7 cmH_2O. The atelectasis score was significantly better after

Table 1
The extent of atelectasis and postoperative course

	Control Group (n=27)	APRV Group (n=9)	*P* value
Atelectasis			
Radiological atelectasis score			
1 POD	2.2±1.2	2.5±1.4	0.07
7 POD	3.2±2.0	0.4±0.7	<0.01
7 POD (A/W ratio (%))	16.1±9.1	3.1±2.8	<0.01
Postoperative course (P/F)			
1 POD	302.6±62.0	280.0±60.0	>0.05
5 POD	230.7±67.0	312.0±54.3	<0.01
10 POD	272.7±89.0	379.1±49.0	<0.01
Acute rejection (within 30 POD)	7	2	1.00
Vascular complications	2	1	0.55
Pneumonia (within 21 POD)	3	0	0.53
Mechanical ventilation (days)	5.1±4.2	4.6±2.3	0.60
ICU stay (days)	8.3±7.6	7.0±3.3	0.77
1 year mortality, no. (%)	1 (3.7)	1 (12.5)	0.41
2 year mortality, no. (%)	3 (11.1)	1 (12.5)	1.00
Hospital stay (days)	42.3±16.3	37.3±27.3	0.46

Data are expressed as the mean ± SD or number. APRV=airway pressure release ventilation, POD=postoperative day, A/W=ratio of atelectatic area/whole lung area on CT thorax, P/F=ratio of PaO_2 to FiO_2.

APRV compared to that after SIMV in the control on the seventh postoperative day (Table 1). Although the PaO_2 to FiO_2 ratios in the APRV were greater than those observed in the control, no significant differences were found between the two groups regarding the postoperative course (Table 1). APRV did not appear to induce significant changes in the portal vein blood-flow (949.1±570.6 ml/minute before APRV compared to 1110.0±367.2, 1025.9±482.4 and 1113.6±319.6 ml/minute; P=0.73 after 12, 24 and 36 hours of APRV, respectively). The resistive indexes (a reflection of increased hepatic vascular resistance) on Doppler ultrasonography also did not change significantly (baseline 0.8±0.1 compared to 0.7±4.5, 0.8±4.6 and 0.8±2.3 after 12, 24 and 36 hours of APRV; P=0.51). The hepatic vein blood-flow remained triphasic pattern throughout the study period.

In this study, APRV improved atelectasis in patients after LDLT without compromising hepatic blood-flow. The P_{high} titrated in this study differed from the higher P_{high} titration (>14 cmH_2O) previously reported when APRV was used for patients with acute respiratory distress syndrome[3]. During positive pressure mechanical ventilation, hepatic perfusion can be affected by the MAP[4]. We therefore paid special attention to the following three points in order to avoid excessive MAP. First, we set up the initial MAP of APRV using the MAP obtained during SIMV prior to changing to APRV. Consequently, our MAP (13.9 cmH_2O) was similar to that reported by Saner et al, who studied the use of high positive end-expiratory pressure strategies after LDLT[5]. Second, we tried to preserve spontaneous breathing during APRV, which is important in maintaining hepatic perfusion[4]. Third, we set a relatively long T_{low} and short T_{high} during APRV in our patients.

In conclusion, the present study demonstrated that judicious use of APRV could improve atelectasis without compromising hepatic blood-flow after LDLT. An adequately powered randomised controlled trial is needed to confirm whether routine use of APRV can improve patient-centred outcomes, including length of intensive care and hospital stay after LDLT.

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Benefit of intermittent pneumatic compression of lower limbs in reducing venous thromboembolism in hospitalised patients: interactions between risk and effectiveness

Venous thromboembolism (VTE) is an important, preventable cause of morbidity and mortality in hospitalised patients[1,2]. Our recent analysis of the Australian and New Zealand Intensive Care Society Centre for Outcomes and Resource Evaluation showed that acute pulmonary embolism accounted for 0.9% of all emergency intensive care admissions and over 20% of these patients required mechanical ventilation, 4.2% had a cardiac arrest prior to intensive care admission and the associated mortality was high (14.8%)[1]. Furthermore, omission of early mechanical or pharmacological thromboprophylaxis in critically ill patients was associated with an increased risk of both crude and adjusted mortality[3], particularly substantial in patients who had severe critical illness.

Use of thromboprophylaxis in many institutions has improved in the past decade; however, recent evidence suggested that many hospitalised patients remained not treated with early thromboprophylaxis when it was indicated. This may be, in part, due to the concern that pharmacologic thromboprophylaxis may increase risk of bleeding. Our recent work showed that many critically ill patients may have an increased risk of in vitro thrombotic tendency[4], and VTE can still occur in patients who have a mild to moderate degree of acquired coagulopathy[5]. Perhaps the best thromboprophylaxis strategy for patients who are at high risk of developing VTE and, at the same time, at risk of bleeding or with acquired coagulopathy may be mechanical thromboprophylaxis. Our recent meta-analysis showed that intermittent pneumatic compression of the lower limbs was indeed useful in preventing VTE in hospitalised patients[6]. It was more effective than no thromboprophylaxis in reducing VTE, more effective than thromboembolic deterrent stockings in reducing deep vein thrombosis and appeared to be as effective as pharmacological thrombo-

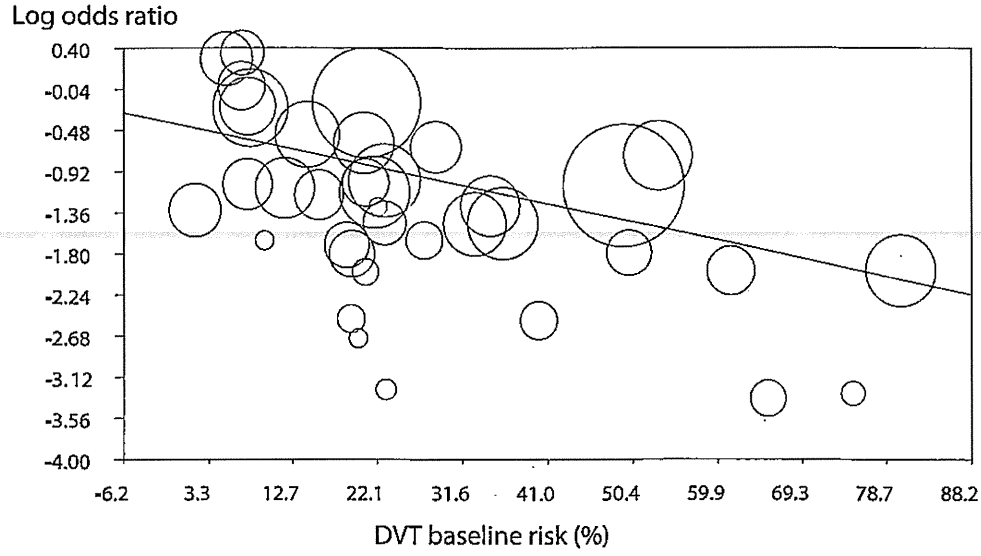

Figure 1: The protective effect of intermittent pneumatic compression on risk of deep vein thrombosis was stronger with increasing risk of baseline risk of deep vein thrombosis. Size of the marker is directly proportional to the size of the trial. Slope of meta-regression=-0.02, 95% confidence interval -0.03 to -0.01; P <0.01. DVT=deep vein thrombosis.