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Impact of ABO-incompatibility on hepatocellular carcinoma recurrence after living donor liver transplantation

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ABSTRACT

Background: ABO-incompatible (ABO-I) living donor liver transplantation (LDLT) has been reported to have acceptable outcomes in the era of rituximab-based prophylaxis. However, the outcomes of ABO-I LDLT for hepatocellular carcinoma (HCC) remain to be elucidated. This study aimed to clarify the impact of ABO-Incompatibility on oncologic outcomes of LDLT for HCC.

Methods: Patients with HCC who underwent ABO-I LDLT were randomly matched by 1:2 ratio to those who underwent ABO-compatible (ABO-C) LDLT according to propensity score. HCC recurrence and patient survival were analyzed using the Kaplan-Meier method and log-rank test.

Results: Between January 2012 and December 2015, a total of 160 patients underwent LDLT for HCC confirmed by pathology analysis of liver explants. Thirty-nine consecutive patients underwent ABO-I LDLT for HCC, and 78 ABO-C LDLT patients were selected by propensity score matching, which made no significant difference between the two groups in baseline, perioperative, and tumor characteristics. The 1-, 3-, and 5-year recurrence-free survival rates in the ABO-I and ABO-C LDLT groups were 76.9%, 68.5%, 63.6% and 74.4%, 70.5%, 70.5%, respectively ($p = 0.77$). The site distribution of initial recurrence showed no significant difference between the two groups. The overall survival rates over the same period in the ABO-I and ABO-C LDLT groups were 82.1%, 73.5%, 73.5% and 92.2%, 80.3%, 80.3%, respectively ($p = 0.34$).

Conclusions: ABO-I LDLT, having no adverse impact on oncological outcomes, can be a feasible transplant option for HCC.

Introduction

Hepatocellular carcinoma (HCC) is the fifth most common malignant tumor worldwide and is the third leading cause of cancer-related death, occurring frequently in association with chronic hepatitis B or C viral infection [1]. Living donor liver transplantation (LDLT) for HCC has been reported to have comparable oncologic outcomes to liver transplantation (LT) using deceased donors [2,3]. Actually LDLT presents HCC patients with a propitious opportunity for treatment in times of donor shortage. Notwithstanding, in some patients, when no compatible living donor is available, ABO-incompatible (ABO-I) LDLT can be a treatment of last resort, because the availability of a living donor would likely shorten waiting time for surgery, thereby preventing disease progression which might occur while anticipating a ABO-compatible (ABO-C) living or deceased donor.

ABO-I LDLT has been reported to have acceptable outcomes in the era of rituximab-based prophylaxis [4–6], and becomes more prevalent with improved survival. However, the oncologic outcomes of ABO-I LDLT for HCC have never been studied. A concern may arise that the additional immunosuppression required for ABO-I LDLT may increase the likelihood of HCC recurrence after LDLT, because the immunosuppressants inhibit the tumor surveillance properties of the immune system. To address this issue, this study aimed to investigate the impact of ABO-incompatibility on

Abbreviations: ABO-C, ABO-compatible; ABO-I, ABO-incompatible; ACR, acute cellular rejection; AFP, alpha-fetoprotein; CT, computed tomography; GRWR, graft-to-recipient body weight ratio; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; IQR, interquartile range; LDLT, living donor liver transplantation; LT, liver transplantation; MELD, Model For End-Stage Liver Disease; MMF, mycophenolate mofetil.

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oncological outcomes and survivals of patients with HCC following LDLT.

Methods

Patients and study design

The study included consecutive adult patients (18 years or older) who underwent ABO-I LDLT for HCC at National Cancer Center, Korea between January 2012 and December 2015. All medical records were reviewed retrospectively.

The current study enrolled the patients who was newly diagnosed with HCC and had no prior treatment for HCC (treatment-naïve). Patients who underwent LDLT due to combined hepatocellular-cholangiocarcinoma, liver cirrhosis without HCC, and other diseases were excluded. Tumor contraindications for LDLT were the presence of extrahepatic disease or main portal vein tumor thrombus. Intrahepatic vascular invasion was not considered a contraindication to LDLT.

The selection criteria for ABO-I LDLT both in donors and recipients were not different from those for ABO-C LDLT previously reported [7–10]. The expected survival and donor risk were fully understood by both the donor and recipient.

Patients with HCC who underwent ABO-I LDLT were randomly matched by 1:2 ratio to those who underwent ABO-compatible (ABO-C) LDLT during the study period according to propensity score. The study variables included basic patient characteristics, operative details, pathologic reports, HCC recurrence, and patient survival. All LDLT procedures were evaluated and approved by the Korean Network for Organ Sharing affiliated to the Ministry of Health and Welfare of Korea. This study was approved by the Institutional Review Board of National Cancer Center, Korea, and informed consent was waived. (IRB number: NCC2017-0260).

Surgical procedure

A single in-house surgeon (S.H.K) was a main operator for all the procedures on LDLT including donor and recipient operations. In all patients, the right lobe of living donor was used. The technical details of donor surgery were specified previously [11–16]. Following total hepatectomy in the recipient, implantation started with the right hepatic vein anastomosis. Any sizable (5 mm or larger in diameter) venous branch of the middle hepatic vein or inferior right hepatic vein of the graft was reconstructed. Considering its size and redundancy, the right portal vein of the graft was anastomosed to either the right or main portal vein of the recipient. Following reperfusion, hepatic artery anastomosis was performed under a surgical microscope. Bile duct was reconstructed with end-to-end duct-to-duct anastomosis.

Immunosuppression

For all LDLT recipients, Basiliximab (20 mg) was used as an induction agent during LDLT and on day 4 after surgery, and maintenance immunosuppressive therapy included corticosteroids, tacrolimus and mycophenolate mofetil (MMF). Corticosteroids were gradually tapered off and stopped within 6 months after LDLT. Tacrolimus was initiated on postoperative day 1 with the blood level adjusted to maintain a trough concentration of 8–12 ng/ml during the first month, and the trough level was maintained at 5–8 ng/ml thereafter. MMF was administered twice daily from postoperative day 2 at a dose of 1.5 g/day, and was reduced in response to adverse effects, such as diarrhea or leukopenia.

For desensitization in the ABO-I LDLT patients, a single intravenous dose of rituximab (300 mg per m^2 body surface area) was given before LDLT. Intravenous immunoglobulin (0.8 g/kg) was administered on postoperative days 1 and 4. Pretransplant plasmapheresis was performed prior to March 2014, and then was stopped. No other methods, such as splenectomy, graft local infusion, or preoperative MMF, were used [5,6].

Infection prophylaxis

Patients with hepatitis B virus (HBV) were administered hepatitis B immunoglobulin, in addition to entecavir or tenofovir for HBV prophylaxis following LDLT. Patients who were suspected with hepatitis C virus (HCV) recurrence were administered pegylated-interferon and ribavirin after confirmation of HCV RNA levels and elevated liver-enzyme levels. For prophylaxis against other infections, the patients were administered ticarcillin–clavulanate for one week, fluconazole for one month, and trimethoprim–sulfamethoxazole for one year. Cytomegalovirus prophylaxis was not performed routinely. A cytomegalovirus antigenemia assay was performed twice a week until discharge, every week until one month postoperatively, and every two weeks or once a month thereafter.

Follow-up and surveillance

In ABO-I LDLT patients, B cell ($CD19^+$) subpopulations were measured by the flow cytometry [17]. Follow-up of HCC patients after LDLT included computed tomography (CT) scans of the abdomen and chest and measurement of alpha-fetoprotein levels every 3 months during the first 2 years, every 4 months during the third year, and biannually thereafter.

Magnetic resonance imaging and positron emission tomographic–CT imaging were additionally performed if recurrent HCC was suspected. Biopsy was done when the diagnosis of HCC recurrence was difficult by imaging test.

Statistical analysis

Data are presented as number (%) or median (interquartile range (IQR)) unless otherwise indicated. Comparisons between the two groups were made using Chi-square test or Fisher's exact test for categorical variables. For continuous variables, Student's *t*-test or Mann-Whitney *U* test was used according to the normality of the distribution.

Patients were randomly matched to 1:2 ratio using greedy algorithms with a caliper width of 0.1 standard deviation of the logit of the propensity score without replacement. To adjust for the biases resulted from the inability to conduct a randomized controlled trial, as many variables as possible were investigated retrospectively. Variables or individuals with data loss of 5% or more were excluded from the analysis. The propensity score was calculated using a binary logistic regression, and the following served as contributors: age, sex, viral status, Child–Pugh score, Model for End-Stage Liver Disease (MELD) score, alpha-fetoprotein, operation time, cold ischemic time, warm ischemic time, intraoperative blood loss, graft recipient body weight ratio, graft fatty change, number of tumors, largest tumor size, Edmond–Steiner grade, microvascular invasion, major vessel invasion, and T stage (the 7th edition of The American Joint Committee on Cancer).

HCC recurrence and patient survival in accordance with ABO incompatibility were analyzed by Kaplan–Meier method and log-rank test. A P value < 0.05 was considered statistically significant. Calculations were made using the SPSS 24.0 statistical software package (IBM, Inc., Chicago, IL, USA) and R 3.3.3 (https://www.r-project.org).

Table 1
Initial isoagglutinin titers according to ABO type (donor to recipient).

Variables	ABO-I (n = 39)	Initial isoagglutinin titers
ABO type (donor to recipient)		
AB → A	7 (17.9%)	8 (2–32)
AB → B	7 (17.9%)	8 (4–16)
AB → O	1 (2.6%)	8 (8–8)
A → B	5 (12.8%)	16 (8–32)
A → O	8 (20.5%)	32 (8–128)
B → A	3 (7.7%)	16 (8–16)
B → O	8 (20.5%)	16 (4–128)

Data are presented as number (%) or median (range).

Results

A total of 160 patients underwent LDLT for HCC confirmed by pathology analysis of liver explants. Of those, 39 consecutive patients without suitable ABO-C living donors underwent ABO-I LDLT and fulfilled the inclusion criteria. Rituximab was administered 7–14 days before LDLT. Plasmapheresis was performed a median of 2.0 times (1.0–2.3 times) before surgery in 21 ABO-I LDLT patients. The data on the blood type combinations between donor and recipient were provided with the titer of each combination group in Table 1. The most common combination of the ABO type of donor to recipient was A to O in 8 patients (20.5%). The median value for initial isoagglutinin titers prior to desensitization was 16 (range, 2–128). The titer was reduced to 4 (range, 0–16) at the time of LDLT.

The median value for initial B cell ($CD19^+$) subpopulations was 14.4% (range, 0.1–47.3%) at the beginning before administration of rituximab and 0.2% (range, 0.0–2.9%) at the time of ABO-I LDLT. B cells were not detected from circulation for 12 weeks after ABO-I LDLT, and displayed rebound elevations from 16 weeks after LDLT, but the peak values still remained below the initial level throughout one year after LDLT (Fig. 1).

Baseline characteristics of the propensity-matched groups

Using the propensity score matching method, 39 and 78 patients with ABO-I and ABO-C, respectively, were selected. The patients of ABO-C group underwent LDLT after a median waiting time of 17 days (range, 2–81 days), and those of ABO-I group did after a median waiting time of 20 days (range, 2–79 days) ($P = 0.12$).

The baseline characteristics of living donors and recipients are summarized in Table 2. No significant difference was observed for all the variables, including baseline patient characteristics, details of surgery, and pathological reports between the two propensity score-matched groups.

HCC recurrence and patient survival

The median follow-up period was 40.2 months (IQR, 28.3–48.8). No mortality occurred within 30 postoperative days for both groups. No antibody-mediated rejection was observed in ABO-I LDLT patients. No acute celluar rejection occurred in the two study groups. Four patients developed hepatic artery thrombosis, two for each group ($p = 0.60$), which was successfully treated with intraarterial thrombolysis.

The 1-, 3-, and 5-year recurrence-free survival rates in the ABO-I and ABO-C LDLT groups were 76.9%, 68.5%, 63.6% and 74.4%, 70.5%, 70.5%, respectively ($p = 0.772$; Fig. 2A). The overall survival rates over the same period in the ABO-I and ABO-C LDLT groups were 82.1%, 73.5%, 73.5% and 92.2%, 80.3%, 80.3%, respectively ($p = 0.341$; Fig. 2B).

A total of 10 ABO-I and 15 ABO-C LDLT patients died by the end of the study. HCC recurrence was the cause of death in 16 patients (6 ABO-I, 10 ABO-C). The causes of death in the remaining patients included: sepsis (4 ABO-I, 3 ABO-C), lymphoma (1 ABO-C), and cardiac arrest (1 ABO-C).

Subgroup analysis in accordance with the Milan criteria

On the basis of pretransplant imaging, 27(69.2%) of 39 ABO-I LDLT patients and 52(66.7%) of 78 ABO-C LDLT patients were defined within the Milan criteria. However, based on explant

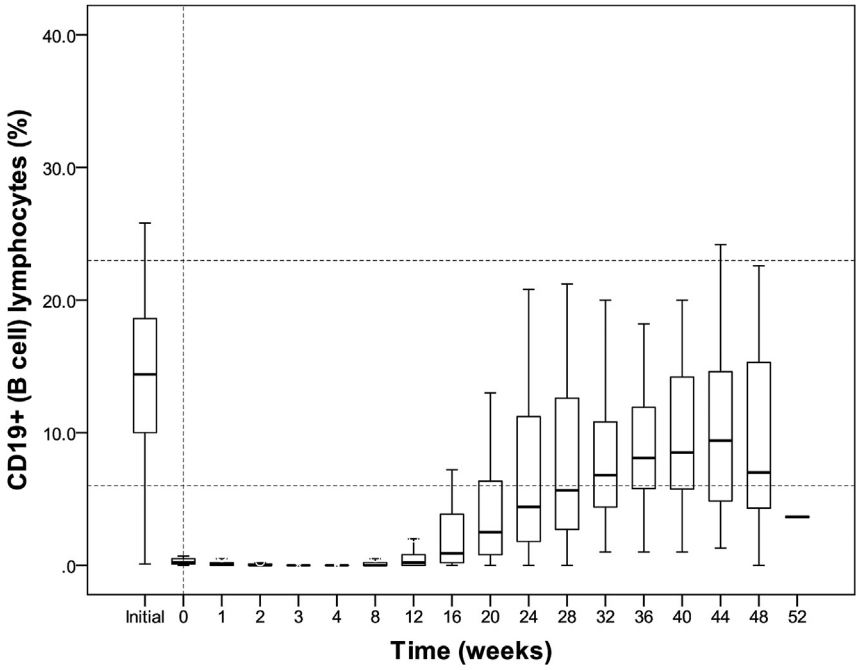

Fig. 1. The changes of the $CD19^+$ lymphocyte (B cell) subpopulations over time in ABO-I LDLT patients. Abbreviations: ABO-I, ABO-incompatible; LDLT, living donor liver transplantation.

Table 2
Baseline characteristics of the propensity-matched groups.

Characteristics	ABO-C (N = 78)	ABO-I (N = 39)	Total (N = 117)	*P*
Age (years)				
Recipient	55 (51–61)	54 (51.5–57.5)	55 (51–60)	0.48
Donor	32 (23–43)	31 (23.5–48.5)	32 (23–46)	0.79
Sex (male/female)				
Recipient	59 (75.6)/19 (24.4)	27 (69.2)/12 (30.8)	86 (73.5)/31 (26.5)	0.60
Donor	48 (61.5)/30 (38.5)	24 (61.5)/15 (38.5)	72 (61.5)/45 (38.5)	>0.99
Viral status (HBV/HCV/both/none)	65 (83.3)/3 (3.8)/2 (2.6)/8 (10.3)	33 (84.6)/0 (0.0)/0 (0.0)/6 (15.4)	98 (83.8)/3 (2.6)/2 (1.7)/14 (12.0)	0.38
Child-Pugh score	5 (5–7)	6 (5–7)	6 (5–7)	0.39
MELD score	10 (8–13)	10 (8–13)	10 (8–13)	0.90
AFP (ng/mL)	11.6 (4.0–220.3)	15.4 (5.4–192.6)	11.7 (4.8–220.3)	0.83
Operation time (min)				
Recipient	384 (343–429)	379 (340–429)	383 (343–429)	0.99
Donor	166 (146–184)	165 (147–189)	165 (146–184)	0.85
Cold ischemic time (min)	86 (71–102)	80 (71–105)	86 (71–103)	0.69
Warm ischemic time (min)	20 (17–24)	21 (16–24)	20 (17–24)	0.76
EBL (ml)	1200 (600–2500)	1500 (700–2600)	1300 (700–2500)	0.65
GRWR	0.97 (0.72–1.23)	0.97 (0.80–1.21)	0.97 (0.74–1.21)	0.75
Graft fatty change (%)	5.0 (0.0–10.0)	5.0 (0.0–17.5)	5.0 (0.0–10.0)	0.74
Number of tumors	2 (1–4)	2 (1–4)	2 (1–4)	0.35
Largest tumor size (cm)	2.2 (1.5–3.5)	2.5 (1.8–3.5)	2.2 (1.5–3.5)	0.36
Edmond-Steiner grade (I/II/III/IV)	4 (5.1)/13 (16.7)/42 (53.8)/19 (24.4)	1 (2.6)/9 (23.1)/16 (41.0)/13 (33.3)	5 (4.3)/22 (18.8)/58 (49.6)/32 (27.4)	0.46
Major vessel invasion (no/yes)	72 (92.3)/6 (7.7)	34 (87.2)/5 (12.8)	106 (90.6)/11 (9.4)	0.58
Microvascular invasion (no/yes)	50 (64.1)/28 (35.9)	24 (61.5)/15 (38.5)	74 (63.2)/43 (36.8)	0.95
T Stage (AJCC 7th) (1/2/3/4)	15 (19.2)/45 (57.7)/13 (16.7)/5 (6.4)	11 (28.2)/21 (53.8)/7 (17.9)/0 (0.0)	26 (22.2)/66 (56.4)/20 (17.1)/5 (4.3)	0.32

Data are presented as number (%) or median (interquartile range).; Abbreviations: ABO-C, ABO-compatible; ABO-I, ABO-incompatible; AFP, alpha-fetoprotein; EBL, estimated blood loss; GRWR, graft recipient body weight ratio; HBV, hepatitis B virus; HCV, hepatitis C virus; MELD, Model For End-Stage Liver Disease.

pathology that were actually used in analysis of survival and recurrence, HCC within the Milan criteria was found in 20 (33.3%) and 40 patients (66.7%) with ABO-I and ABO-C LDLT, respectively. No significant difference of recurrence-free survival (P=0.75; Fig. 3A) and overall survival rates (P=0.55; Fig. 3B) was found between the two groups.

HCC beyond the Milan criteria was found in 19 (33.3%) and 38 patients (66.7%) with ABO-I and ABO-C LDLT, respectively. No significant difference of recurrence-free survival (P=0.62; Fig. 3C) and overall survival rates (P=0.39; Fig. 3D) was found between the two groups.

Sites of initial recurrence

The two most common initial recurrence sites were lung (n = 10, 8.5%) and liver (n = 10, 8.5%). The liver (n = 6, 15.4%) was the most common site for patients with ABO-I LDLT while the lung (n = 7, 9.0%) was the most common site for patients with ABO-C

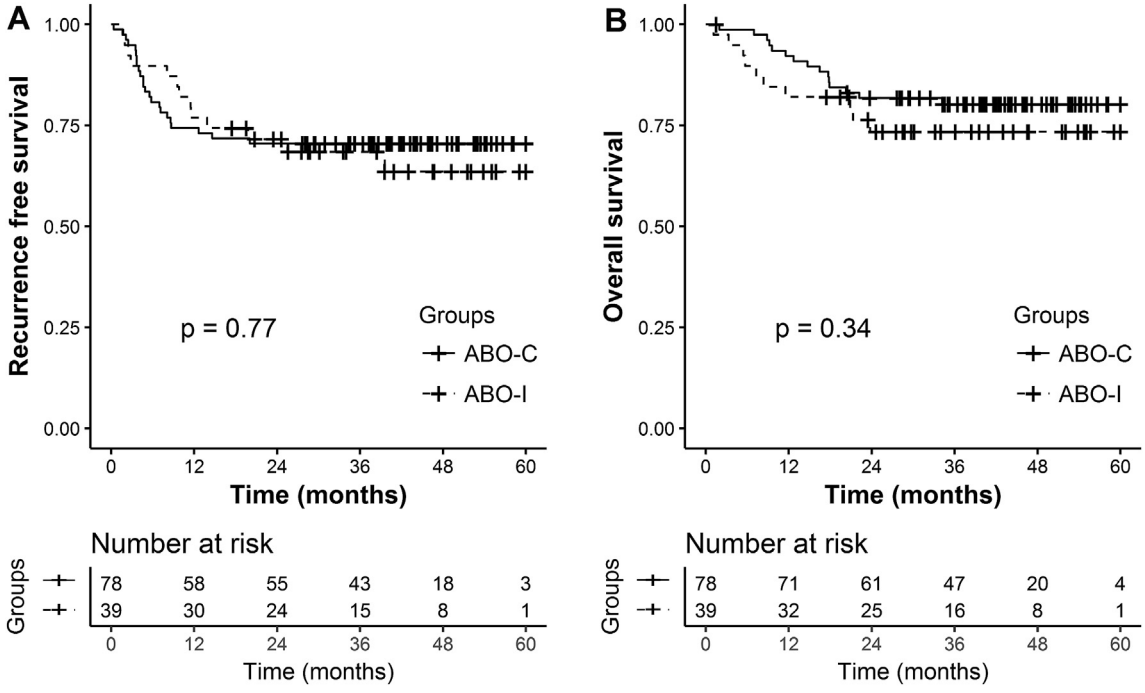

Fig. 2. (A) recurrence-free survival and (B) overall survival according to ABO compatibility.

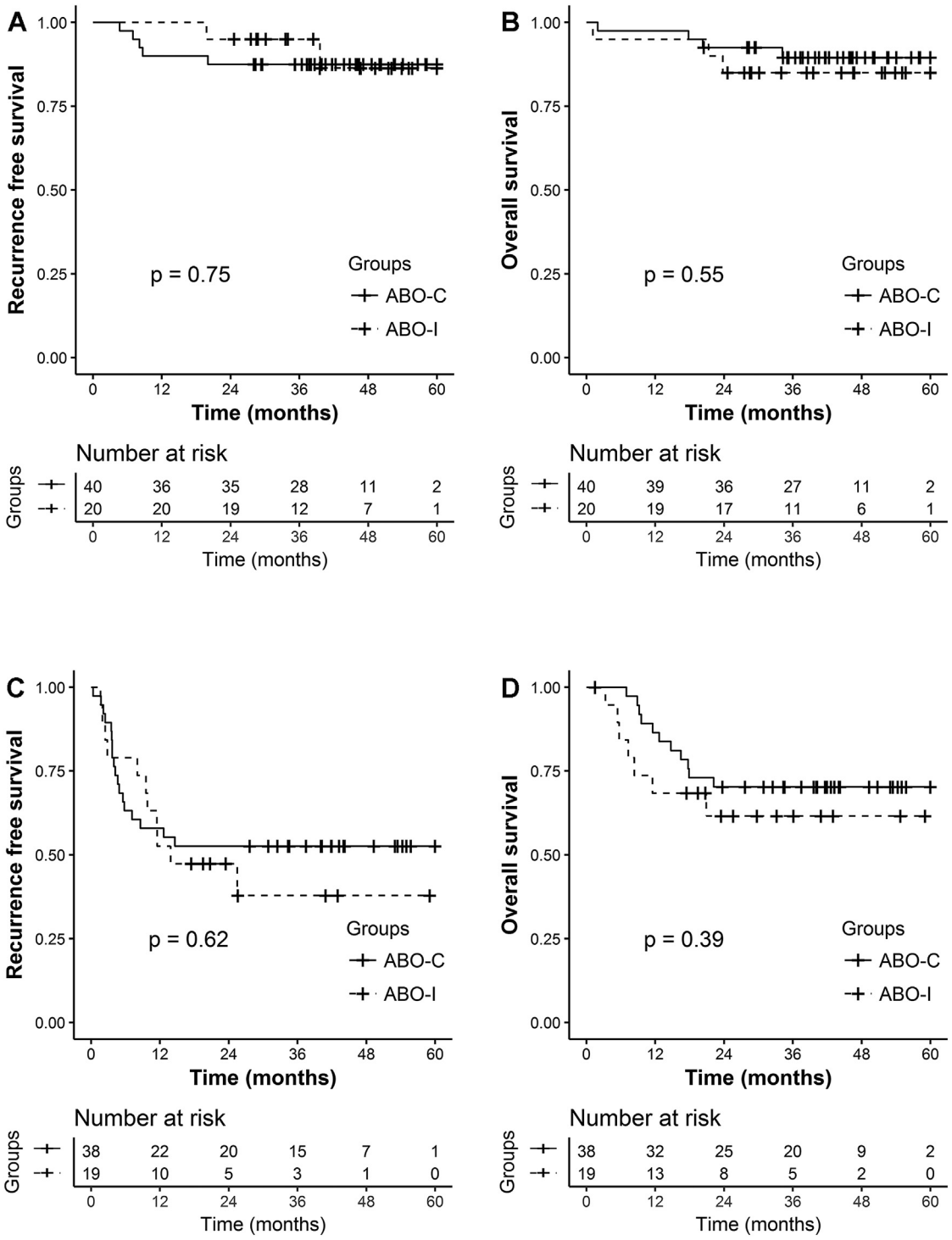

Fig. 3. (A) recurrence-free survival and (B) overall survival according to ABO compatibility in patients with HCC within the Milan criteria. (C) recurrence-free survival and (D) overall survival according to ABO compatibility in patients with HCC beyond the Milan criteria. Abbreviations: HCC, hepatocellular carcinoma.

LDLT. There was no significant difference in the distribution of initial recurrence sites between the two groups ($P = 0.36$).

For patients with HCC beyond the Milan criteria, the lung was the most common site (n = 9, 15.8%) and the distribution of initial recurrence sites were not significantly different between the two groups ($P = 0.18$). Five (26.3%) of 19 patients with ABO-I LDLT had recurrence in the graft liver and 6 (15.8%) of 38 patients with ABO-C LDLT had recurrence in the lung (Table 3).

Discussion

This is a comparative study between ABO-I and ABO-C LDLT for HCC with respect to HCC recurrence and overall survival. The main finding of this study is that rituximab was shown to be effective in preventing antibody-mediated rejection as a desensitizing regimen and not associated with HCC recurrence in ABO-I LDLT. This study included a relatively homogeneous group consisting of LDLT

Table 3
The sites of initial recurrence.

Sites	ABO-C (n = 78)	ABO-I (n = 39)	Total (n = 117)	*P*
Total (n = 117)				0.36
Liver	4 (5.1)	6 (15.4)	10 (8.5)	
Lung	7 (9.0)	3 (7.7)	10 (8.5)	
Lymph node	3 (3.8)	1 (2.6)	4 (3.4)	
Bone	4 (5.1)	0 (0.0)	4 (3.4)	
Others	3 (3.8)	1 (2.6)	4 (3.4)	
Multiple sites	2 (2.6)	2 (5.1)	4 (3.4)	
Within Milan criteria (n = 60)				0.85
Liver	1 (2.5)	1 (5.0)	2 (3.3)	
Lung	1 (2.5)	0 (0.0)	1 (1.7)	
Lymph node	1 (2.5)	1 (5.0)	2 (3.3)	
Bone	1 (2.5)	0 (0.0)	1 (1.7)	
Others	0 (0.0)	0 (0.0)	0 (0.0)	
Multiple sites	1 (2.5)	0 (0.0)	1 (1.7)	
Beyond Milan criteria (n = 57)				0.18
Liver	3 (7.9)	5 (26.3)	8 (14.0)	
Lung	6 (15.8)	3 (15.8)	9 (15.8)	
Lymph node	2 (5.3)	0 (0.0)	2 (3.5)	
Bone	3 (7.9)	0 (0.0)	3 (5.3)	
Others	3 (7.9)	1 (5.3)	4 (7.0)	
Multiple sites	1 (2.6)	2 (10.5)	3 (5.3)	

Data are presented as number (%).

patients for HCC, and utilized propensity score matching including all covariates that could affect the outcomes, which could lead to decrease the selection bias both by reducing the difference of the baseline characteristics of patients and by eliminating any confounding effects of other variables, aside from ABO incompatibility, including differences of surgical indications between deceased donor LT and LDLT (e.g., extended criteria are frequently used for LDLT), of biological behavior of a tumor resulting from different waiting time for LT, and of ischemic time [18]., In this study, all ABO-I LDLTs were performed as the only option for curative treatment in patients who has no compatible living donor. At the authors' institution, deceased donor LT is performed in less than 5% of all patients undergoing LT while most patients undergo LDLT. And HCC is the main indication in more than 70% of the LDLT patients, reflecting the current situation of a national cancer center in a region showing a low rate of deceased donor organ recovery in the world. The ABO-I LDLT program was launched in 2012, with rituximab, immunoglobulin, and plasmapheresis added to the conventional immunosuppressive regimen used in ABO-C LDLT, and even stopped plasmapheresis since March 2014. This simplified protocol could obviate the complications and high costs by additional desensitizing procedures, such as local graft infusion or splenectomy. This rituximab-based regimen provided comparable outcomes between ABO-I and ABO-C LDLTs [5,6]. The good result with ABO-I LDLT was the cornerstone on which HCC could be included as an indication for LT despite ABO incompatibility.

The observation of no significant difference in oncologic outcomes among patients with HCC according to ABO incompatibility is very interesting. The general consensus is that pharmacological immunosuppression or a poor immunological state negatively affects post-LT outcomes of HCC and increases the risk of postoperative recurrence [19]. So, high-dose immunosuppressive agents can weaken innate immune activity and contribute to HCC recurrence after LT. Actually several studies have demonstrated that higher doses of calcineurin inhibitors are correlated with a higher risk of HCC recurrence and lower post-LT overall or recurrence-free survival rates [20,21]. On the contrary, there was a report that human immunodeficiency virus infection had a minimal effect on the risk of tumor recurrence among patients who underwent LT for HCC [22]. The value of immunosuppression in LT patients with HCC still remains debatable as of now.

Rituximab, a monoclonal chimeric human anti-CD20 antibody, was known to deplete peripheral blood B cells [23]. Although plasmapheresis was used in the early period of this study, all ABO-I LDLT patients were given rituximab. So the only difference from the standpoint of immunosuppression was whether or not to use rituximab between the two groups. Accordingly, from the comparable outcomes between the two groups, it can be inferred that depletion of B cells by rituximab doesn't affect HCC recurrence after LDLT. This inference might seem to be contradictory to a recent report showing a role of B cell in HCC that tumor-infiltrating B cells functionally interact with tumor-infiltrating T cells, which is linked to an enhanced local immune activation and contributes to better prognosis for patients with HCC [24]. However, CD20 antigen is specifically expressed on B-cell lineage elements except Pro-B cells and plasma cells [25], so the target of suppression by rituximab was not the whole B cells but only B cells possessing CD 20 antigen. However, the exact mechanism for rituximab-induced immune system impairment, and its possible relationship with HCC recurrence, remains unclear, and further studies are needed to clarify whether rituximab might affect HCC recurrence after LT.

In the subgroup analysis, as expected, irrespective of ABO incompatibility, HCC recurrence was observed to be increase in patients with HCC beyond the Milan criteria than in those within. However, ABO-I LDLT had comparable results to ABO-C LDLT with regard to HCC recurrence and patient survival rates regardless of whether the tumor was within or beyond the Milan criteria. And the site distribution of initial recurrence showed no significant difference between the two groups.

Limitations of this study consist mainly in its retrospective, nonrandomized design from a single institution. Randomized controlled trials are considered the gold standard for evaluating the effect of different interventions on outcomes. However, it is very difficult to perform randomized controlled trial comparing ABO-I and ABO-C LDLT in clinical practice, due to not only the difficulty of patient recruitment, but also current preference for ABO-C over ABO-I LDLT. Therefore, in the present study, as many variables as possible was retrospectively investigated to overcome the effects of confounders other than ABO incompatibility through propensity score matching. Another drawback of this study is the majority (83.8%) of HBV patients. Thus, further studies are needed to validate these results in patients with HCV or alcoholic or nonalcoholic

steatohepatitis.

In conclusion, this study demonstrated no adverse impact of ABO incompatibility on oncological outcomes following LDLT for HCC by showing no significant differences in recurrence and patient survival between ABO-I and ABO-C LDLT patients with HCC, giving evidence that ABO-I LDLT can be considered a feasible choice of treatment for HCC in patients awaiting LT with no compatible donor.

Conflict of interest and funding

No conflict of interest/No financial support.

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