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Original Article

Stratified Analysis of Survival Benefit for ABO-incompatible Deceased-donor Liver Transplantation: Multicenter Propensity Score-matched Study

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Abstract

Background and Aims: Liver transplantation (LT) using ABO-incompatible (ABOi) grafts can extend the donor pool to a certain extent and hence reduce the waiting time for transplantation. However, concerns of the impending prognosis associated with this option, especially for patients with liver failure and higher model for end-stage liver disease (MELD) scores, who tend to be more fragile during the waiting period before LT. ***Methods:*** Recipients undergoing LT for acute-on-chronic liver failure or acute liver failure were retrospectively enrolled at four institutions. Overall survival was compared and a Cox regression analysis was performed. Propensity score matching was performed for further comparison. Patients were stratified by MELD score and cold ischemia time (CIT) to determine the subgroups with survival benefits. ***Results:*** Two hundred ten recipients who underwent ABOi LT and 1,829 who underwent ABO compatible (ABOc) LT were enrolled. The 5-year overall survival rate was significantly inferior in the ABOi group compared with the ABOc group after matching (50.6% vs. 75.7%, $p<0.05$). For patients with MELD scores ≤30, using ABOi grafts achieved a comparable overall survival rate as using ABOc grafts ($p>0.05$). Comparison of the survival rates revealed no statistically significant difference for patients with MELD scores ≥40 ($p>0.05$). For patients with MELD scores of 31–39, the overall survival rate was significantly inferior in the ABOi group compared with the ABOc group ($p<0.001$); however, the rate was increased when the liver graft CIT was<8 h. ***Conclusions:*** For recipients with MELD scores ≤30, ABOi LT had a prognosis comparable to that of ABOc LT and can be regarded as a feasible option. For recipients with MELD scores ≥40, ABOi should be adopted with caution in emergency cases. For recipients with MELD scores of 31–39, the ABOi LT prognosis was worse. However, those patients benefited from receiving ABOi grafts with a CIT of <8 h.

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Keywords: Liver transplantation; ABO-incompatible; Model for end-stage liver disease score; Cold ischemia time; Propensity score matching.

Abbreviations: ABOc, ABO compatible; ABOi, ABO incompatible; ACLF, acute-on-chronic liver failure; AMR, antibody-mediated rejection; CIT, cold ischemia time; DDLT, deceased-donor liver transplantation; ECD, extended criteria donor; IVIG, intravenous immunoglobulin; LDLT, living donor liver transplantation; LT, liver transplantation; MELD, model for end-stage liver disease; MMF, mycophenolate mofetil; PSM, propensity score matching.

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Introduction

Liver transplantation (LT) is considered the most effective treatment option for end-stage liver disease, which is the final complication of a spectrum of liver diseases. With progress in surgical techniques, immunosuppressive regimens, and perioperative management, patients with benign end-stage liver disease can achieve 5-year patient survival rates up to 86%.[1] However, the high mortality among patients on

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waiting lists remains a major challenge for LT. The shortage of donor grafts and consequent long waiting lists at times cost many lives. Many patients die either waiting to reach the top of the waiting list or because suitable donor grafts are not available.[2] Consequently, ABO-incompatible (ABOi) LT has become more common as a way to address the shortage of liver grafts.[3,4] Under most circumstances, ABO-compatible (ABOc) LT is recommended as the most ideal method. The use of new, effective immunosuppressants, such as rituximab, intravenous immunoglobulin (IVIG), and plasma exchange, for ABOi LT has made it an optional choice to rescue critical patients with acute-on-chronic liver failure (ACLF) or acute liver failure.[5] The Korean experience indicated that ABOi living donor LT is a potentially feasible option for patients with hepatocellular carcinoma, especially those with compensated cirrhosis.[6] Nevertheless, antibody-mediated rejection (AMR) and consequent hepatic vascular and biliary complications were frequent in patients with ABOi LT.[4,6] Earlier reports on the prognosis of ABOi LT were controversial, which may be due to significant differences in the baseline data of the study groups. Here, patients with severe liver failure who underwent ABOi deceased-donor liver transplantation (DDLT) at four centers were retrospectively evaluated. Stratification and analysis of long-term prognosis was performed to identify subgroups with survival benefits.

Methods

Selection criteria for DDLT patients

Patients who received DDLT between July 2015 and July 2019 at four institutions (the First Affiliated Hospital of Zhejiang University School of Medicine, the Third Affiliated Hospital of Sun Yat-Sen University, Shulan (Hangzhou) Hospital and the First Affiliated Hospital of Zhengzhou University) were retrospectively reviewed. The inclusion criteria were (1) adult DDLT, (2) recipients diagnosed with ACLF or acute liver failure, and (3) whole-graft LT. The exclusion criteria were (1) recipients who underwent retransplantation, (2) recipients who received multiorgan transplantation, and (3) recipients who were diagnosed with hepatic malignant tumors.

The primary endpoint was the comparison of overall patient and graft survival rates in the ABOi and ABOc groups. Secondary endpoints focused on the comparison of complications after LT in the two groups. All liver grafts were procured from civilian organ donation. None were obtained from executed prisoners.[7] LT was approved by the liver transplantation committee of each institution and was performed after informed consent was obtained from the patients. The study was approved by the China Liver Transplant Registry with approval number 2020058, and by the ethics committee. It was performed following the ethical principles of the Declaration of Helsinki.

Protocol for perioperative immunosuppression antiviral prophylaxis

All patients in the cohort underwent orthotopic LT or piggyback LT based on hemodynamic stability without splenectomy. Patients in the ABOi LT group received a single dose of rituximab (375 mg/m^2) and IVIG (0.4 g/kg) just before the operation, regardless of the preoperative condition. Intravenous methylprednisolone (10 mg/kg) and basiliximab (20 mg) were administered to all patients during the operation to induce immunosuppression.[8] All patients infected with HBV were treated with entecavir or tenofovir combined with hepatitis B immunoglobulin to maintain a high concentration of HBsAb after the operation.

Patients in the ABOi group were treated with a triple regimen consisting of tacrolimus, mycophenolate mofetil (MMF), and methylprednisolone. Patients in the ABOc group were given both tacrolimus and MMF. IVIG was given for 7–10 consecutive days after LT. Steroids were added if early allograft dysfunction or acute rejection occurred. If the anti-blood type isoagglutinin titers increased to more than 1:64 or AMR occurred within 1 week after ABOi LT, plasma exchange was performed to reduce the antibody titer, and rituximab (187.5 mg/m^2) was given to stabilize liver function.

Monitoring of complications and postoperative follow-up

Liver and renal function and changes in hemagglutinin titer were monitored, and liver biopsies was performed when acute rejection was suspected. The prevalence of peripheral blood lymphocyte subpopulations was checked pre-LT and then every 3 days post-LT for 3 months. AMR was diagnosed by acute tissue injuries, such as vascular inflammation, bile duct inflammation damage, increasing titers of specific antibodies, and histological staining for C4d.[9] The time at which retransplantation was considered because of graft loss was recorded. Graft survival was the interval between the date of LT and the date of the decision for retransplantation.

Statistical analysis

Continuous variables were reported as means ± SD or medians and interquartile range (IQR). Discrete variables were reported as numbers and percentages. Recipient baseline characteristics were compared with *t*-tests, nonparametric tests, and chi-square tests. Kaplan-Meier survival analysis was used to evaluate the graft survival and patient overall survival rates, and differences in survival were compared with log-rank tests. The risks of overall survival and graft survival were compared by Cox regression analysis with robust standard errors, which accounted for the clustering of propensity score matched pairs. Propensity score matching (PSM) was performed with Greedy matching to reduce the effect of potential confounding factors, including donor age, donor steatosis, donation type, recipient age, recipient model for end-stage liver disease (MELD) score, recipient Child-Pugh score, intraoperative blood loss, warm ischemia time (WIT), and cold ischemia time (CIT), using a caliper width of 0.2 standard deviations of the log of the propensity score. Absolute standardized differences were used to diagnose balance after matching, all of which were <0.25. SAS (version 9.1) and R (version 3.6.1) were used for statistical analysis, and $p<0.05$ was considered statistically significant.

Results

Demographic and other clinical parameters of the entire cohort

Two hundred ten recipients who underwent ABOi LT and 1,829 recipients who underwent ABOc LT were retrospectively evaluated in this study. The baseline clinical characteristics of these recipients are shown in Table 1. The mean follow-up was 15.5 (5.0, 26.1) months. The mean recipient age in the ABOi LT group was significantly lower than that in the ABOc LT group, and the ABOi group had a more HBV-induced patients. The mean MELD and Child-Pugh scores of the ABOi group were higher than those of the ABOc group. The WIT and CIT in the ABOi LT group were higher than those in the ABOc LT group. Not surprisingly, the mean pretransplant wait was longer in the ABOc group than in the ABOi group and the

Table 1. Comparison of donor, recipient baseline clinical characteristics and perioperative details in the ABOi and ABOc groups in whole cohort

Patients	ABOi LT, *n*=210	ABOc LT, *n*=1,829	*p*-value	*SMD*
Donor				
Age in yr	44.7 (34.7–53.2)	46.3 (35.8–63.6)	0.477	0.052
Sex, male	177 (84.3%)	1,499 (82.0%)	0.404	0.059
Steatosis, yes	30 (14.3%)	255 (13.9%)	0.892	0.014
Donor type, DCD	146 (69.5%)	1,350 (73.8%)	0.183	0.365
BMI in kg/m^2	22.5 (21.0–24.2)	23.1 (21.2–24.9)	0.138	0.111
Graft weight in g	1,344 (1,138–1,474)	1,350 (1,160–1,580)	0.175	0.101
Recipient				
Age in yr	46.4 (39.1–53.3)	49.3 (41.3–55.9)	0.002	0.230
Sex, male	174 (82.9%)	1,412 (77.2%)	0.062	0.136
Etiology of cirrhosis			0.859	0.016
Hepatitis B	166 (79.0%)	1,383 (75.6%)		
Hepatitis C	8 (3.8%)	79 (4.3%)		
Alcoholic	25 (11.9%)	240 (13.1%)		
Autoimmune	10 (4.8%)	77 (4.2%)		
Other	13 (6.2%)	141 (7.7%)		
MELD	34 (31–40)	28 (18–36)	<0.001	0.889
CHILD	12 (11–13)	11 (9–12)	<0.001	0.647
Waiting time in d	3 (1–11)	15 (5–32)	<0.001	0.291
Perioperative				
Operative time in h	6.7 (4.6–7.0)	6.6 (5.2–7.9)	<0.001	0.411
WIT in min	7 (0–11)	3 (1–7)	<0.001	0.640
CIT in h	9.0 (6.5–11.2)	7.0 (5.0–8.2)	<0.001	0.640
Intraoperative blood loss in mL	1,000 (800–2,000)	1,000 (500–1,800)	0.103	0.119
Intraoperative blood transfusion in U	4 (2–8)	4 (2–8)	0.692	0.029

DCD, donation after cardiac death; BMI, body mass index; MELD, model for end-stage liver disease; WIT, warm ischemia time; CIT, cold ischemia time; ABOc, ABO compatible; ABOi, ABO incompatible; LT, liver transplantation; SMD, standard deviation mean difference.

LT operative time was longer in the ABOc group.

Patient overall survival and graft survival outcomes of patients in the ABOi and ABOc LT groups were compared (Fig. 1A, B). In the ABOi LT group, the 1-, 3-, and 5-year overall survival rates were 62.5%, 59.7% and 51.3%, and the 1-, 3-, and 5-year graft survival rates were 59.1%, 55.6% and 50.8%, respectively. In the ABOc LT group, the 1-, 3-, and 5-year overall survival rates were 88.7%, 86.5% and 85.9%, and the 1-, 3-, and 5-year graft survival rates were 88.1%, 85.3% and 84.8%, respectively. Both the overall survival and graft survival rates in the ABOi group were shorter than those in the ABOc group (both $p<0.0001$).

Cox regression analysis of survival outcomes of the entire cohort

Univariate and multivariate Cox regression analysis was used to identify risk factors associated with recipient death and graft loss in the entire study cohort. In the univariate analysis, ABOi, CIT, WIT, intraoperative blood loss, intraoperative blood transfusion, and recipient MELD and Child-Pugh scores were risk factors for recipient death. Multivariate analysis found that ABOi, CIT, intraoperative blood loss, intraoperative blood transfusion, and recipient MELD score were independent risk factors for recipient death (Table 2). Univariate analysis found that ABOi, donor body mass index (BMI), CIT, WIT, intraoperative blood loss, intraoperative blood transfusion, recipient MELD and Child-Pugh score were risk factors for graft loss. Multivariate analysis identified ABOi, CIT, intraoperative blood loss, intraoperative blood transfusion, and recipient MELD score were independent risk factors for graft loss (Table 3). PSM was performed to eliminate differences in the baseline clinical characteristics of the ABOi and ABOc groups that ere independent risk factors.

Survival outcomes after PSM

PSM was performed at a ratio of 1:1 to eliminate confounders and avoid existing selection bias that affected survival outcomes, including donor age, donor steatosis, donation type, recipient age, recipient MELD score, recipient Child-Pugh score, intraoperative blood loss, WIT, and CIT. Each group included 204 patients. The baseline clinical characteristics of the patients in both groups are shown in Table 4. No significant between-group differences in donor, recipient, and perioperative clinical characteristics were observed.

Blood type combinations between donors and recipients included A-to-O (*n*=28), A-to-B (*n*=17), B-to-O (*n*=44), B-

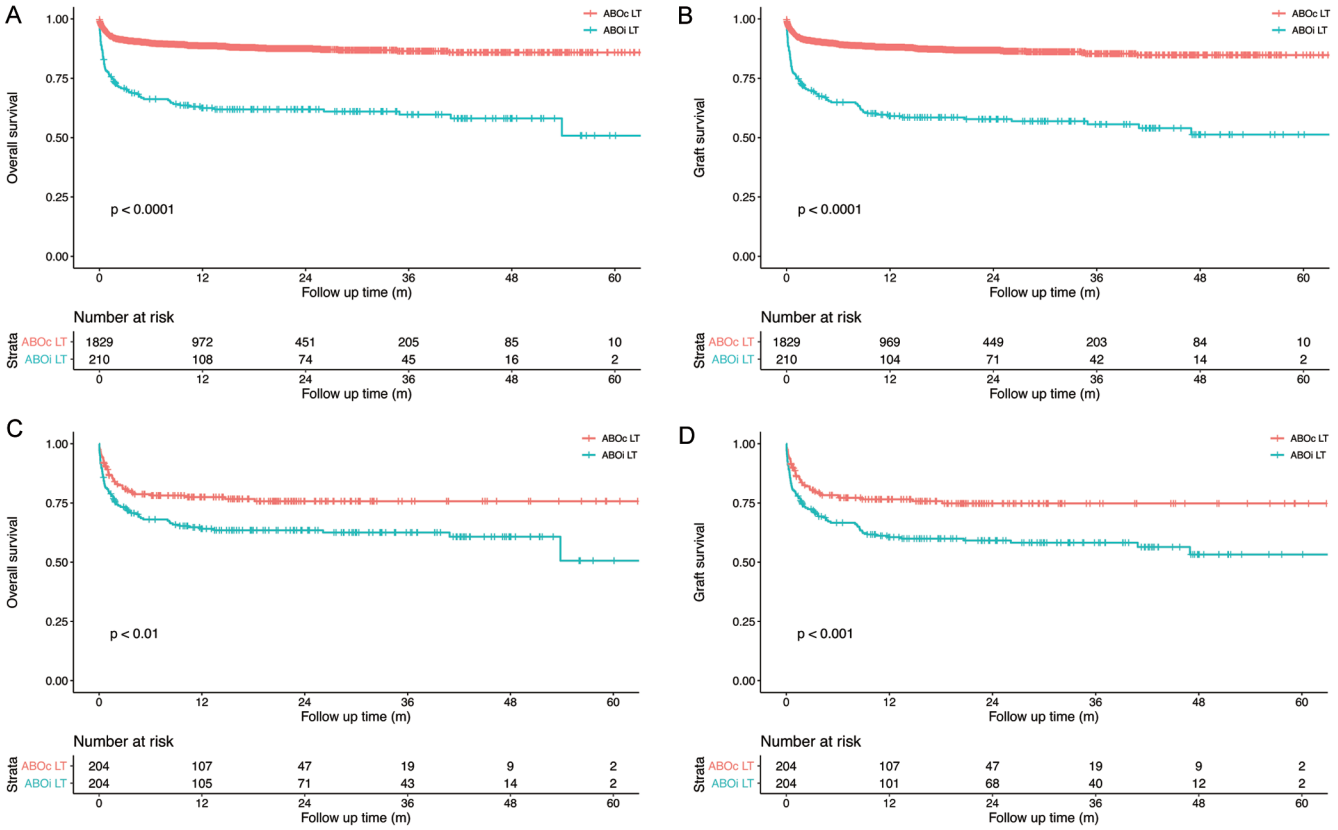

Fig. 1. Comparison of the overall survival and graft survival rates in ABOi and ABOc LT recipients. (A–D) In the entire cohort (A and B) and after propensity score matching (C and D). ABOc, ABO compatible; ABOi, ABO incompatible.

Table 2. Cox regression analysis of risk factors associated with recipient overall survival in whole cohort

Factor	Univariate			Multivariate		
	HR	95% CI	*P*-value	HR	95% CI	*p*-value
ABOi	4.161	3.148–5.502	<0.001	2.809	2.061–3.828	<0.001
Donor age in yr	1.008	0.998–1.018	0.114			
Donor sex, male	0.913	0.645–1.292	0.607			
Donor type, DCD	1.096	0.844–1.422	0.493			
Donor BMI in kg/m^2	0.961	0.923–1.001	0.056			
Graft weight in g	1.000	1.000–1.000	0.482			
WIT in min	1.022	1.002–1.042	0.033	0.997	0.976–1.019	0.812
CIT in h	1.146	1.102–1.192	<0.001	1.097	1.052–1.144	<0.001
Recipient age in yr	1.004	0.992–1.016	0.546			
Recipient sex, male	0.886	0.645–1.218	0.457			
Etiology of cirrhosis, HBV	1.108	0.845–1.453	0.459			
Recipient BMI in kg/m^2	0.999	0.962–1.038	0.981			
MELD	1.059	1.043–1.075	<0.001	1.034	1.015–1.054	<0.001
CHILD	1.290	1.196–1.391	<0.001	1.090	0.991–1.199	0.078
Intraoperative blood loss in mL	1.000	1.000–1.000	<0.001	1.000	1.000–1.000	0.002
Intraoperative blood transfusion in U	1.057	1.044–1.070	<0.001	1.038	1.018–1.058	<0.001

DCD, donation after cardiac death; BMI, body mass index; MELD, model for end-stage liver disease; WIT, warm ischemia time; CIT, cold ischemia time; HBV, Hepatitis B Virus; ABOi, ABO incompatible; HR, hazard ratio; CI, confidence interval.

Table 3. Cox regression analysis of risk factors associated with recipients' graft survival in whole cohort

Factor	Univariate			Multivariate		
	HR	95% CI	*P*-value	HR	95% CI	*p*-value
ABOi	4.241	3.243–5.546	<0.001	2.904	2.157–3.908	<0.001
Donor age in yr	1.006	0.997–1.016	0.183			
Donor sex, male	0.999	0.721–1.383	0.995			
Donor type, DCD	1.066	0.829–1.370	0.618			
Donor BMI in kg/m^2	0.961	0.924–0.999	0.048	1.001	0.962–1.043	0.945
Graft weight in g	1.000	1.000–1.000	0.383			
WIT in min	1.023	1.004–1.043	0.017	0.999	0.979–1.021	0.958
CIT in h	1.144	1.102–1.188	<0.001	1.092	1.048–1.137	<0.001
Recipient age in yr	1.002	0.990–1.014	0.777			
Recipient sex, male	0.845	0.620–1.152	0.287			
Etiology of cirrhosis, HBV	1.091	0.840–1.415	0.514			
Recipient BMI in kg/m^2	0.996	0.960–1.033	0.837			
MELD	1.056	1.041–1.072	<0.001	1.032	1.014–1.051	0.001
Child	1.280	1.191–1.376	<0.001	1.086	0.992–1.190	0.076
Intraoperative blood loss in mL	1.000231	1.000–1.000	<0.001	1.000	1.000–1.000	0.002
Intraoperative blood transfusion in U	1.054	1.041–1.067	<0.001	1.036	1.017–1.056	<0.001

DCD, donation after cardiac death; BMI, body mass index; MELD, model for end-stage liver disease; WIT, warm ischemia time; CIT, cold ischemia time; HBV, Hepatitis B Virus; ABOi, ABO incompatible; HR, hazard ratio; CI, confidence interval.

Table 4. Comparison of donor, recipient baseline clinical characteristics and perioperative details between ABOi and ABOc groups after propensity score matching

Patients	ABOi LT, *n*=204	ABOc LT, *n*=204	*p*-value	SMD
Donor				
Age in yr	45.0 (35.1–53.3)	45.7 (35.9–54.4)	0.964	0.005
Sex, male	165 (80.9%)	172 (84.3%)	0.361	0.088
Steatosis, yes	29 (14.2%)	28 (13.7%)	0.886	0.019
Donor type, DCD	141 (69.1%)	145 (71.0%)	0.665	0.044
BMI in kg/m^2	22.5 (21.0–24.5)	22.5 (21.1–24.2)	0.999	0.003
Graft weight in g	1,330 (1,154–1,472)	1,312 (1,145–1,520)	0.697	0.039
Recipient				
Age in yr	46.9 (39.9–53.4)	48 (39.4–54.1)	0.588	0.053
Sex, male	170 (83.3%)	168 (82.4%)	0.793	0.026
Etiology of cirrhosis			0.999	0.002
Hepatitis B	161 (78.9%)	159 (77.9%)		
Hepatitis C	8 (3.9%)	8 (3.9%)		
Alcoholic	24 (11.8%)	25 (12.3%)		
Autoimmune	10 (4.9%)	10 (4.9%)		
Other	11 (5.4%)	10 (4.9%)		
MELD	34 (31–40)	37 (31–40)	0.529	0.063
CHILD	12 (11–13)	12 (11–13)	0.844	0.019
Waiting time in d	3 (1–11)	10 (4–26)	0.003	0.346
Perioperative				
Operative time in h	5.7 (4.7–7.0)	6.8 (5.2–8.0)	<0.001	0.418
WIT in min	6 (0–11)	6 (1–9)	0.364	0.090
CIT in h	8.7 (6.5–11.0)	8.0 (7.0–10.9)	0.865	0.016
Intraoperative blood loss in mL	1,050 (800–2,000)	1,000 (500–2,000)	0.782	0.027
Intraoperative blood transfusion in U	4 (2–8)	4 (2–9)	0.988	0.003

DCD, donation after cardiac death; BMI, body mass index; MELD, model for end-stage liver disease; WIT, warm ischemia time; CIT, cold ischemia time; ABOc, ABO compatible; ABOi, ABO incompatible; LT, liver transplantation; SMD, standard deviation mean difference.

Table 5. Comparison of post liver-transplantation complications between ABOi and ABOc groups after propensity score matching

Patients	ABOi LT, *n*=204	ABOc LT, *n*=204	*p*-value
Acute cellular rejection	8 (3.9%)	9 (4.4%)	0.804
Antibody-mediated rejection	12 (5.9%)	0 (0%)	<0.001
Graft-versus-host disease	3 (1.5%)	2 (1.0%)	0.653
Early allograft dysfunction	98 (48.0%)	77 (37.7%)	0.036
Primary nonfunction	4 (2.0%)	2 (1.0%)	0.411
Acute kidney injury	98 (48.0%)	55 (27.0%)	<0.001
Biliary complication (biliary leakage / stenosis)	47 (23.0%)	16 (7.8%)	<0.001
Nonanatomical biliary stenosis	35 (17.2%)	8 (3.9%)	<0.001
De novo diabetes	69 (33.8%)	52 (25.5%)	0.065
Hyperlipidemia	65 (31.9%)	57 (27.9%)	0.387
Hepatic artery complications (stenosis / thrombosis)	30 (14.7%)	6 (2.9%)	<0.001
Portal vein complications (stenosis / thrombosis)	10 (4.9%)	8 (3.9%)	0.630
Infectious complication	32 (15.7%)	35 (17.2%)	0.688
Retransplantation	9 (4.4%)	2 (1.0%)	0.032

ABOc, ABO compatible; ABOi, ABO incompatible; LT, liver transplantation.

to-A (*n*=16), AB-to-O (*n*=32), AB-to-A (*n*=40), and AB-to-B (*n*=27) after PSM. Patient overall survival and graft survival outcomes in ABOi and ABOc LT groups after PSM were compared (Fig. 1C, D). In the ABOi LT group, the 1-, 3-, and 5-year overall survival rates were 64.1%, 62.5%, and 50.6%, respectively and the 1-, 3-, and 5-year graft survival rates were 60.6%, 58.2%, and 46.5%, respectively. In the ABOc LT group, the 1-, 3-, and 5-year overall survival rates were 77.5%, 75.7%, and 75.7%, respectively. The 1-, 3-, and 5-year graft survival rates were 76.6%, 74.8%, and 74.8%, respectively. Both the overall survival and graft survival rates in the ABOi group were inferior to those in the ABOc group ($p<0.01$ and $p<0.001$, respectively). Comparisons of perioperative morbidity in the ABOi and ABOc groups after PSM are shown in Table 5. Patients in the ABOi LT group were more likely to suffer from biliary and hepatic artery complications, AMR, early allograft dysfunction, and acute kidney injury. The percentage of patients requiring retransplantation was 4.4% in the ABOi group and only 1.0% in the ABOc group.

Comparison of lymphocyte subpopulations in ABOi LT recipients

Rituximab was given to the patients in ABOi LT group before the operation, and decreased the number of $CD19^+$ B cells to almost zero at 3 weeks and at 6 months after LT (Fig. 2A). Compared with the ABOc group, the percentage of $CD19^+$ B cells in ABOi LT recipients significantly decreased from postoperative day 3 until month 3 ($p<0.05$), and the percentage of $CD19^+$ B cells gradually decreased for 3 months after the operation in both groups.

The percentages of $CD3^+$, $CD4^+$, and $CD8^+$ T cells also changed after rituximab administration (Fig. 2B). Increases in $CD3^+$ and $CD8^+$ T cell percentages were observed for 3 months after the operation in the ABOi LT group, and decreased for 1 year thereafter. The percentage of $CD4^+$ T cells manifested an opposite trend of that of $CD8^+$ T cells, with an increase from 38.9% during LT to 50.7% after 3 months and then declined to 33.3% by 6 months. The percentage of $CD3^+$ T cells increased slightly after LT for 3 months and then decreased to 75% at 1 year.

Subgroup analysis stratified by MELD score

Subgroup analysis stratified by the MELD score was adopted to identify the interval during which the overall survival and graft survival prognosis declined. In total, 45 patients in the

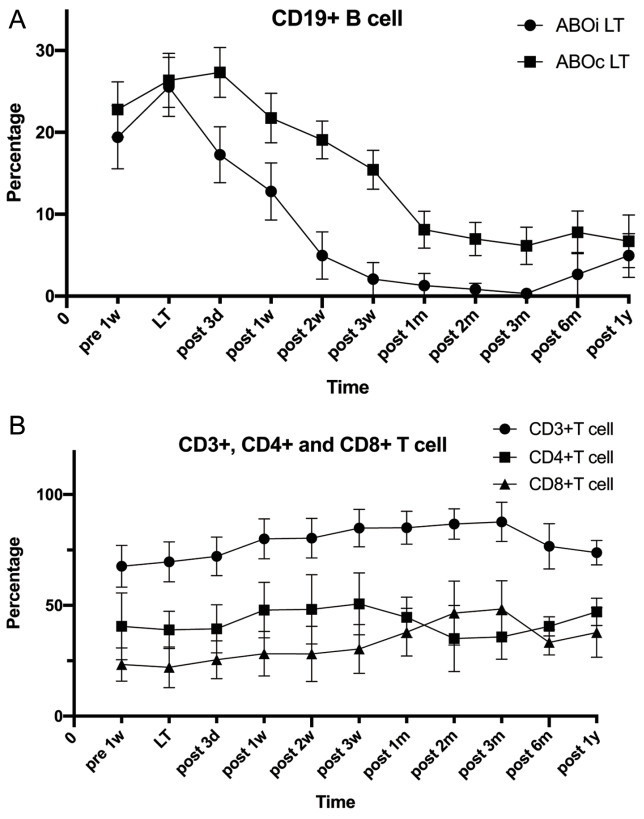

Fig. 2. Changes of $CD19^+$ B-cell kinetics. (A–B) In ABOi (*n*=104) and ABOc (*n*=98) group (A) and changes of the $CD3^+$, $CD4^+$, and $CD8^+$ T cell subpopulations (B) of ABOi group peri-operative. ABOc, ABO compatible; ABOi, ABO incompatible.

ABOc LT group and 50 patients in the ABOi LT group had a MELD score ≤30. After comparison, 3-year overall survival was 88.3% and graft survival was 85.6% in the ABOc group, and 3-year overall survival and graft survival rates were both 89.6% in the ABOi group, (both $p>0.05$; Fig. 3A, B). Overall survival and graft survival were also compared in patients with a MELD score ≥40. The 3-year overall survival and graft survival rates were 64.5% and 64.5% in the ABOc group ($n=75$), and the 3-year overall survival and graft survival rates were 52.9% and 45.6% in the ABOi group ($n=67$, both $p>0.05$; Fig. 3C, D). For patients with MELD scores from 31–39, the 3-year overall survival and graft survival rates were 79.1% and 78.2% in the ABOc group ($n=84$), and were 56.2% and 51.2% in the ABOi group ($n=87$, both $p<0.001$; Fig. 3E, F). In addition, the $CD19^+$ B-cell percentage decreased faster in patients with a MELD score ≤30 than in patients with a score from 31–39 in the ABOi LT group from 3 days to 1 week after the operation ($p<0.05$; Fig. 3G).

Subgroup analysis stratified by CIT

Subgroup analysis classified by CIT was also adopted to identify the impact of CIT on the overall survival and graft survival prognosis after ABOi LT. Patients who received liver grafts with a CIT≥8 h ($n=114$) had an worse prognosis, and the 3-year overall survival and graft survival rates were 48.5% and 45.8%, respectively. The 3-year overall survival and graft survival rates were 81.1% and 76.3% for a CIT of <8 h ($n=90$), respectively (both $p<0.0001$; Fig. 4A, B). The same trend was observed in patients with MELD scores from 31–39. The 3-year overall survival and graft survival rates were 44.9% and 41.5% for CITs≥8 h ($n=59$) in the ABOi LT group, and the 3-year overall survival and graft survival rates were 80.3% and 71.7% for CITs<8 h ($n=28$, both $p<0.01$; Fig. 4C, D). For patients with MELD scores ≥40, the 3-year overall survival and graft survival were 34.4% and 31.3%, respectively, in cases ($n=32$) with CITs≥8 h. These values were also shorter than the 3-year overall survival and graft survival of CIT>8 h recipients ($n=35$), which were 71.8% and 66.1%, respectively (both $p<0.01$; Fig. 4E, F). For patients with a MELD score ≤30, the overall survival and graft survival were comparable when the CIT was longer than 8 h (both $p>0.05$; Fig. 4G, H). In addition, overall survival and graft survival were similar for ABOi and ABOc grafts with a CIT of <8 h (both $p>0.05$; Fig. 5A, B).

Discussion

Currently, the shortage of ideal donor livers is the bottleneck that restricts further development of clinical LT. Methods to expand the sources of donor liver and optimize potential extended criteria donor (ECD) liver is an area of great interest. Numerous clinical studies have shown that the reasonable adoption of ECD liver grafts has a satisfactory prognosis.[10–12] Because ABOi liver grafts serve as ECD grafts, ensuring the long-term survival of recipients and reducing the incidence of complications are also remarkably important.

The China Organ Transplant Response System has been widely adopted since 2013 to equitably and transparently allocate organs.[7] According to our organ allocation policy, ABOi LT is not the first priority compared with ABOc LT. However, for patients with acute ACLF or ACLF, receiving ABOi grafts is the only solution to increase the 90-day overall survival rate. Based on a European survey, the 28-day mortality rate among patients who had ACLF was 33.9% because of severe systemic inflammatory responses and single- or multiple-organ system failures.[13] The 28- and 90-day mortalities were 41.9% and 56.1%, respectively, according to the Asian Pacific Association for the Study of the Liver (APASL) ACLF and 37.6% and 50.4%, respectively, according to the European Association for the Study of the Liver (EASL) ACLF.[14] We believe that emergency ABOi LT should be regarded as the optimal and advocated method under those circumstances if ABOc LT is difficult to achieve. In the last two decades, the prognosis of ABOi LT recipients improved following the introduction of desensitization therapy and improvements in strategies such as plasma exchange, rituximab treatment, MMF, IVIG, and splenectomy.[3,4,15] Recently, ABOi LT has gained acceptance in emergency settings and, to some extent, in hepatocellular carcinoma.

In the entire study cohort, MELD and Child-Pugh scores of the ABOi group were significantly higher, and the age of the recipients was significantly lower, than those of the ABOc group, indicating that ABOi LT was more often adopted in the salvage of severe liver failure patients. The waiting time for LT was thus consequently shorter. Because ABOi liver grafts are more commonly used in emergency LT, they are more likely to be procured or transported from another surgical center, resulting in a longer CIT. In our study cohort, 57.6% of the ABOi grafts had a CIT of >8 h, and 49.0% were donations after cardiac death, which resulted in inferior overall survival and graft survival compared with other institutions. The allocation of ABOi LT also contributes to an increased ECD graft rate. Multivariate Cox analysis demonstrated that ABOi, CIT, intraoperative blood loss, intraoperative blood transfusion, and recipient MELD score were all independent risk factors for recipient death and graft loss. The hazard ratios of ABOi LT were 4.161 for recipient death and 4.241 for graft loss compared with ABOc LT. To reduce selection bias caused by inconsistency, PSM was performed to verify the real impact of ABOi on recipients and liver grafts based on the results of Cox regression analysis. After screening the patients in the two groups, the baseline clinical characteristics did not significantly differ, permitting further analysis. The overall survival and graft survival in the ABOi group were also significantly lower than those in the ABOc group after PSM. In addition, the real 3-year overall survival and graft survival were 75.7% and 74.8%, respectively, after adjusting for CIT and other risk factors, and the respective rates were 86.5% and 85.2% before PSM.

Stewart *et al*.[16] also concluded That adult ABOi LT was limited to emergent circumstances because the 1-year graft survival was only 61.9% in the ABOi group compared with 73.2% in the ABOc group in a matched control group. In addition, graft losses in the ABOi group occurred within 3 months after LT, which is similar to our findings. However, Shen *et al*.[17] compared 35 ABOi LT recipients with 66 ABOc LT recipients in 2014 and found that the 3-year graft survival was 80.0% in the former group and 86.3% in the ABOc group without any significant difference. Toso *et al*.[18] divided the recipients into ABOi ($n=14$), ABOc ($n=29$) and ABO-identical ($n=65$) groups and observed no significant difference in 5-year overall survival and graft survival among these groups. Patients enrolled in our study were also treated with rituximab and IVIG before the operation, and a quadruple regimen consisting of tacrolimus, MMF, methylprednisolone, and IVIG was given as a postoperative immunosuppressive regimen in the ABOi LT group. The differences from Shen *et al*.[17] and Toso *et al*.[18] might be due to the fact that the recipients in our study were all critically ill. After PSM, the MELD and Child-Pugh scores of the two groups increased to 34 (31–40), 37 (31–40), and 12 (11–13), and 12 (11–13), respectively. WIT and CIT increased to 6 (0–11), 6 (1–9), and 8.7 (6.5–11.0), and 8.0 (7.9–10.9), which greatly reduced the survival rate of the recipients.

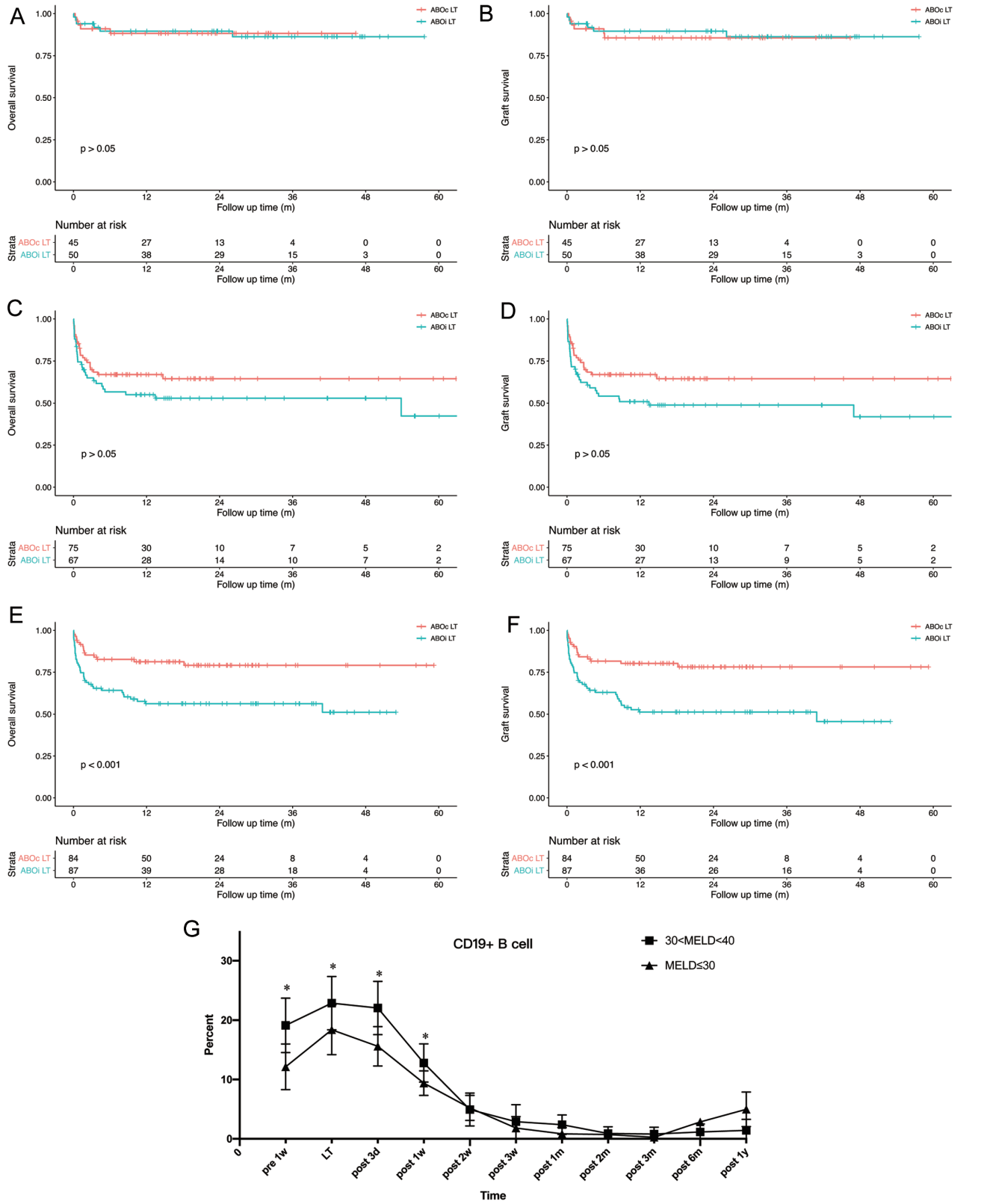

Fig. 3. Comparison of the overall survival rates and graft survival rates. (A–G) Overall survival (A) rates and graft survival (B) rates between ABOi and ABOc LT recipients with the MELD score ≤30, with the MELD score ≥40 (C and D), with MELD scores of 31–39 (E and F), and changes of $CD19^+$ B-cell kinetics in ABOi group (G) in patients with the MELD scores ≤30 (*n*=38) and 30–40 (*n*=66). ABOc, ABO compatible; ABOi, ABO incompatible; MELD, model for end-stage liver disease.

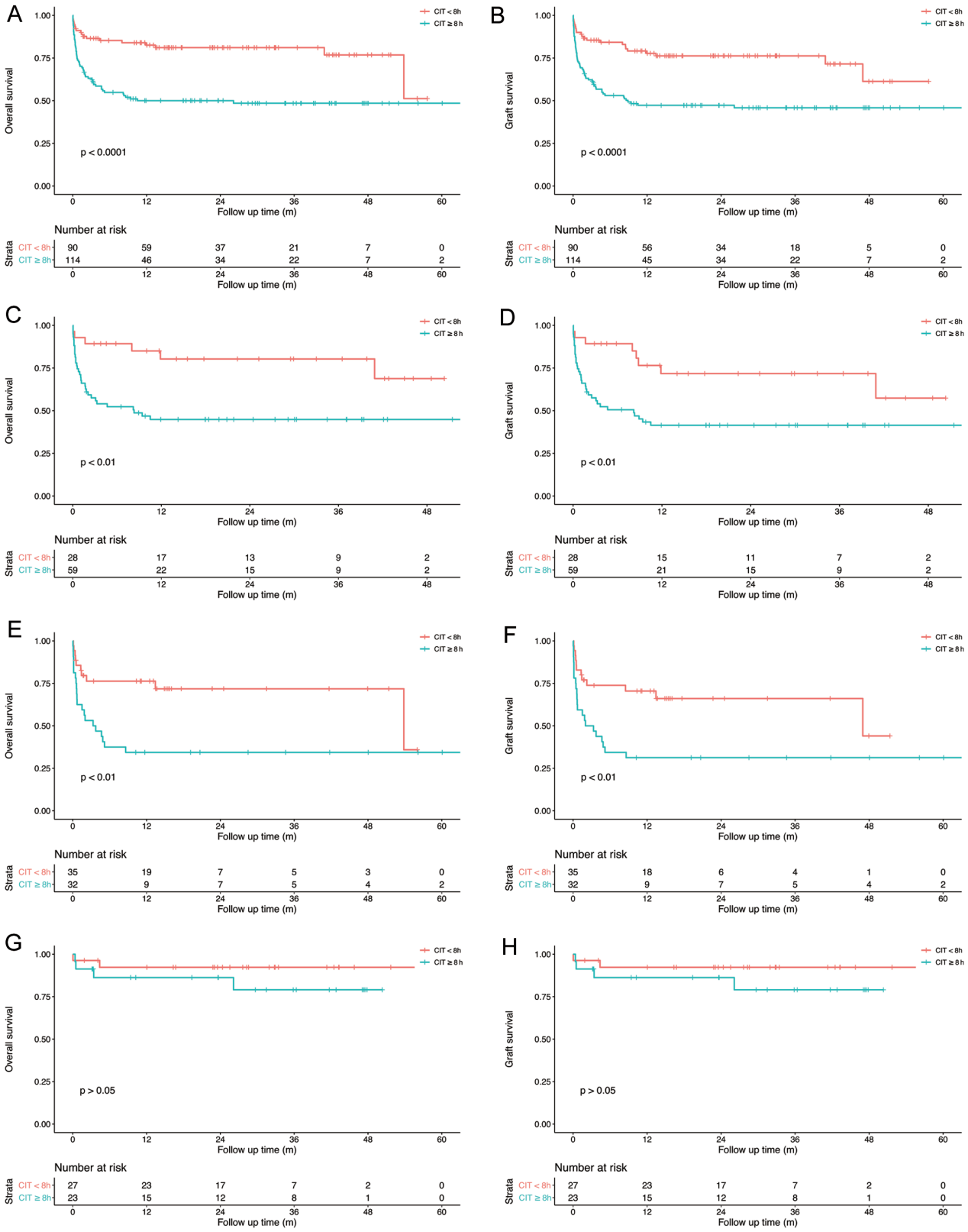

Fig. 4. Comparison of the overall survival rates and graft survival rates. (A–H) Overall survival (A) rates and graft survival (B) rates in ABOi group between liver graft CIT≥8 h and <8 h, with MELD scores of 31–39 and liver graft CITs≥8 h and <8 h (C and D), with MELD scores ≥40 and liver graft CITs≥8 h and <8 h (E and F), with MELD scores ≤30 and liver graft CITs≥8 h and <8 h (G and H). ABOc, ABO compatible; ABOi, ABO incompatible; CIT, cold ischemia time; MELD, model for end-stage liver disease.

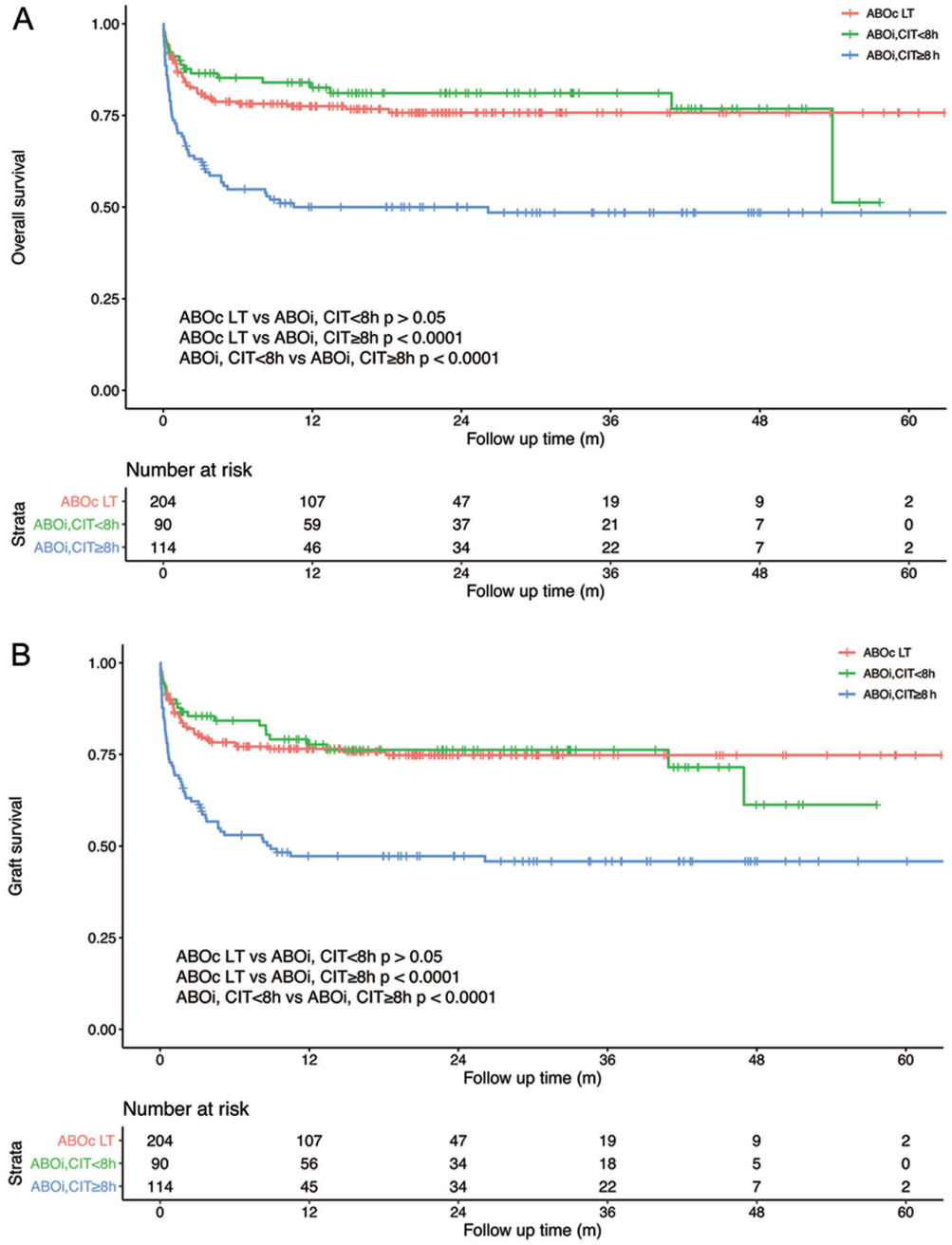

Fig. 5. Comparison of the overall survival rates and graft survival rates. (A–B) Overall survival (A) rates and graft survival (B) rates with CITs≥8 h and <8 h in the ABOi vs. the ABOc group. ABOc, ABO compatible; ABOi, ABO incompatible; CIT, cold ischemia time.

Considering the relatively high acuity condition of the recipients, a 5-year overall survival rate of ABOc recipients just exceeding 50% is quite acceptable. Additionally, the large sample size enrolled made widening the gap between the ABOi and ABOc groups easier.

Many postoperative complications were frequent in ABOi LT recipients and were similar to other reports, including biliary complications. Nonanastomotic biliary stenosis, and hepatic artery thrombosis were more likely to occur in ABOi LT groups, although the incidence decreased following the wide adoption of a standardized antibody-reducing immunosuppressive protocol.[19,20] AMR is monitored by measuring peripheral blood lymphocyte subpopulations and isoagglutinin titers and is prone to occur in ABOi LT groups.[19] At present, the advent of extracorporeal therapies, including total plasma exchange and antigen-specific immunoadsorption, has facilitated the depletion of resident isoagglutinins, which reduces the chance of AMR.[21,22]

The planning of living donor liver transplantation (LDLT) could reserve adequate time for pretransplant treatment for recipients receiving ABOi liver grafts to reduce anti-A/B antibody titers and suppress B cells before transplantation,

which is not possible to achieve in DDLT. Yoon *et al*.[6] used predesensitization to overcome the ABO blood group barrier, including pretransplant rituximab administration and plasma exchange, with the goal of achieving an isoagglutinin titer of ≤1:8 2 to 3 weeks prior to LDLT. No significant differences were observed in the long-term overall survival and recurrence-free survival rates between patients receiving ABOc or ABOi liver grafts. Kim *et al*.[23] adopted similar predesensitization protocols until the titers of isoagglutinins for the donor ABO blood groups ≤1:16. Rituximab is an effective treatment for desensitization but has no effect once the AMR process is initiated. Some studies have shown that using rituximab alone achieved sufficient desensitization for ABOi LDLT without administering plasma exchange.[24] Several studies reported that the use of effective predesensitization protocols overcame the ABO blood type barrier in 95% of recipients. Several issues, including the identification of high-risk patients for AMR and corresponding effective treatment strategies, need to be updated.[25,26] Nonetheless, a similar desensitization treatment was adopted just prior to LT or even during LT using a deceased-donor graft. Shen *et al*.[17] reported a rapid reduction in the $CD20^+$ B-cell percentage 1 day postoperatively after a single dose of rituximab. In our study, $CD19^+$ B cells, expressed from pro-B cells to memory B cells, were used as a mirror of $CD20^+$ B-cell expression and detected circulating rituximab in vivo.[27,28] Consequently, the $CD19^+$ B-cell percentage was found to decrease just prior to LT and reached almost zero between 3 weeks and 6 months after LT with rituximab and IVIG.

Patients with MELD scores from 31–39 were found to have a worse prognosis than those with ABOi and ABOc LT by grouping the MELD scores. For patients with a less severe condition and MELD scores ≤30, adopting ABOi liver grafts had a prognosis of overall survival and graft survival similar to that of the ABOc group. In addition, for the most severe patients, with MELD scores ≥40, adopting ABOi liver grafts resulted in inferior but not significantly different overall survival and graft survival. Previous studies have shown that patients with relatively severe ESLD conditions preoperatively may have a higher frequency of B lymphocytes. The same dose of rituximab may not be sufficient to remove all $CD20^+$ B cells, resulting in subsequent AMR and even graft failure.[29,30] Egawa *et al*.[31] reported that fulminant hepatic failure occurred if rituximab was administered within 6 days before living donor LT. Furthermore, administering multiple doses of rituximab has been proven to significantly increase the incidence of fungal and cytomegalovirus infections,[32] which are life threatening in patients with higher preoperative MELD scores. All the above mentioned factors would lead to poor outcomes in patients with high MELD scores, especially in the ABOi group compared with the ABOc group.

The United Network for Organ Sharing Policy 5.3.D.5 defines the classification interval for a candidate with a MELD or pediatric end-stage liver disease (PELD) score of at least 30 to accept a liver from a deceased donor with any blood type. The definition is slightly different from our classification interval, but ABOi LT has always been considered a life-saving procedure in the most critical setting. In the era of rituximab and IVIG, the limitation of the MELD score should be broadened. For patients who have a less severe condition, accepting ABOi LT is also advisable as long as protocols are strictly monitored. Liver grafts with longer a CIT were regarded as extended criteria donor grafts with a higher risk of early allograft dysfunction. Several studies have proven that receiving a liver graft with CIT of <8 h result in a satisfactory prognosis.[33,34] The survival rate was significantly lower for patients who received a liver graft with CIT≥8 h compared with a CIT of <8 h in the ABOi LT group. This phenomenon is more important in patients with MELD scores from 31–39 and MELD scores ≥40 but was not reflected in patients with MELD scores ≤30. Thus, for patients with MELD scores >30 who are willing to adopt ABOi LT, a CIT of <8 h would be beneficial.

This study was also subject to limitations. Namely, the number of $CD20^+$ B cells was not conventionally measured in some centers, and the data of lymphocyte subpopulations could be missing. Our data on the kinetics of lymphocyte subpopulations were not sufficient to clearly address the worse clinical overall survival and graft survival rates. In addition, blood Group A was not categorized into A1 and A2 in some centers, and we consequently could not analyze the difference in prognosis among different blood groups. However, this study has sufficient value to group the MELD score and identify the groups of patients who actually have reduced overall survival and graft survival rates for ABOi LT, which has not been reported before. Furthermore, to the best of our knowledge, our investigation enrolled the largest number of patients receiving ABOi DDLT at 4 transplantation centers in Asia for this retrospective study, and PSM was adopted to eliminate selection bias.

In conclusion, our experience demonstrated that the prognosis of ABOi LT was not as good as that of ABOc LT, and the difference was significant even after PSM. For recipients with MELD scores ≤30, receiving an ABOi liver graft had a prognosis comparable to that of ABOc. For recipients with MELD scores ≥40, ABOi should be adopted with caution in emergency cases. For recipients with MELD scores from 31–39, overall survival and graft survival of ABOi LT were significantly worse, which actually worsened the prognosis of ABOi LT. Finally, the prognosis of recipients utilizing ABOi LT was be improved by using grafts with a CIT of <8 h, especially for MELD scores from 31–39.

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Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Our manuscript has 14 authors, all of whom contributed significantly to this study. Conceived and designed the experiments (MY, XW, QW, YY, XX), collected the data (MY, AK, RW, BP, BC), analyzed the data (MY, XW, KW, ZZ, DL), wrote the paper (MY, XW), and supervised the paper (SZ, WG, SZ, YY, XX).

Ethical statement

LT was approved by the liver transplantation committee of each institution and was performed after informed consent was obtained from the patients. The study was approved by the China Liver Transplant Registry with approval number 2020058, and by the ethics committee. It was performed following the ethical principles of the Declaration of Helsinki.

Data sharing statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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