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Impact of the Kasai Procedure and the Length of Native Liver Survival Time on Outcomes of Liver Transplantation for Biliary Atresia

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The aim is to explore the impact of the Kasai procedure (KP) and the length of native liver survival time (NLST) on outcomes of liver transplantation (LT). Patients with biliary atresia (BA), who underwent LT in Beijing Friendship Hospital from January 2017 to December 2019, were enrolled and divided into non-KP (N-KP) and post-KP (P-KP) groups. The patients in the P-KP group were further divided into early failure (KP-EF) defined by NLST <1 year, medium failure (KP-MF, NLST 1-5 years), and late failure (KP-LF, NLST >5 years) subgroups. Clinical data at baseline and during follow-up were collected. The inverse probability of treatment weighting method was used to evaluate the independent effect of KP and the length of NLST on clinical outcomes. Among 197 patients with BA, the N-KP group accounted for 43 (21.8%), KP-EF 71 (46.1%), KP-MF 59 (38.3%), and KP-LF 24 (15.6%) cases, respectively. The N-KP and KP-EF groups had significantly longer hospitalization and intensive care unit stays after LT. Graft and overall survival rates were 93.0% in the N-KP group and 97.4% in P-KP group, respectively. The mortality rate in the P-KP group were significantly lower compared with that of the N-KP group with a hazard ratio (HR) of 0.2 ($P = 0.02$). The risks of biliary and vascular complications and cytomegalovirus (CMV) infection after LT were significantly higher in KP-EF group than those in the KP-MF and KP-LF groups (HRs = 0.09, 0.2, and 0.3, respectively; all $P < 0.001$). The KP significantly improved after LT overall survival. Patients with early native liver failure after KP have significantly higher risks for biliary and vascular complications and CMV infection.

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Biliary atresia (BA) is the leading cause of pediatric cholestatic liver disease worldwide and more commonly occurs in the Asia-Pacific region (1.04-1.78/10,000).[1-3] It is characterized by rapidly progressive extrahepatic bile duct fibrosclerosing injury leading to cholestatic cirrhosis within a short period of time.[4,5] Without portoenterostomy (Kasai procedure [KP]), the initial first-line management for BA, patients universally die of liver failure within 2 years of life.[6] Therefore, BA is the leading indication for liver transplantation (LT) in the pediatric population worldwide, including China. According to the Chinese Liver Transplantation Registry, BA is the prime indication (77%) for LT in the pediatric population.

Abbreviations: ALT, alanine aminotransferase; BA, biliary atresia; CI, confidence interval; CIT, cold ischemia time; CMV, cytomegalovirus; DDLT, deceased donor liver transplantation; DRI, donor risk index; DWIT, donor warm ischemia time; EBV, Epstein-Barr virus; FK-506, tacrolimus; GEV, gastroesophageal varices; GRWR, graft-to-recipient weight ratio; GWIT, graft warm ischemia time; HR, hazard ratio;

There are 2 types of patients with BA who eventually receive LT. The patients with BA type Ⅰ require primary LT as the only management choice without prior KP, whereas the patients with BA type Ⅱ have KP first followed by salvage LT.[7,8] There are 2 different views on whether KP affects the clinical outcomes after LT. One view is that KP has no significant effect on the overall patient survival after LT,[9,10] whereas the other view believes that KP has a significant adverse effect on long-term survival[11,12] because of the increased infectious and biliary complications after salvage LT.[3,10] Therefore, the effect of KP on the prognosis of LT in patients with BA need to be further studied, particularly when confounding factors could be controlled effectively besides KP.

Patients with BA treated with KP often show different lengths of native liver survival time (NLST), which ranges from 59.6% to 63.5% at 1 year,[13,14] approximately 50% at 2 years,[15,16] and 31% to 36% at 10 years post KP (P-KP).[7,17] The literature on the effect of NLST on post-LT outcomes is scarce and varied. For example, compared with patients with BA with KP late failure (KP-LF; ≥1 year), patients with BA with KP early failure (KP-EF; <1 year) had a higher infection rate and a lower overall survival rate after LT.[3,12] However, another study found that the patients with KP-EF had lower biliary complications, which had no significant effect on the overall survival rate after LT.[18] Therefore, in this study, we explored the impact of KP and the length of NLST after KP on the clinical outcomes of LT.

ICU, intensive care unit; IS, immunosuppression; KP, Kasai procedure; KP-EF, Kasai procedure early failure; KP-LF, Kasai procedure late failure; KP-MF, Kasai procedure medium failure; LDLT, living donor liver transplantation; LT, liver transplantation; MMF, mycophenolate mofetil; N-KP, non-Kasai procedure; NLST, native liver survival time; PELD, Pediatric End-Stage Liver Disease; PFIC, progressive familial intrahepatic cholestasis; P-KP, post–Kasai procedure; PTLD, posttransplant lymphoproliferative disease; TB, total bilirubin.

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Potential conflict of interest: Nothing to report.

Patients and Methods

STUDY POPULATION

This study enrolled patients with BA who were admitted to the Liver Transplantation Center of Beijing Friendship Hospital, Capital Medical University from January 2017 to December 2019 and who met the inclusion and exclusion criteria. The study conformed to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a prior approval by the Ethics Committee of Beijing Friendship Hospital (No. 2018-P2-207-01). We confessed that no organs from executed prisoners were used for LT in this study.

The inclusion criteria were (1) patients diagnosed with BA at admission and (2) patients with complete follow-up data. The exclusion criteria were the following: (1) no LT during hospitalization; (2) pathological examination of explant livers not supportive of the diagnosis of BA but, rather, comparable with progressive familiar intrahepatic cholestasis or Alagille syndrome, further confirmed by genetic tests; and (3) retransplantation.

The enrolled patients with BA were divided into a non-KP (N-KP) group and a post-KP (P-KP) group. The latter group was further split into the following 3 subgroups according to the length of NLST (determined by age at LT): <1 year was the KP-EF group, 1 to 5 years was the medium-term failure (KP-MF) group, and >5 years was the KP-LF group.

CLINICAL DATA PRIOR TO LT

The medical records of all enrolled patients were reviewed. Pre-LT demographic data included age at KP and LT, sex, height, weight, body mass index,

blood type, and routine laboratory data and imaging results, which were retrieved from the hospital electronic database. Child-Pugh-Turcotte scores and Pediatric End-Stage Liver Disease (PELD) scores were calculated.[19] The *z* scores for weight, height, and spleen size reference to age were calculated.[20,21] Indications for LT of the enrolled patients, such as protracted jaundice, cholangitis, gastroesophageal varices (GEV) bleeding, severe hypersplenism, growth retardation, massive ascites, and liver failure, were collected. We defined massive ascites according to clinical presentation and ultrasound findings proposed by the European Association for the Study of the Liver[22] and Chinese guidelines[23] on the management of ascites.

HISTOLOGICAL ASSESSMENTS OF LIVER EXPLANTS

The liver explants of all patients were obtained after LT. Representative tissue blocks were obtained from both the left and right lobes, which were fixed in 10% neutral formalin and embedded in paraffin. Sections were cut and stained with hematoxylin-eosin, reticulin, Masson trichrome, periodic acid–Schiff with diastase, rhodanine stain, and Perls' Prussian blue stain. Stage of liver fibrosis was assessed using a standardized scoring system.[24] A liver pathologist and a hepatologist independently evaluated the slides blinded to clinical information.

INFORMATION OF LT SURGERY AND DATA OF PERITRANSPLANT CARE

The type of liver allografts was divided into living donor LT (LDLT) and deceased donor LT (DDLT). Donor warm ischemia time (DWIT) is defined as "the interval from withdrawal of life support to initiation of cold organ preservation."[25,26] Graft cold ischemia time (CIT) was defined as "the interval from initiation of donor in vivo cold organ preservation to removal of the graft from 4°C cold storage."[25] Graft warm ischemia time (GWIT) is defined as "the interval from removal from cold storage to establishment of reperfusion of the liver graft."[25,27] We also collected data regarding graft-to-recipient weight ratio (GRWR), operative time, blood loss, intensive care unit (ICU) stay after LT, and duration of hospitalization. The donor risk index (DRI) of DDLT was calculated according to the standard method.[28]

POST-LT FOLLOW-UP DATA

The following follow-up data were retrieved: (1) values of alanine aminotransferase (ALT) and total bilirubin (TB) at weeks 1, 2, and 4 after LT; (2) short-term (<1 month after LT) and long-term (≥1 month after LT) complications such as surgical complication(s), infection, rejection, and posttransplant lymphoproliferative disease (PTLD); and (3) graft and overall survival rates.

STATISTICAL ANALYSIS

Statistical analyses were performed using either SPSS software (version 21.0; IBM Corp., Armonk, NY) or SAS software (version 9.4; SAS Institute Inc., Cary, NC). A Mann-Whitney U test or a Kruskal-Wallis test was used for continuous variables, and a chi-square test or Fisher's exact test was used for categorical variables when applicable. The 1-year, 2-year, and 3-year graft and overall survival rates and cumulative incidence of complications were assessed by Kaplan-Meier curve and compared by log-rank test. The inverse probability of treatment weighting method was used to adjust confounding variables and to further evaluate the independent effect of KP and the length of NLST on the outcomes of LT. A bilateral P value of <0.05 was considered statistically significant.

Results

COMPARISON OF DEMOGRAPHIC, LABORATORY, AND HISTOLOGICAL CHARACTERISTICS BEFORE LT BETWEEN THE N-KP AND P-KP GROUPS

A total of 197 pediatric patients with BA who underwent LT from January 2017 to December 2019 in Beijing Friendship Hospital were qualified and enrolled in this study (Fig. 1). A total of 43 patients did not have KP before LT (N-KP group), whereas 71, 59, and 24 patients belonged to the KP-EF, KP-MF, and KP-LF groups, respectively. The demographic, laboratory,

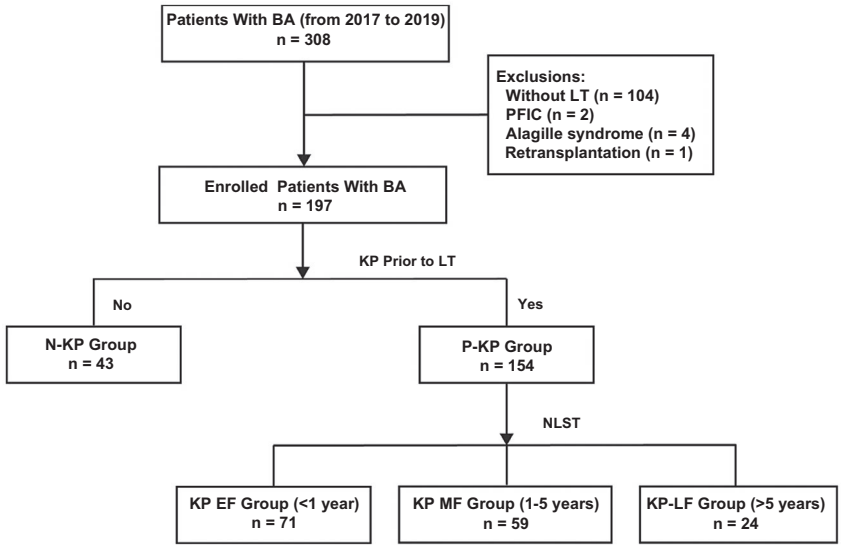

FIG. 1. Flowchart of the enrolled patients with BA in this study.

and histological data before LT are shown in Table 1. The female:male ratio was comparable among the 3 KP groups. There was no significant difference in the age at the time of KP among these groups. The median age at the LT in the N-KP and KP-EF groups was significantly younger than those in the KP-MF and KP-LF groups (6.4 [interquartile range, 5.3-8.0] and 7.7 [interquartile range, 6.3-9.5] versus 22.9 [interquartile range, 14.8-36.3] and 82.2 [interquartile range, 68.1-104.5] months; $P < 0.001$). The z scores for weight were significantly lower in the N-KP and KP-EF groups (−0.9 [interquartile range, −1.8 to 0.1] and −1.2 [interquartile range, −2.2 to −0.2]) than those in the KP-MF and KP-LF groups (−0.5 [interquartile range, −1.1 to 0.3] and −0.6 [interquartile range, −1.2 to 0.3]; $P = 0.005$).

Cholestatic parameters in all groups (N-KP versus KP-EF versus KP-MF versus KP-LF) as indicated by TB (medians: 361.9 versus 291.7 versus 34.8 versus 16.3 μmol/L; $P < 0.001$) and total bile acid (medians: 199.9 versus 188.7 versus 104.5 versus 27.9 μmol/L; $P < 0.001$) were significantly higher in the N-KP and KP-EF groups. Hepatic synthetic function comparison (N-KP versus KP-EF versus KP-MF versus KP-LF) showed statistically lower albumin (medians: 33.1 versus 32.4 versus 37.1 versus 39.2 g/L; $P < 0.001$) and higher international normalization ratios (medians: 1.5 versus 1.4 versus 1.1 versus 1.2; $P < 0.001$) levels in the N-KP and KP-EF groups. The PELD scores and Child-Pugh-Turcotte scores, the models representing overall severity, were significantly higher in the N-KP and KP-EF groups than those in the KP-MF and KP-LF groups (all $P < 0.001$).

ALT levels were significantly higher in the N-KP and KP-EF groups (medians: 202.0 and 114.0 U/L) in comparison with the KP-MF and KP-LF groups (medians: 90.0 and 49.0 U/L; $P < 0.001$). However, gamma-glutamyl transpeptidase levels were similar among all 4 groups (medians: 198.0 versus 259.0 versus 210.0 versus 135.0 U/L; $P = 0.08$). The platelet count, a marker representing hypersplenism, was significantly lower in the KP-LF group (median: 73×10^9/L) in comparison with the N-KP, KP-EF, and KP-MF groups (medians: 171, 178, and 133×10^9/L; $P < 0.001$). These data suggested that the overall disease severity was milder along with time, that is, the KP-EF group was similar to the N-KP group but significantly more severe than the KP-MF and KP-LF groups. However, the KP-LF group had more severe portal hypertension.

Histological findings showed that 86.0% and 88.7% of patients in the N-KP and KP-EF groups, respectively, had stage 4 fibrosis, known as cirrhosis. These were significantly higher than 59.3% and 33.3% in patients with cirrhosis in the KP-MF and KP-LF groups, respectively ($P < 0.001$; Supporting Fig. 1 and Supporting Table 1). The histological findings correlated well with the clinical findings.

TABLE 1. Demographic and Laboratory Data

Parameter	N-KP	P-KP			*P* Value
		KP-EF (<1 Year)	KP-MF (1-5 Years)	KP-LF (>5 Years)	
Total cases	43 (21.8)	71 (36.0)	59 (29.9)	24 (12.2)	
Male	19 (44.2)	39 (54.9)	27 (45.8)	15 (62.5)	0.38
Age at KP, days	–	60 (42-72)	56 (34-70)	59 (30-84)	0.44
Age at LT, months	6.4 (5.3-8.0)	7.7 (6.3-9.5)	22.9 (14.8-36.3)	82.2 (68.1-104.5)	<0.001
Weight, kg	7.0 (6.4-7.9)	7.0 (6.3-8.0)	11.5 (9.6-14.0)	23.0 (17.6-30.0)	<0.001
z score of weight	–0.9 (–1.8 to 0.1)	–1.2 (–2.2 to –0.2)	–0.5 (–1.1 to 0.3)	–0.6 (–1.2 to 0.3)	0.005
Height, cm	65.0 (62.0-67.5)	66.0 (63.0-70.0)	80.0 (74.5-93.0)	123.5 (112.3-139.0)	<0.001
z score of height	–0.9 (–2.3 to 0.1)	–1.0 (–2.5 to –0.1)	–0.9 (–1.9 to –0.1)	0.1 (–0.5 to 1.0)	0.001
Body mass index, kg/m^2	16.7 (15.4-18.3)	16.1 (14.9-17.8)	16.4 (15.5-17.8)	14.8 (13.6-16.0)	0.005
Z score of spleen size	5.7 (4.4-6.9)	4.1 (3.0-5.7)	6.3 (5.0-7.5)	9.6 (6.9-10.7)	<0.001
ALT, U/L	202.0 (136.0-345.0)	114.0 (54.0-184.0)	90.0 (46.0-165.0)	49.0 (34.0-94.0)	<0.001
Gamma-glutamyl transpeptidase, U/L	198.0 (67.0-707.0)	259.0 (108.0-439.0)	210.0 (149.0-353.0)	135.0 (84.0-277.0)	0.08
Albumin, g/L	33.1 (26.8-37.2)	32.4 (29.0-35.3)	37.1 (33.0-40.7)	39.2 (33.7-41.9)	<0.001
TB, μmol/L	361.9 (270.6-485.4)	291.7 (103.6-397.2)	34.8 (15.9-88.9)	16.3 (11.9-25.1)	<0.001
Total bile acid, μmol/L	199.9 (131.8-260.7)	188.7 (105.6-311.6)	104.5 (47.8-151.2)	27.9 (16.9-48.0)	<0.001
Cholinesterase, KU/L	2.8 (2.2-4.1)	3.0 (2.3-4.4)	4.5 (3.1-5.9)	4.8 (4.0-6.1)	<0.001
Creatinine, μmol/L	16.2 (14.2-30.2)	20.2 (14.5-28.2)	22.6 (16.5-30.7)	29.6 (26.5-38.2)	<0.001
Platelet count, ×10^9/L	171 (128-241)	178 (131-242)	133 (104-175)	73 (65-101)	<0.001
Prothrombin activity, %	46.1 (32.5-62.8)	53.8 (37.8-71.6)	82.2 (60.6-102.8)	67.6 (58.4-83.7)	<0.001
International normalized ratio	1.5 (1.2-2.0)	1.4 (1.2-1.8)	1.1 (1.0-1.3)	1.2 (1.1-1.3)	<0.001
Child-Pugh-Turcotte score	10 (8-11)	9 (8-10)	6 (5-7)	6 (5-7)	<0.001
PELD score	20 (15-27)	17 (12-25)	1 (–2 to 5)	1 (–1 to 4)	<0.001
Ejection fraction, n = 188	69 (66-73), n = 41	72 (67-75), n = 66	71 (67-75), n = 58	70 (67-73), n = 23	0.34

NOTE: Data represent number (percentage) for categorical variables or median (interquartile range) for continuous variables.

COMPARISON OF INDICATIONS FOR LT BETWEEN THE N-KP AND P-KP GROUPS

The decision for LT was made by a multidisciplinary team including transplant surgeons, hepatologists, social workers, transplant pharmacists, nutritionists, and nurse coordinators. The main clinical indications for LT were significantly different among the groups. Jaundice was seen in 100% and 87.3% of patients in the N-KP and KP-EF groups, which were significantly higher than 33.9% in the KP-MF and 8.3% in the KP-LF groups ($P < 0.001$). Liver failure was significantly more frequent in the N-KP (32.6%) and KP-EF (23.9%) groups, which were significantly higher than in the KP-MF (1.7%) and KP-LF (0%) groups ($P < 0.001$). Cholangitis occurred in 38.0%, 50.8%, and 20.8% patients in the KP-EF, KP-MF, and KP-LF groups, respectively, which were significantly higher than in the N-KP group (0%; $P < 0.001$). Growth retardation existed in 34.9% of patients in the N-KP group, 42.3% in the KP-EF group, 25.4% in the KP-MF group, and 0% in the KP-LF group ($P < 0.001$). The frequency of GEV bleeding was 54.2% and 25.4% in the KP-LF and KP-MF groups, respectively, which were significantly higher than in the KP-EF (1.4%) and N-KP (2.3%) groups ($P < 0.001$). As mentioned previously, the patients with GEV bleeding showed no evidence of portopulmonary hypertension. The frequency of severe hypersplenism was also significantly higher in the KP-LF (25.0%) group than in the other groups ($P = 0.004$; Table 2).

All of the patients enrolled in this study had normal cardiac functions (Table 1), and none of the patients had evidence of cirrhotic cardiomyopathy. In addition, there was no evidence of hepatopulmonary syndrome or portopulmonary hypertension in these patients.

TABLE 2. Comparisons of Indications for LT

Indication	N-KP	P-KP			*P* Value
		KP-EF (<1 Year)	KP-MF (1-5 Years)	KP-LF (>5 Years)	
Jaundice	43 (100.0)	62 (87.3)	20 (33.9)	2 (8.3)	<0.001
Cholangitis	0	27 (38.0)	30 (50.8)	5 (20.8)	<0.001
GEV bleeding	1 (2.3)	1 (1.4)	15 (25.4)	13 (54.2)	<0.001
Severe hypersplenism	1 (2.3)	3 (4.2)	2 (3.4)	6 (25.0)	0.004
Growth retardation	15 (34.9)	30 (42.3)	15 (25.4)	0	<0.001
Massive ascites	0	1 (1.4)	1 (1.7)	1 (4.2)	0.56
Liver failure	14 (32.6)	17 (23.9)	1 (1.7)	0	<0.001

NOTE: Data represent number (percentage).

COMPARISON OF PERI-LT CHARACTERISTICS BETWEEN THE N-KP AND P-KP GROUPS

According to the graft type, we divided the 197 enrolled patients into the LDLT group (n = 154) and the DDLT group (n = 43). There was no significant difference in the incidence of overall complications and survival between the 2 groups (Supporting Table 2). Among the 43 patients who received DDLT, 37 had whole LT and 6 patients had technical variant grafts (3 reduced-size donors and 3 split-liver donors). There was no significant difference in overall complications, biliary complications, or overall survival rates between the whole deceased donor grafts and technical variant transplants. The DRI of these 43 patients with DDLT was calculated, which showed that 55.8% (24/43) of the patients had high DRIs (>2.0). However, there was no significant difference in overall complications and survival rates in general between the DRI ≤2.0 and DRI >2.0 groups.

More patients in the N-KP (86%), KP-EF (83.1%), and KP-MF (76.3%) groups received LDLT than those in the KP-LF (54.2%) group ($P = 0.02$). A total of 5 patients had interposition grafts (interposition patch of portal vein from the recipients themselves), 2 in the N-KP and 3 in the P-KP groups ($P = 0.80$). There was no significant difference in overall vascular complications between the interposition graft and noninterposition graft groups, most likely because of the limited case number. CIT increased along with the age at LT, being the longest in the KP-LF group ($P = 0.008$). The GRWR was also gradually and significantly lower along with the age at LT ($P < 0.001$). DWIT, GWIT, operative time, and blood loss during the operations were all comparable among the groups. ICU stay after LT was significantly longer in the N-KP (median, 3.9 days) and KP-EF (median, 3.8 days) groups than in KP-MF (median, 3.6 days) and KP-LF (median, 3.1 days) groups ($P = 0.01$). Hospitalization was also significantly longer in the N-KP (median, 30 days) and KP-EF (median, 32 days) groups than in the KP-MF (median, 23 days) and KP-LF (median, 23 days) groups ($P < 0.001$; Table 3).

COMPARISON OF BIOCHEMICAL EVOLUTION BETWEEN THE N-KP AND P-KP GROUPS AFTER LT

In this study, the medium follow-up time was 33.1 (20.7-41.0) months. The majority of patients, 179/197 (90.8%), had corticosteroids and tacrolimus (FK-506) as the initial immunosuppressive (IS) therapy (steroids + FK-506, known as a combination regimen), whereas 18/197 (9.2%) patients required corticosteroids, FK-506, and mycophenolate mofetil (MMF) as the initial IS therapy (steroids + FK-506 + MMF, known as a triple regimen). All patients in the N-KP group and 88.3% of patients in the P-KP group received the combination regimen. Among the P-KP group, 18.6% of patients with KP-MF and 16.7% of patients with KP-LF received the triple regimen, which were significantly higher than patients with N-KP (0%) and patients with KP-EF (4.2%; $P = 0.001$). There was no significant difference in initial IS combination regimen between patients who received LDLT and those who received DDLT (90.9% versus 90.7%; $P > 0.99$). Compared with the patients who received ABO-compatible LT, more patients who received ABO-incompatible LT required the triple regimen as the

TABLE 3. Comparison of Peri-LT Characteristics

Parameter	N-KP	P-KP			*P* Value
		KP-EF (<1 Year)	KP-MF (1-5 Years)	KP-LF (>5 Years)	
Donor type					0.02
LDLT	37 (86.0)	59 (83.1)	45 (76.3)	13 (54.2)	
DDLT	6 (14.0)	12 (16.9)	14 (23.7)	11 (45.8)	
Interposition graft	2 (4.7)	2 (2.8)	1 (1.7)	0 (0)	0.80
Piggyback hepatic vein construction	39 (90.7)	61 (85.9)	45 (76.3)	13 (54.2)	0.003
ABO mismatch	10 (23.3)	11 (15.5)	6 (10.2)	0	0.04
DWIT, minutes	3.0 (2.0-3.0)	3.0 (2.0-3.0)	3.0 (2.0-4.0)	3.0 (2.0-5.0)	0.72
CIT, minutes	46.0 (31.0-104.0)	64.0 (44.0-106.0)	75.0 (44.0-207.0)	89.0 (64.0-502.7)	0.008
GWIT, minutes	40.0 (35.0-46.0)	39.0 (33.0-45.0)	39.0 (34.0-45.0)	40.5 (32.2-56.0)	0.85
GRWR, %	3.4 (2.9-3.8)	3.3 (2.8-4.0)	2.4 (2.0-3.1)	2.0 (1.7-2.7)	<0.001
Operative time, minutes	390 (350-440)	375 (350-435)	380 (325-435)	398 (327-480)	0.66
Blood loss during LT, mL	150 (100-250)	150 (100-300)	120 (100-200)	200 (124-338)	0.07
ICU stay, days	3.9 (2.3-5.6)	3.8 (2.9-4.9)	3.6 (2.6-4.6)	3.1 (1.9-3.8)	0.01
Hospitalization, days	30 (21-47)	32 (24-47)	23 (18-32)	23 (15-35)	<0.001

NOTE: Data represent number (percentage) for categorical variables or median (interquartile range) for continuous variables.

initial IS therapy (combination regimen, 92.9% versus 77.8%; triple regimen, 7.1% versus 22.2%; $P = 0.02$).

We analyzed the impact of KP on the evolution of the recipients' ALT and TB at 1, 2, and 4 weeks after LT (Supporting Fig. 2 and Supporting Table 3). Compared with the N-KP group, the KP-EF, KP-MF, and KP-LF groups all had a transit increase in ALT levels at 1 week after LT, which were sharply down after 2 weeks in all groups. By the end of 4 weeks after LT, ALT returned to a normal range in the majority of patients without a statistical difference among the different groups (N-KP versus KP-EF versus KP-MF versus KP-LF: 85.4% versus 77.5% versus 86.4% versus 79.2%, $P = 0.53$). As for the median evolution of TB, the levels initially dropped in the N-KP, KP-EF, and KP-MF groups. In contrast, the TB levels in the KP-LF group had an initial increase at 1 week after LT ($P < 0.001$). TB levels dropped gradually in all groups at 2 and 4 weeks after LT. By the end of 4 weeks after LT, TB returned to a normal range in the majority of patients without a statistical difference among the different groups (N-KP versus KP-EF versus KP-MF versus KP-LF: 80.5% versus 85.9% versus 79.7% versus 70.8%, $P = 0.40$). These data suggested that the evolution of ALT and TB had similar trends despite the fact that the baseline levels of ALT and TB were significantly higher in the N-KP and KP-EF groups.

COMPARISON OF POST-LT COMPLICATIONS BETWEEN THE N-KP AND P-KP GROUPS

As for the surgical complications after LT, there was a trend of higher incidence of biliary stenosis and hepatic artery occlusion in the N-KP group than in all the P-KP groups ($P = 0.06$ and 0.09). However, after adjusting for confounding factors (eg, sex, age at KP, *z* score for weight, *z* score for height, donor type, ABO mismatch, CIT, DWIT, GRWR, liver fibrosis stage), there was no significant difference in surgical complications between the N-KP and P-KP groups (all $P \geq 0.05$; Fig. 2). In the P-KP groups, the younger of the recipients, the higher incidence of biliary stenosis, hepatic and portal vein stenosis though without statistical difference ($P = 0.13$, 0.48, and 0.22, respectively; Supporting Fig. 3). However, the risk of biliary and vascular complications after LT was significantly higher in the patients with KP-EF than in the ≥1-year P-KP patients (adjusted hazard ratios [HRs], 0.09 and 0.2; all *P* values <0.001). The patients with KP-EF who received DDLT had significantly higher hepatic artery–related complications (25.0% versus 0%; $P = 0.004$). The reoperation rate was also significantly higher in the KP-EF group (HR, 0.4; $P = 0.02$, Fig. 3).

	P-KP (N = 154)	N-KP (N = 43)	Primary HR (95% CI)	*P* Value	Adjusted HR (95% CI)	Adjusted *P* Value
Mortality	4 (2.6)	3 (7.0)	0.4 (0.08-1.6)	0.18	0.2 (0.04-0.7)	0.02
Graft failure	4 (2.6)	3 (7.0)	0.4 (0.08-1.6)	0.18	0.2 (0.04-0.7)	0.02
Biliary complications	15 (9.7)	6 (14.0)	0.7 (0.3-1.7)	0.41	0.8 (0.2-2.8)	0.78
Stenosis	9 (5.8)	6 (14.0)	0.4 (0.1-1.1)	0.07	0.5 (0.1-1.8)	0.31
Bile leakage	8 (5.2)	1 (2.3)	2.2 (0.3-17.4)	0.46	3.8 (0.1-121.4)	0.46
Vascular complications	23 (14.9)	6 (14.0)	1.0 (0.4-2.5)	0.99	1.2 (0.4-3.8)	0.72
Hepatic artery	5 (3.2)	4 (9.3)	0.3 (0.09-1.2)	0.10	0.3 (0.07-1.4)	0.13
Hepatic vein	13 (8.4)	1 (2.3)	3.6 (0.5-27.4)	0.22	6.7 (0.3-148.0)	0.23
Portal vein	8 (5.2)	1 (2.3)	2.1 (0.3-17.1)	0.47	3.7 (0.2-77.5)	0.40
Intestinal perforation	6 (3.9)	2 (4.6)	0.8 (0.2-4.1)	0.82	1.1 (0.2-8.2)	0.93
EBV infection	106 (68.8)	25 (58.1)	1.3 (0.8-2.0)	0.26	1.2 (0.7-2.1)	0.46
CMV infection	50 (32.5)	22 (51.2)	0.5 (0.3-0.8)	0.009	0.7 (0.4-1.4)	0.34
Rejection rate	23 (14.9)	8 (18.6)	0.8 (0.3-1.7)	0.50	0.8 (0.3-2.2)	0.70
PTLD	10 (6.5)	4 (9.3)	0.7 (0.2-2.2)	0.56	1.0 (0.2-5.6)	0.96
Cholangitis	13 (8.4)	2 (4.6)	1.8 (0.4-7.8)	0.46	2.6 (0.3-26.0)	0.42
Reoperation rate	28 (18.2)	11 (25.6)	0.7 (0.3-1.3)	0.25	1.0 (0.4-2.4)	0.96

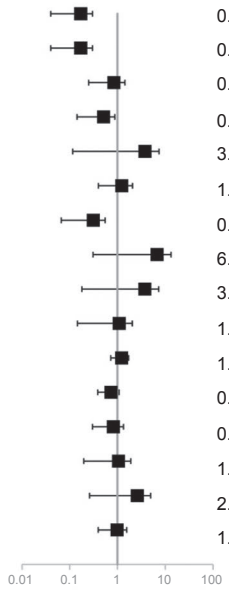

FIG. 2. The impact of KP on survival and complications after LT after adjusting for confounding factors by inverse probability of treatment weighting. After adjusting for confounding factors, there were significant lower overall and graft survival rates in the P-KP group than in the N-KP group but no significant differences on complications.

As for post-LT infections, there was a significantly higher rate of cytomegalovirus (CMV) infections in the N-KP group than in the P-KP group ($P = 0.007$; Fig. 4). In the P-KP group, the younger of the recipients, there was a higher incidence of CMV infection (N-KP, 51.2%; KP-EF, 38.0%; KP-MF, 33.9%; and KP-LF, 12.5%; $P = 0.01$), especially beyond 1 month after LT (Supporting Table 4). After adjusting the confounding factors, the rate of CMV infection in the KP-EF group was also significantly higher than in the ≥1-year P-KP patients (HR, 0.3; $P < 0.001$; Fig. 3). As for Epstein-Barr virus (EBV) infection, there was no significant difference between the N-KP and P-KP groups, even after adjusting the confounding factors. In addition, there was a significantly higher incidence of EBV infection in patients with KP-LF who received DDLT than those who received LDLT (81.8% versus 15.4%; $P = 0.003$).

As for rejection, the patients with KP-LF had a significantly higher rate of biopsy-proven early rejection (12.5%) in comparison with the patients with N-KP (0.0%), KP-EF (1.4%) and KP-MF (1.7%; $P = 0.02$). The rate of PTLD was comparable among the groups ($P = 0.19$; Supporting Table 4).

COMPARISON OF POST-LT GRAFT AND OVERALL SURVIVAL RATES BETWEEN THE N-KP AND P-KP GROUPS

The graft and overall survival rates of 43 N-KP patients at 1 year, 2 years, and 3 years after LT in this cohort were 96.4%, 96.4%, and 96.4%, respectively. A total of 3 patients in the N-KP group and 4 patients in the P-KP group died of sepsis and hemorrhagic shock, occurring within 1 year after LT (Supporting Table 5). Univariate analysis showed that there was no significant difference of graft and overall survival rates between N-KP and P-KP groups (all *P* values ≥0.05, Fig. 5). The graft and overall survival rates were all significantly lower in the N-KP group (93.0% and 93.0%) than in the P-KP group (97.4% and 97.4%) after adjusting the confounding factors (HRs, 0.2 and 0.2; all *P* values = 0.02; Fig. 2). Among the P-KP patients, there was no significant difference in overall survival between patients with KP-EF and the ≥1-year P-KP patients (HR, 10.4; $P = 0.12$; Fig. 3).

	≥1 Year (N = 83)	<1 Year (N = 71)	Primary HR (95% CI)	*P* Value	Adjusted HR (95% CI)	Adjusted *P* Value
Mortality	3 (3.6)	1 (1.4)	2.6 (0.3-25.0)	0.41	10.4 (0.5-198.9)	0.12
Biliary complications	5 (6.0)	10 (14.1)	0.4 (0.1-1.2)	0.11	0.09 (0.03-0.3)	<0.001
Stenosis	2 (2.4)	7 (9.9)	0.2 (0.05-1.1)	0.07	0.1 (0.02-0.7)	0.02
Bile leakage	4 (4.8)	4 (5.6)	0.9 (0.2-3.4)	0.83	0.1 (0.03-0.5)	0.003
Vascular complications	9 (10.8)	14 (19.7)	0.5 (0.2-1.2)	0.14	0.2 (0.06-0.4)	<0.001
Hepatic artery	2 (2.4)	3 (4.2)	0.6 (0.1-3.4)	0.54	0.05 (0.0-0.8)	0.03
Hepatic vein	5 (6.0)	8 (11.3)	0.5 (0.2-1.6)	0.26	0.2 (0.06-0.7)	0.01
Portal vein	2 (2.4)	6 (8.4)	0.3 (0.06-1.4)	0.12	0.1 (0.02-0.9)	0.04
Intestinal perforation	3 (3.6)	3 (4.2)	0.8 (0.2-4.2)	0.84	2.3 (0.5-11.1)	0.28
EBV infection	57 (68.7)	49 (69.0)	1.1 (0.7-1.6)	0.73	0.8 (0.6-1.2)	0.29
CMV infection	23 (27.7)	27 (38.0)	0.7 (0.4-1.2)	0.19	0.3 (0.1-0.5)	<0.001
Rejection rate	15 (18.1)	8 (11.3)	1.7 (0.7-4.1)	0.21	0.8 (0.3-2.4)	0.70
PTLD	8 (9.6)	2 (2.8)	3.5 (0.8-16.6)	0.11	2.2 (0.4-13.9)	0.38
Cholangitis	8 (9.6)	5 (7.0)	1.4 (0.5-4.4)	0.53	9.9 (3.1-32.0)	<0.001
Reoperation rate	13 (15.7)	15 (21.1)	0.7 (0.4-1.5)	0.40	0.4 (0.2-0.8)	0.02

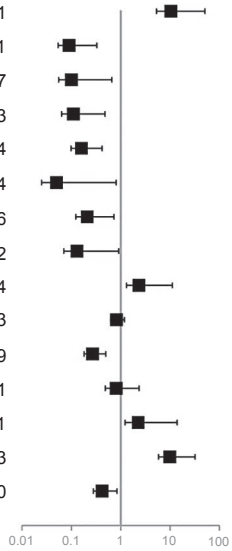

FIG. 3. The impact of the NLST on survival and complications after LT after adjusting for confounding factors by inverse probability of treatment weighting. There were significantly lower rates of biliary and vascular complications and the CMV infection rate in the >1-year patients than in the ≤1-year patients.

Discussion

KP is an initial lifesaving surgery for patients with BA, which can delay or even spare LT. However, this surgical procedure alters local anatomy, which may result in increased surgical difficulty in subsequent LTs. The KP's effect on the incidence of surgical complications and overall patient survival after LT is inconsistently reported, largely because of coexisting confounding factors. Most studies showed that the initial KP had no benefit or even adverse effect on post-LT complications or survival.[9,10,12,29] In this study, we demonstrate that the initial KP does have a significant protective effect on post-LT survival and does not significantly increase the incidence of post-LT surgical complications or infections after adjusting for confounding factors such as donor type, ABO mismatch, PELD score, weight and height *z* scores, CIT, DWIT, GRWR, and cirrhosis. Therefore, our study validates the essential role of KP as the first-line treatment option for patients with BA by not only improving the NLST but also by prolonging post-LT survival.

When we further divided P-KP patients into 3 subgroups according to their NLST—KP-EF (<1 year), KP-MF (1-5 years), and KP-LF (>5 years)—there was no significant difference in the overall survival rate among the subgroups. However, after adjusting for major confounding factors, we found that patients with KP-EF had a higher rate of biliary and vascular complications and a higher rate of CMV infection than ≥1 year P-KP patients. These findings were similarly documented by Neto et al.[3] However, Kitajima et al. reported a higher incidence of biliary complications (biliary stenosis and bile leakage) in patients aged 5 to 17 years.[18] The exact reason for this difference remains unknown, but recurrent cholangitis might be a contributing factor, being lower (20.8%) in our cohort and higher (35.7%) in the study by Kitajima et al. Vascular complications also occurred mainly in patients with short-term NLST (<1 year), with higher complications of the hepatic artery, hepatic vein, and portal vein, than in those with NLST ≥1 year. Previous studies have also suggested that the incidence of hepatic artery and portal vein complications decreased over 1 year of age.[3,12,18]

One of the most common nonoperative complications in post-LT patients with BA is nonhepatotropic virus infections. The incidence of EBV infection in post-LT patients was 66.5%, and CMV was 36.5% in this study, which was comparable with that reported by another study from China (57.8% and 36.6%).[30] In our study,

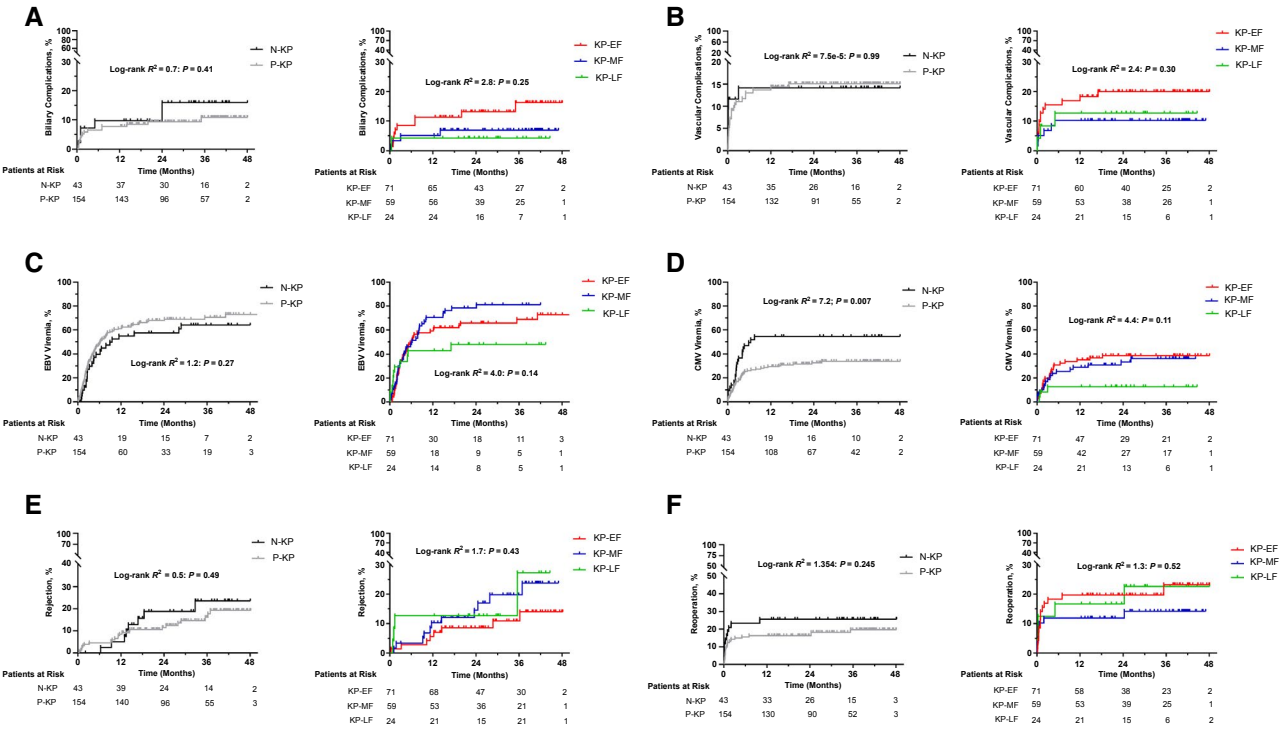

FIG. 4. Comparison of surgical and nonsurgical complications after LT between N-KP and P-KP groups. (A) The rate of overall biliary complications was not significantly different between N-KP and P-KP groups. There were trends of decreases in biliary complications and durations of NLST. (B) The rate of overall vascular complications was no significant difference between the N-KP and P-KP groups. The KP-EF group had the highest incidence of vascular complications among the P-KP groups. (C) The rate of EBV infection was not significantly different between the N-KP and P-KP groups and among the P-KP groups. (D) There was a significantly higher rate of CMV infection in the N-KP group than in the P-KP group, and an increase trend was observed when extending the NLST. (E) The rate of rejection was not significantly different between the N-KP and P-KP groups and among the P-KP groups. (F) There was a higher reoperation rate in the N-KP group than in the P-KP groups, but was not significantly different among KP-EF, KP-MF and KP-LF.

the incidence of CMV infection was significantly higher in patients without initial KP. With the increase of the NLST P-KP, the incidence of CMV infection after LT has significantly declined, being 3.7 times higher in <1 year patients than in ≥1 year patients. A previous study found that CMV targeted bile duct epithelial cells in the liver, and perinatal CMV infection might be 1 of the most important causes for BA.[31] Patients with BA with coexisting CMV infection often showed poor prognosis with lower jaundice clearance, short-term NLST, and high mortality P-KP.[32] This may be related to the reduced function of regulatory T cells,[33] resulting in excessive bile duct injury and fibrosis.

GEV bleeding in previous studies was reported in 14% to 29% of P-KP patients with BA.[34-37] This was in parallel to the finding in our study in which 18.8% patients experienced GEV bleeding in the P-KP group, with the highest occurrence in the KP-LF group (54.2%). These patients with KP-LF were characterized by severe portal hypertension but had significantly better liver synthetic function, less severe cholestasis, and lower fibrosis stage. Portal hypertension persisted despite regression of liver fibrosis after successful KP,[38] which is 1 of the important indications of LT[39] in P-KP patients with BA.

This study carefully explored the effect of Kasai surgery and NLST on the prognosis after LT, which provides invaluable information and scientific evidence for the better care of patients with BA. However, this study also has some limitations. First, this is a single-center study with a relatively small number of cases, which may lead to potential selection bias and thus needs to be further confirmed by multicenter large sample studies. Second, we could not provide information regarding long-term allograft outcomes and late complications of IS because of the limited follow-up time. Continuous and regular follow-up has been conducted in our center to answer this important question.

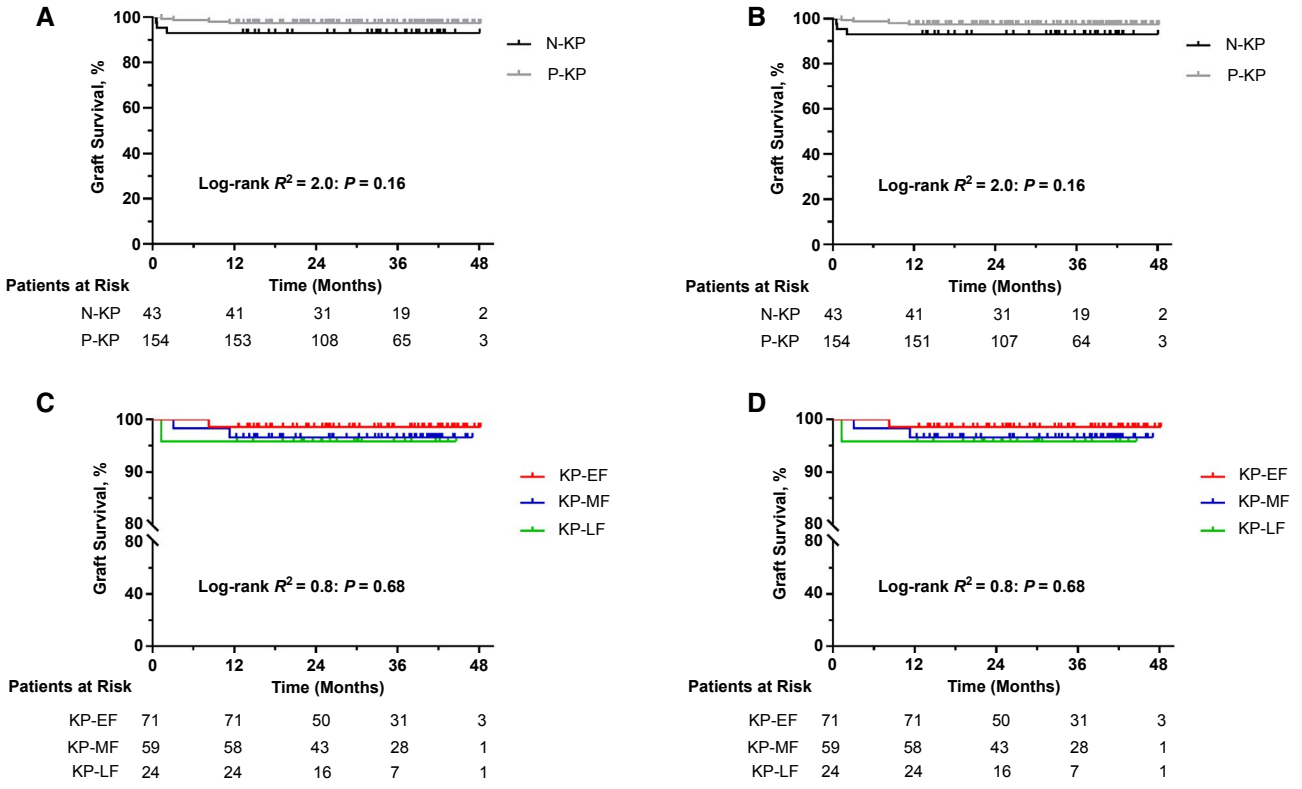

FIG. 5. Comparison of overall and graft survival rates after LT between the N-KP and P-KP groups. (A and B) No significant differences of overall and graft survival rates were observed between the N-KP and P-KP groups. (C and D) There were no significant differences in overall and graft survival rates among the 3 P-KP groups.

In conclusion, our data suggest that a previous KP does have a protective effect on post-LT graft and overall survival irrespective of NLST P-KP. The younger the recipients, the higher incidence of biliary and vascular complications and CMV infection after LT. Extra care is thus warranted for these patients.

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