



Original Article



Prognostic Factors Related to In-hospital Death in Children with Biliary Atresia: Analysis of a Nationwide Inpatient Database

Yu Shi^{1,2,3,4,5#}, Yi-Zhou Jiang^{1,2,3,4#}, Guang-Peng Zhou^{1,2,4}, Ying Shi⁶, Lan-Xia Gan⁶, Yuan-Yuan Kong², Hai-Bo Wang⁷, Zhi-Jun Zhu^{1,2,4*} and Li-Ying Sun^{1,2,3,4*}

¹Liver Transplantation Center, Beijing Friendship Hospital, Capital Medical University, Beijing, China; ²National Clinical Research Center for Digestive Diseases, Beijing Friendship Hospital, Capital Medical University, Beijing, China; ³Department of Critical Liver Diseases, Liver Research Center, Beijing Friendship Hospital, Capital Medical University, Beijing, China; ⁴Clinical Center for Pediatric Liver Transplantation, Capital Medical University, Beijing, China; ⁵National Clinical Research Center for Cardiovascular Diseases, Fuwai Hospital Chinese Academy of Medical Sciences, Shenzhen, Guangdong Province, China; ⁶China Standard Medical Information Research Center, Shenzhen, Guangdong, China; ⁷Clinical Trial Unit, Precision Medicine Institute, First Affiliated Hospital of Sun Yat-Sen University, Guangzhou, China

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Abstract

Background and Aims: Patients with biliary atresia (BA) are prone to hepatic decompensation, which might eventually lead to death. This study aimed to identify the possible risk factors affecting in-hospital death in BA patients in China. **Methods:** We collected data from the Hospital Quality Monitoring System, a national inpatient database. All patients aged up to 2 years old with a diagnosis of BA were included. The subjects were divided to three groups, including Kasai portoenterostomy (KP), liver transplantation (LT), and no surgery. Logistic regression with Firth's method was performed to identify potential influencing variables associated with in-hospital death. **Results:** During the year 2013 to 2017, there were 14,038 pediatric admissions with a diagnosis of BA. The proportion of in-hospital death in pediatric BA admissions was 1.08%. Compared with patients under six months, there was a higher risk of in-hospital death for children aged six months to 1 year and 1–2 years old. Clinical signs, including cirrhosis, variceal bleeding, and hepatic encephalopathy, were significantly associated with the risk of in-hospital death. In no surgery group, compared to those in Beijing and Shanghai, BA patients admitted in other districts had a lower risk of in-hospital death (OR=0.39, 95% CI: 0.21, 0.70). However,

in the LT group, patients admitted in other districts had a higher risk of in-hospital death (OR=9.13, 95% CI: 3.99, 20.87). **Conclusions:** In-hospital survival remains unsatisfactory for pediatric BA patients with severe complications. Furthermore, more resources and training for BA treatment, especially LT, are essential for districts with poor medical care in the future.

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Introduction

Biliary atresia (BA) is a rare progressive obstructive cholangiopathy of intrahepatic or extrahepatic bile ducts with unknown pathogenesis, leading to cholestasis and cirrhosis in children.^{1–4} BA is the most common cause of end-stage liver disease in children and is even fatal in the first two years of life if untreated.^{5,6} The incidence of BA varies from 1:7,000 to 1:19,000 worldwide and has been more common in Asia than in the USA and Europe.^{7–11}

To date, there is no curative drug therapy for BA patients. Since the development of Kasai portoenterostomy (KP) in 1959 helped restore bile flow, the survival rate has been improved markedly.¹² However, that disease would deteriorate in most patients even after the KP and finally progress to hepatic decompensation, which requires frequent hospitalizations.^{13–15} Liver transplantation (LT) has been another treatment option since 1967, and BA has gradually become the most common indication for LT in childhood.¹⁶ Now, sequential treatment with an initial KP followed by LT for BA patients with end-stage liver disease has been the accepted standard therapy.⁶ The 10-year survival rates are currently more than 85%.¹⁷

Keywords: Biliary atresia; In-hospital death; Liver transplantation; Kasai portoenterostomy.

Abbreviations: BA, biliary atresia; CI, confidence interval; HQMS, hospital quality monitoring system; ICD, International Classification of Diseases; IQR, interquartile range; KP, kasai portoenterostomy; LDLT, living donor liver transplantation; LT, liver transplantation; OR, odds ratio.

*These authors contributed equally to this work.

***Correspondence to:** Zhi-Jun Zhu and Li-Ying Sun, Liver Transplantation Center, National Clinical Research Center for Digestive Diseases, Beijing Friendship Hospital, Capital Medical University, No. 101 Lu Yuan Dong Road, Tongzhou District, Beijing 110112, China. ORCID: <https://orcid.org/0000-0001-7031-2083> (ZJZ), <https://orcid.org/0000-0003-1101-7994> (LYS). Tel/Fax: +86-10-80838168, E-mail: zhu-zhijun@outlook.com (ZJZ) or Tel/Fax: +86-10-80838166, E-mail: sunlx@outlook.com (LYS)

Despite significant progress in surgical techniques, there are still challenges in the clinical management of BA. BA children often suffer portal hypertension and end-stage liver disease before LT. It has been reported that 30–40% of BA patients have esophageal/gastric varix, and about 10–25% go through variceal bleeding after KP.^{18,19} Variceal bleeding is the leading cause of death in children with portal hypertension.²⁰ Other severe conditions, including infection and encephalopathy, could result in a poor prognosis. Furthermore, inadequate medical care and economic situation have been reported to be associated with BA morbidity and clinical outcome.^{21,22} Therefore, optimal BA management and medical care improvement might be pivotal to reducing BA-related death.

With evidence of higher waitlist mortality than older children,²³ children below 2 years of age have been considered a more vulnerable group. Until now, previous studies were conducted in one or few medical centers and therefore lacked data about the general profile of BA in China. Therefore, we used data from a nationwide database to provide comprehensive epidemiological information of BA patients among those below two years of age in China. We further assessed the effects of possibly influential factors on in-hospital death for BA patients.

Methods

Data source

This study was based on the Hospital Quality Monitoring System (HQMS), a mandatory patient-level registration database of the standardized electronic inpatient discharge records in China, under the administration of the Bureau of Medical Administration and Medical Service Supervision, National Health and Family Planning Commission of the People's Republic of China.^{24–26} The HQMS collected data from tertiary- and second-class hospitals in 31 provinces. More than 300 variables on the front page of patient medical records, including demographic information, surgery, and diagnosis (one primary/principal diagnosis and 13 secondary diagnosis), are automatically submitted to HQMS with quality control when health care providers complete the data. The diagnosis was coded based on the International Classification of Diseases, revision 10 (ICD-10) coding system, and text description.

Population selection

Based on data analysis, we found that children less than 2 years old accounted for 93.69% of all hospitalizations for BA patients. We only included pediatric patients under two years with a primary or secondary diagnosis of BA in the HQMS database between 2013 and 2017. These patients were identified via the following ICD-10 diagnosis codes (Q44.301, Q44.200, Q44.201 in the National Edition; Q44.201, Q44.202, Q44.203 in the Beijing Edition; Q44.301, Q44.200, Q44.200x003, Q44.201 in the Clinical Edition).

Variables

Demographic characteristics such as age, sex, nationality, type of admission, length of stay, hospitalization charges, geographic location of family and admitted hospital, and hospital level were collected from the database. For each admitted hospital, caseloads for BA were calculated as the total number of discharges with BA diagnosis during 2013–

2017. The month of hospital discharge was divided into four groups: winter (December–February), spring (March–May), summer (June–August), and autumn (September–November). Surgical procedures and other variables including disease-related clinical manifestations were identified by ICD-10 codes, respectively (see details in Supplementary Tables 1 and 2). On the basis of surgical procedures, the subjects were classified into three groups, including no surgery, KP, and LT. The clinical outcome of interest was in-hospital death.

Ethical approval

Data collection and analysis were performed following the ethical standards of the Helsinki Declaration. The study was approved by the Ethics Committee of Beijing Friendship Hospital, Capital Medical University (Approval ID: 2019-P2-154-01).

Statistical analysis

Continuous variables with highly skewed distribution are expressed as the median and interquartile range (IQR). Categorical variables are presented as frequency and percentage (%). Due to a low proportion of in-hospital death, univariable and multivariable logistic regression with Firth's method was performed to assess the associations between the potentially influential factors and in-hospital death. All statistical analyses were performed using SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA), with a two-tailed level of significance set at 0.05. A forest plot was depicted using R version 3.5.0 (forestplot package).

Results

Demographics and burden of BA hospitalization

During the period from 2013 to 2017, there were a total of 14,038 admissions for BA patients under 2-years-old. The basic demographics are presented in Table 1. The median age was 2.2 months. Percentages of male (50.09%) and female (49.91%) patients were nearly equal. There were 10 times or more Han Chinese than minority patients, though there was a high proportion of patient with missing data. More pediatric BA patients were admitted in hospitals in spring (26.79%) and summer (25.41%). Most of pediatric BA patients (92.67%) were hospitalized in tertiary class A hospital. The median of hospital stay was 13.0 days (IQR: 6.0–20.0), and the total cost of each hospitalization was RMB 14,129.64 (IQR: 5,537.95–33,281.35). Over 70% BA patients were admitted to hospital through routine, followed by nearly 20% through emergency or referral. The percentage of in-hospital death among all admissions for BA patients was 1.08% ($n=151$), and causes of death were shown in Supplementary Table 3.

Cross-district attendance for BA in China

As shown in Figure 1A, the hospitals in Shanghai, Beijing and Chongqing received 91.48%, 85.24% and 62.6% of pediatric BA patients from other districts, respectively. And up to 100.00% of pediatric BA patients resided in Tibet went to the hospitals in other districts, followed by Gansu (89.72%), Anhui (86.41%) and Inner Mongolia (86.18%; Fig. 1B).

Table 1. Demographic characteristics and burden of BA patients under 2 years of age

Variable	N (%) / Median (IQR)
Age (month)	2.2 (1.3–5.0)
Sex	
Male	7,031 (50.09%)
Female	7,007 (49.91%)
Nationality	
Han	8,149 (58.05%)
Others	695 (4.95%)
Missing	5,194 (37.00%)
Season	
Spring	3,761 (26.79%)
Summer	3,567 (25.41%)
Autumn	3,351 (23.87%)
Winter	3,359 (23.93%)
Length of stay (days)	13.0 (6.0–20.0)
Hospital level	
Tertiary class A hospital	13,009 (92.67%)
Tertiary class B hospital	1,028 (7.32%)
Second class hospital	1 (0.01%)
Type of admission	
Emergency or Referral	2,983 (21.25%)
Routine	10,094 (71.90%)
Other	961 (6.85%)
Total costs (RMB)	14,129.64 (5,537.95–33,281.35)
In-hospital death	
Yes	151 (1.08%)
No	13,887 (98.92%)

IQR, interquartile range.

Subgroup analysis according to the procedure during hospitalization

As shown in Table 2, 1,573 (11.21%) admissions underwent the KP, and 706 (5.03%) admissions underwent LT. The median age of patients undergoing LT was 7.2 months, which was statistically greater than those without surgery and undergoing the KP. All LTs were performed in tertiary class A hospitals, and up to 95.61% of LTs were performed in hospitals which received more than 100 admissions for BA during the five-year period. A majority of LTs (89.52%) were performed in Beijing and Shanghai, and over 72% of admissions underwent KPs in other provinces or districts. The in-hospital death in the LT group reached to 5.10% ($n=36$), much higher than that in the KP group (0.70%) and non-surgery group (0.88%).

Up to 37.96% of individuals undergoing LT were diagnosed with cirrhosis. Variceal bleeding was observed in 4.82% of pediatric patients undergoing LT, more than three times that in those undergoing no surgery (1.40%) and those undergoing the KP (0.57%). A relatively low incidence (3.26%) of hepatic encephalopathy was noted in those undergoing LT. The incidence of encephalopathy was lower in those not undergoing LT (lower than 1% both in non-surgery and KP group, Table 2).

Univariable and multivariable analysis of in-hospital death in all BA patients

Univariable analysis showed that pediatric patients aged under one year but over 6 months ($OR=7.77$, 95% CI: 5.49, 10.99), and those over 1 year but under 2 years of age ($OR=2.50$, 95% CI: 1.53, 4.09) had higher in-hospital death than those under 6 months of age. Compared with individuals who were routinely admitted, patients admitted via emergency or referral had a higher risk of in-hospital death ($OR=1.59$, 95% CI: 1.11, 2.27). BA patients admitted in other districts had lower risk of in-hospital death than those in Beijing and Shanghai ($OR=0.72$, 95% CI: 0.52, 0.99). Patients undergoing LT had a higher risk of in-hospital death than those who did not undergo surgery ($OR=6.07$, 95% CI: 4.13, 8.92). Severe clinical manifestations including cirrhosis ($OR=3.24$, 95% CI: 2.33, 4.49), hepatic encephalopathy ($OR=17.08$, 95% CI: 9.13, 31.95) and variceal bleeding ($OR=16.68$, 95% CI: 10.75, 25.88) were associated with a higher risk of in-hospital death (Table 3).

Age, type of admission, LT surgery and severe clinical features were also significantly associated with in-hospital death in multivariable analysis. Moreover, multivariable analysis showed that pediatric patients had a higher risk of death in

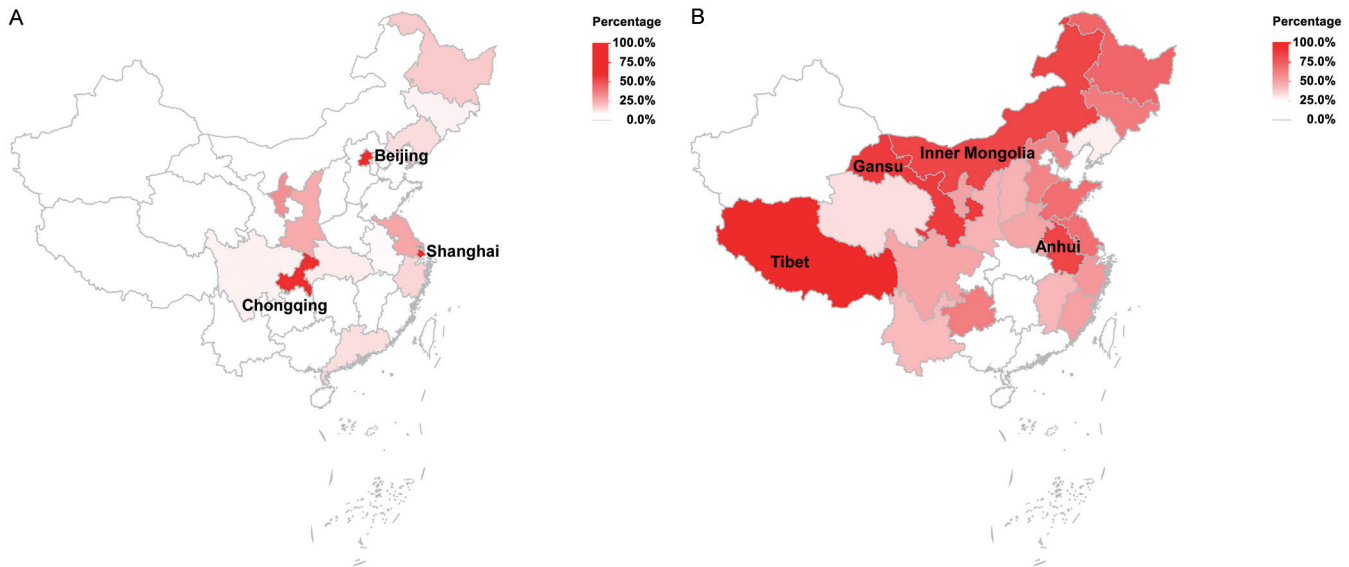


Fig. 1. Cross-district attendance of BA. (A) The percentage of the hospitals in different districts which received BA pediatric patients from other districts. (B) The percentage of BA pediatric patients from different districts who went to the hospitals in other districts.

hospitals which had received less than 100 BA patients during the five-year period (OR=1.65, 95% CI: 1.03, 2.66).

Univariable analysis of BA patients in the KP group

Because of few in-hospital deaths ($n=11$), only univariable regression was used to assess the associations between demographic factors, clinical features and in-hospital death. The results showed that there was a higher risk of in-hospital death in individuals with variceal bleeding (OR=54.58, 95% CI: 10.61, 280.84) than in those without variceal bleeding. As no hepatic encephalopathy occurred in the KP group, the effect of this complication on in-hospital death could not be evaluated. All other factors had no statistical association with the risk of in-hospital death (data not shown).

Multivariable analysis of BA patients in the non-surgery and LT groups

Among patients without surgery, patients aged under 1 year but over 6 months (OR=5.54, 95% CI: 3.47, 8.84), and those aged more than 1 year but less than 2 years (OR=2.19, 95% CI: 1.17, 4.09) had a higher risk of in-hospital death than those at less than 6 months of age. BA patients had a higher risk of death in hospitals which had received less than 100 pediatric BA patients during the five-year period (OR=2.35, 95% CI: 1.26, 4.38). Similarly, there was a higher risk of in-hospital death in patients admitted via emergency or referral (OR=1.99, 95% CI: 1.28, 3.10). Compared with those in Beijing and Shanghai, BA patients admitted in other districts or provinces had lower risk of in-hospital death (OR=0.39, 95% CI: 0.21, 0.70). A statistically higher risk of in-hospital death was observed in individuals with cirrhosis (OR=1.62, 95% CI: 1.01, 2.60), hepatic encephalopathy (OR=8.01, 95% CI: 3.67, 17.51) and variceal bleeding (OR=7.81, 95% CI: 4.39, 13.88; Fig. 2).

It is noteworthy that in the LT group, the results showed that BA patients admitted in other districts had higher risk of in-hospital death than those in Beijing and Shanghai (OR=9.13, 95% CI: 3.99, 20.87). However, no significant

association was found between other demographic and clinical features, and the risk of in-hospital death (Fig. 2).

Discussion

This is the first nationwide study to assess the disease burden of BA hospitalization in China. It included 14,038 admissions for pediatric patients under 2 years of age with a diagnosis of BA between 2013 and 2017. We found that age, caseloads for BA, type of admission, and the presence of severe complications, including cirrhosis, hepatic encephalopathy, and variceal bleeding, were associated with in-hospital death. Moreover, BA patients who underwent LT in hospitals of economically developed cities or districts might have a lower risk of in-hospital death.

Previous studies demonstrated that children below two years of age have higher mortality than older children, and 50–75% of children with BA require LT in the first 2 years.²³ Therefore, patients less than 2 years of age were chosen as the target study population. Our study observed the seasonal predominance of hospitalization in spring and summer (March to August), similar to Korea²⁷ and Japan.²⁸ Regarding the medical cost, the median direct medical costs for BA patients in Canada were \$4,210 per year, much higher in those who underwent LT.²⁹ In the USA, children undergoing LT accumulated \$458,059 in costs per patient.³⁰ As this study showed, the median medical cost was 14,129.64 RMB for each BA hospitalization in China, and with the extra expenses on cross-district traveling and accommodation with frequent hospitalizations, many families have to face a weighty financial burden.

KP has been the most common surgical procedure to improve the survival of BA patients with native liver.³¹ Age at the time of KP has been considered an important prognostic factor in the children after Kasai surgery.^{26,27} Previous studies showed that in infants who underwent the KP within 60 days of life, 57–90% had successful restoration of bile flow, while the rate dropped to <20% if the procedure was performed after 90 days of life.^{32–34} In the USA, the median age at the timing of the KP was 63 days (IQR, 47, 76).³⁵ The data in our study showed that KP was performed at 0.17

Table 2. Demographics and clinical features of patients based on subgroup analysis

Variable	Non-surgery (n=11,759)	KP (n=1,573)	LT (n=706)	P
Age (month)	2.2 (1.2–4.9)	2.0 (1.0–2.3)	7.2 (5.9–9.8)	<0.001 ^a
Sex				0.002 ^b
Male	5,960 (50.68%)	756 (48.06%)	315 (44.62%)	
Female	5,799 (49.32%)	817 (51.94%)	391 (55.38%)	
Level of hospital				<0.001 ^c
Tertiary class A hospital	10,817 (91.99%)	1,486 (94.47%)	706 (100.00%)	
Tertiary class B hospital	941 (8.00%)	87 (5.53%)	0 (0%)	
Second class hospital	1 (0.01%)	0 (0%)	0 (0%)	
Caseloads for BA				<0.001 ^b
≥100	9,046 (76.93%)	1,403 (89.19%)	675 (95.61%)	
<100	2,713 (23.07%)	170 (10.81%)	31 (4.39%)	
Type of admission				<0.001 ^b
Routine	8,343 (70.95%)	1,225 (77.88%)	526 (74.50%)	<0.001 ^b
Emergency or referral	2,578 (21.92%)	231 (14.69%)	174 (24.65%)	
Other	838 (7.13%)	117 (7.44%)	6 (0.85%)	
Nationality				<0.001 ^b
Han	6,797 (57.80%)	1,134 (72.09%)	218 (30.88%)	
Others	490 (4.17%)	203 (12.91%)	2 (0.28%)	
Missing	4,472 (38.03%)	236 (15.00%)	486 (68.84%)	
District				<0.001 ^b
Beijing/Shanghai	4,610 (39.20%)	425 (27.02%)	632 (89.52%)	
Others	7,149 (60.80%)	1,148 (72.98%)	74 (10.48%)	
In-hospital death				<0.001 ^b
No	11,655 (99.12%)	1,562 (99.30%)	670 (94.90%)	
Yes	104 (0.88%)	11 (0.70%)	36 (5.10%)	
Severe complications				
Cirrhosis				<0.001 ^b
No	9,960 (84.70%)	1,278 (81.25%)	438 (62.04%)	
Yes	1,799 (15.30%)	295 (18.75%)	268 (37.96%)	
Hepatic encephalopathy				<0.001 ^b
No	11,698 (99.48%)	1,573 (100.00%)	683 (96.74%)	
Yes	61 (0.52%)	0 (0%)	23 (3.26%)	
Variceal bleeding				<0.001 ^b
No	11,594 (98.60%)	1,564 (99.43%)	672 (95.18%)	
Yes	165 (1.40%)	9 (0.57%)	34 (4.82%)	

^aWilcoxon rank-sum test. ^bChi-square test. ^cFisher's exact test. KP, Kasai portoenterostomy; LT, liver transplantation.

years (approximately 62 days; IQR 0.08, 0.19), earlier than the data from 2006 to 2012 in a single-center report from mainland China (73.5 days).³⁶ The small sample size might contribute to the insignificant association between the timing of KP and in-hospital death. The other possible explanation was that the timing of KP does not affect in-hospital prognosis but on relatively long-term outcomes.

Although KP does improve survival for BA patients, up to 50–75% of BA patients ultimately require LT in the first two

years of life.^{23,37,38} In our study, the median age at LT was 0.60 years (approximately 7 months) from 2013 to 2017, which was less than 9.6 months reported in a nationwide investigation from 1996 to 2013 in mainland China.³⁹ This phenomenon may be explained by the fact that grafts from living donors have been increasingly used in China, with more than 70%.³⁹ Living donor liver transplantation (LDLT) has been the primary choice for pediatric recipients. Therefore, the shortage of donor organs has a limited effect on

Table 3. Univariable and multivariable analyses of in-hospital death for all BA patients (n=14,038)

	Univariable ^a		Multivariable ^a	
	OR	P	OR	P
Age				
<6 months	1.00		1.00	
6-<12 months	7.77 (5.49, 10.99)	<0.001	3.66 (2.39, 5.59)	<0.001
12-<24 months	2.50 (1.53, 4.09)	<0.001	1.75 (1.04, 2.94)	0.037
Sex				
Male	1.00		1.00	
Female	1.10 (0.80, 1.52)	0.554	0.97 (0.69, 1.35)	0.847
Caseloads for BA				
≥100	1.00		1.00	
<100	1.39 (0.97, 2.00)	0.074	1.65 (1.03, 2.66)	0.039
Type of admission				
Routine	1.00		1.00	
Emergency or referral	1.59 (1.11, 2.27)	0.012	1.65 (1.14, 2.38)	0.009
Other	1.38 (0.76, 2.50)	0.289	1.20 (0.48, 3.00)	0.696
District				
Beijing/Shanghai	1.00		1.00	
Others	0.72 (0.52, 0.99)	0.045	0.90 (0.57, 1.42)	0.640
Surgery				
Non-surgery	1.00		1.00	
Kasai portoenterostomy	0.82 (0.45, 1.51)	0.527	1.33 (0.69, 2.58)	0.392
Liver transplantation	6.07 (4.13, 8.92)	<0.001	2.63 (1.64, 4.21)	<0.001
Cirrhosis				
No	1.00		1.00	
Yes	3.24 (2.33, 4.49)	<0.001	1.74 (1.19, 2.55)	0.004
Hepatic encephalopathy				
No	1.00		1.00	
Yes	17.08 (9.13, 31.95)	<0.001	4.89 (2.43, 9.87)	<0.001
Variceal bleeding				
No	1.00		1.00	
Yes	16.68 (10.75, 25.88)	<0.001	6.27 (3.78, 10.40)	<0.001

^aLogistic regression with Firth's method. BA, biliary atresia.

the wait time for BA children. In addition, transplantation techniques, especially for younger children, have gradually improved in recent years. Our study showed the percentage of in-hospital death is 5.10% among the LT group. As nearly 60% of deaths in 1-year-old patients occurred during the first 14 days after transplantation,²³ our data indicated a slight improvement of in-hospital prognosis compared with a previous study.³⁹ Thus, a more favorable outcome for LT in BA children has been observed in China recently.

Cirrhosis is a leading cause of death in BA patients.²³ Moreover, severe complications of cirrhosis, including variceal bleeding and encephalopathy, usually lead to a poor prognosis.^{11,38,40–42} Generally, indications for LT in BA patients include failed KP with no effective biliary drainage, progressive manifestations of portal hypertension, and recurrent cholangitis following KP.^{6,38,43} In addition, our study

found that variceal bleeding was significantly associated with in-hospital death in the KP group, while this association was not statistically significant in the LT group. These findings suggested that for BA children who had already developed progressive cirrhosis and its complications, LT might be the optimal treatment option without KP as a “bridge” to reduce the risk of in-hospital death.

Our study showed that hospitals with more BA admissions were associated with a lower risk of in-hospital death. Previous studies have also suggested that the experience of a medical center in BA management and the surgeons' experience are significant modifiable factors related to patients' outcomes.^{44,45} Another result of our study which deserves attention is the absolute predominance of tertiary class A hospitals among the hospitals included, especially for the LT group. Due to the technical difficulties, the pedi-

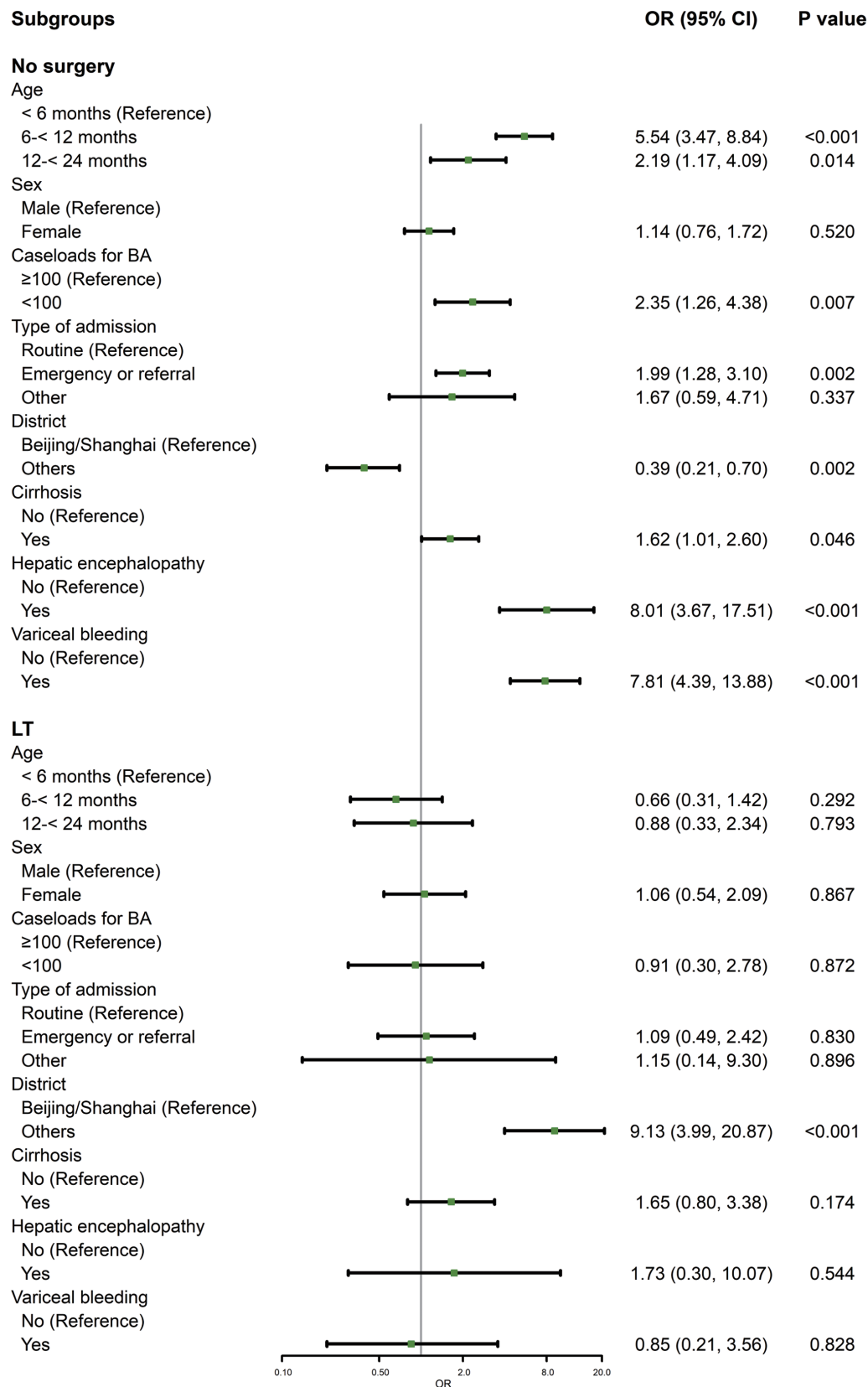


Fig. 2. The effects of the potentially influencing factors on in-hospital death of BA patients in the non-surgery group and LT group.

atric LT procedure requires a higher level of medical care and more skilled, experienced surgeons. Thus, a remarkable preference for cross-district hospitalizations was observed in Shanghai and Beijing, which were deemed as with better medical care in China. Our study also showed that BA patients in the non-surgery group admitted in Beijing and Shanghai had higher in-hospital death than other districts. This phenomenon can be explained by that patients in critical condition tended to be admitted or referred to advanced hospitals in first-tier cities for treatment. In contrast, patients who underwent LT in these two cities had lower death rates. The reasonable explanation was that Beijing and Shanghai have more LT centers according to the China Liver Transplant Registry (<http://www.cltr.org/>) and more skilled and experienced doctors than other districts. Therefore, it contributed to a higher success rate for surgery and more comprehensive perioperative care in these cities. Finally, the study suggested that the unbalanced distribution of health resources related to BA in China should be concerned and would be further addressed to improve the prognosis of BA children.

However, this study has some potential limitations. First, although quality control was performed, case identification relied totally on ICD-10 codes, which might contribute to the incomplete inclusion of BA patients. Second, all patient information was extracted from the front page of patients' medical records without several clinical data, such as the value of transaminase, total bilirubin, blood ammonia, pediatric end-stage liver disease score and ultrasound findings, which might also be associated with in-hospital death of BA. Moreover, the prevalence and treatment varied across different countries, limiting our results' generalizability. Despite these limitations, the main advantage of this study is the large sample size of BA patients from a nationwide database. In addition, the study would help us better understand the overall hospitalization burden of BA in China among children below two years of age and identify specific factors for the prognosis of pediatric BA patients.

Conclusions

In-hospital survival remains unsatisfactory for pediatric BA patients. Moreover, unbalanced distribution of health resources related to BA treatment, especially LT, exists in China. In addition, LT could guarantee the in-hospital outcome of severe BA patients with serious complications. Improving the accessibility to LT and professional training in underdeveloped areas in the future might be crucial for improving the prognosis of BA patients.

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Conflict of interest

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

Author contributions

Contributed to study concept and design (ZJZ, LYS, YZJ),

acquisition of data; analysis and interpretation of data; drafting of the manuscript (LYS, YZJ, GPZ), statistical analysis and analysis of data (LYS, YS, LXG), study supervision; critical revision of the manuscript for important intellectual content (ZJZ, HBW, LYS, YYK)

Data sharing statement

The datasets generated and/or analyzed during the current study are available from the corresponding author on reasonable request.

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