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## ORIGINAL ARTICLE

# Incidence of biliary atresia associated congenital malformations: A retrospective multicenter study in China

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## KEYWORDS

biliary atresia;  
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nonsyndromic

**Summary** *Background:* Some patients with biliary atresia (BA) have associated anomalies. Our study aimed to investigate the incidence of BA-associated malformations in mainland China, and compare the results with those reported in the Western literature.

*Methods:* Clinical data were collected retrospectively from five medical centers in mainland China. BA patients were diagnosed and confirmed by laparotomy with intraoperative cholangiography and liver biopsy. Cases were divided into isolated type BA and BA with associated anomalies, including polysplenia, situs inversus, intestinal malrotation, and cardiovascular anomalies.

*Results:* A total of 851 BA patients were recruited from Tianjin, Beijing, Wuhan, Guangzhou, and Shenzhen. Patients were grouped as follows: Type I, 13 cases (1.5%); Type II, five cases (0.6%); Type III, 833 cases (97.9%). Forty-two (4.94%) patients had 54 associated congenital abnormalities. The intra-abdominal anomalies included polysplenia ( $n = 4$ , 1 fusion between liver and spleen), situs inversus ( $n = 2$ ), and intestinal malrotation ( $n = 3$ ). The cardiovascular anomalies included atrial septal defect and ventricular septal defect ( $n = 29$ ), patent foramen ovale ( $n = 1$ ), patent ductus arteriosus ( $n = 4$ ), and other cardiac malformations ( $n = 3$ , including coronary sinus dilation, left superior vena cava, Tetralogy of Fallot).

Conflict of interests: The authors declare that they have no conflicts of interests.

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**Conclusion:** Our data showed that spleen anomaly is not as common as reported in the Western literature. The difference may suggest different genetic and environmental risk factors for BA. Copyright © 2016, Asian Surgical Association. Published by Elsevier Taiwan LLC. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

## 1. Introduction

Biliary atresia (BA) is one of the most common causes of obstructive jaundice in infancy, characterized by progressive biliary fibrosis, the cause of which is unclear.<sup>1</sup> Most authors believe that the clinical phenotype of BA is associated with genetic heterogeneity. Chromosomal changes have been discovered in some BA patients, and there are reports suggesting the role of genetic predisposition in its pathogenesis of BA.<sup>2</sup> Since Helwig<sup>3</sup> first reported a BA associated with polysplenia in 1929, other associated congenital malformations with BA were also added including situs inversus, intestinal malrotation, cardiopulmonary dysplasia, and other anomalies. The incidence of BA-associated congenital malformations has been reported to range from 3% to 20%.<sup>4–6</sup> Davenport et al.<sup>6</sup> divided BA patients into two categories—acquired/nonsyndromic BA (90%) and embryonic/syndromic BA (10%)—and pointed out that BA patients with spleen malformations may have onset of the pathological process during the embryological phase of organ development.<sup>6</sup> In this study, our aim was to investigate the incidence of BA with associated malformations in the Chinese population and compare our results with those in the Western literature.

## 2. Patients and methods

The clinical data of BA patients were collected retrospectively from five medical centers in China between October 2009 and September 2014, including Tianjin Children's Hospital (Tianjin), Beijing Children's Hospital (Beijing), Wuhan Tongji Hospital (Wuhan), First Affiliated Hospital of Sun Yat-sen University (Guangzhou), and Shenzhen Children's Hospital (Shenzhen). BA patients were diagnosed and confirmed by laparotomy with intraoperative cholangiography and liver biopsy. The preoperative examinations including electrocardiograms, chest X-ray, and abdominal ultrasound were performed routinely after admission; patients with abnormal results would be further examined by echocardiography or computed tomography (CT), and magnetic resonance imaging (MRI) to determine if there is any abnormality. Congenital malformations were assessed with abdominal ultrasound, echocardiography, CT, MRI, etc. All five medical centers used the same form of questionnaire for data collection (e.g., sex, age at surgery, surgical approach, and malformation type). Cases without complete information were excluded. The BA patients were divided into isolated type BA and BA with associated malformations. The latter group includes patients with one or more of the following anomalies: spleen anomalies, laterality anomalies, cardiac anomalies, intra-abdominal vascular anomalies, pancreatic anomalies, and malrotation, etc. This study was approved by the local ethics committee of each center.

Descriptive data were summarized. The age at the time of Kasai operation between isolated BA and BA with associated malformations was compared using *t* test, and a *p* value < 0.05 was considered statistically significant.

## 3. Results

In this study, a total of 851 patients with BA were recruited. The majority of patients had isolated BA (754, 89%). There were 42 BA patients with associated malformations. According to the classification criteria of BA by the Japanese Association of Pediatric Surgery, the patients in our group can also be classified based on the most proximal level of obstruction as follows. Type I refers to atresia of the distal bile duct with a patent common hepatic duct, gall bladder, and cystic duct, with or without cyst (13/851; 1.5%). In Type II, atresia of the common hepatic duct is at different levels; in some cases, the common bile duct, cystic duct, and gall bladder are patent but the common hepatic duct is atretic (5/851; 0.6%). Type III, the most common type, occurs in almost 90% of cases; here, the entire extrahepatic biliary system including the common hepatic duct, gall bladder and the common bile duct are atretic (833/851; 97.9%).<sup>7</sup>

There were 446 boys and 405 girls in our study. Table 1 illustrates the different BA types and the male/female ratio in the five medical centers. The male/female ratio is 1.09/1. The sex distribution of patients with malformations is shown in Table 2. The patients with congenital associated malformations were well distributed in Types I, II, and III. Patients with associated malformations had an extraordinarily high percentage of Type III BA, with malformations more frequently being presented in boys.

Forty-two (4.94%) patients with 54 associated congenital abnormalities were reported. The intra-abdominal anomalies included polysplenia (*n* = 4; 1 case is abnormal fusion between liver and spleen), situs inversus (*n* = 2), and intestinal malrotation (*n* = 3). Cardiovascular anomalies included atrial septal defect (ASD) and ventricular septal defect (VSD; *n* = 29), patent foramen ovale (*n* = 1), patent ductus arteriosus (*n* = 4), and other cardiac malformations (*n* = 3; including coronary sinus dilation, left superior vena cava, Tetralogy of Fallot). The list also included intestinal atresia and anorectal malformation, as shown in Table 3.

Among eight patients with two or more malformations, one boy had splenic and cardiac abnormality; one boy had intestinal atresia and patent foramen ovale; one boy had intestinal atresia, patent foramen ovale, patent ductus arteriosus, and duodenal diaphragm; one boy had ASD and pulmonary stenosis; one boy had ASD, patent ductus arteriosus, coronary sinus dilation, and left superior vena cava; and three girls had ASD and patent ductus arteriosus.

**Table 1** Different types of BA and sex ratio of patients in different areas.

Classification	Tianjin	Beijing	Wuhan	Guangzhou	Shenzhen	Total, n (%)
I	8	0	2	2	1	13 (1.5)
II	4	0	0	0	1	5 (0.6)
III	88	302	245	52	146	833 (97.9)
Total	100	302	247	54	148	851
Male/female	1.04:1	1:1	1.45:1	1.16:1	1:1.23	1.09:1

**Table 2** Sex distribution in subtype and biliary atresia (BA) with associated malformations patients.

Classification	BA with associated malformations			
	Male	Female	Male	Female
I	6	7	2	0
II	4	2	2	0
III	436	396	22	16
Total	446	405	26	16

In our patients group, 206 patients did not undergo surgical procedure and progressed to end-stage liver disease within the 1<sup>st</sup> year of life. For the remaining 645 patients, most underwent Roux-en-Y or Kasai operation ( $n = 638$ ). Six patients had a portocholecystostomy (gallbladder Kasai), and one patient underwent a choledochojejunostomy. There was no significant difference in terms of age for Kasai between patients with isolated BA and those with BA with associated malformations (70.39 and 77.34 days, respectively;  $p = 0.085$ ).

#### 4. Discussion

This is the largest multicenter retrospective study on BA patients with/without malformations in mainland China,

**Table 3** Associated malformations in our study cohort ( $n = 851$ ).

Malformation	<i>n</i>	%
ASD, VSD	29	3.4
Patent ductus arteriosus	4	0.4
Patent foramen ovale	1	0.1
Coronary sinus dilation	1	0.1
Left superior vena cava	1	0.1
Tetralogy of Fallot	1	0.1
Pulmonary stenosis	1	0.1
Intestinal malrotation	3	0.3
Fusion between liver and spleen	1	0.1
Polysplenia	3	0.3
Intestinal atresia	2	0.2
Nephrectasia	3	0.3
Hypospadias	1	0.1
Anorectal malformations	1	0.1
Situs inversus	2	0.2
Total	54	6.34

ASD = atrial septal defect; VSD = ventricular septal defect.

which included 851 cases from five medical centers located in different cities. Our data showed that the overall incidence of associated anomalies in BA patients was 4.94%, and cardiac abnormalities were identified as the most common deformity in our cohort. ASD and VSD were found in 53.7% of BA patients with malformations.

There is a racial variation in the incidence of BA. Studies from Europe and the United States reported an incidence rate of about 0.6–0.8/10,000, and in Asian countries such as Japan the rate is reported as 0.8–1.1/10,000.<sup>8</sup> Taiwan has an incidence of about 1 in 5000, and the male/female ratio is 1.14:1.<sup>9</sup> However, there is no related report concerning the incidence of BA in mainland China. The incidence of BA is considered to be higher in females in the literature reports.<sup>10,11</sup> However, the result in our study was not similar to these countries. BA was found more in boys than in girls in general, with an overall male/female ratio of 1.10:1. One reason for this difference may be that many BA patients in China remained undiagnosed, or only boys with BA were brought by their parents to the medical centers. Therefore, whether the sex ratio in the mainland is really different from other countries requires further study.

BA with associated malformations has been reported in America, United Kingdom, and Canada with the incidence rate varying from 10% to 15%. The overall incidence of associated anomalies in our study was 4.94%, which was consistent with the incidence in Japan and South Asia, wherein the incidence rate ranged from 2% to 5%. The latest study in India reported that the incidence of associated congenital anomalies with BA was up to 29.2%; however, umbilical hernia and inguinal hernia should not be included.<sup>12</sup> Davenport et al<sup>13</sup> suggested that this discrepancy could be partially explained by the higher incidence of the nonsyndromic form of BA in South Asia and Japan compared with the rest of the world.<sup>13</sup> As for sex ratio, female predominance of BA with associated malformations has been reported in other studies; nevertheless, a higher incidence of associated anomalies in boys was found in our study. The incidence and category of BA-associated malformations are listed in Table 4.

Among the 54 associated congenital abnormalities in our study, only four spleen anomalies were identified. Davenport et al<sup>13</sup> reported that BA accompanied with spleen dysplasia syndrome was the most common deformity, accounting for 10% of the cases, and they proposed the term “biliary atresia splenic malformation” (BASM) syndrome for patients with histologically confirmed diagnosis of BA and a macroscopic splenic abnormality. The Biliary Atresia Research Consortium reported a similar incidence of BASM in the United States.<sup>14</sup> In Japan, the latest registry data showed that the incidence of BASM was 4.3%.<sup>15</sup> However,

**Table 4** Incidence and category of BA-associated malformations in different areas.

Area	Year	Total patients, n (%)	Malformation n (%)	Main category of malformations, n (%)						
England <sup>6</sup>	2006	548	56 (10.2)	Cardiac 25 (4.6)	Absent IVC 22 (4)	PDPV 35 (6.4)	Intestinal 34 (6.2)	Situs inversus 21 (3.8)	Pancreatic 6 (1)	SM 56 (10.2)
Taiwan <sup>16</sup>	2010	130	20 (15.4)	Cardiovascular 9 (6.9)			GI and abdominal 10 (7.7)			Double spleen1 (0.7)
Canada <sup>18</sup>	2011	328	44 (13)	Cardiac 26 (7.9)	Vascular 25 (7.6)		Intestinal 19 (5.8)	Abdominal situs 9 (2.7)		Polysplenia 25 (6.5)
North America <sup>14</sup>	2013	289	47 (> 16)	Cardiovascular 47 (16.3)	Pulmonary 4 (1.4)		GI 40 (13.8)	Genitourinary 15 (5.2)		SM 21 (7.3)
Mainland	2014	851	42 (4.94)	Cardiac 37 (4.3)	Vascular 1 (0.1)		Intestinal 4 (0.5)	Situs inversus 2 (0.2)	Other 6 (0.7)	SM 4 (0.5)

BA = biliary atresia; GI = gastrointestinal; IVC = inferior vena cava; PDPV = preduodenal portal vein; SM = spleen malformation.

Yang et al<sup>16</sup> found that BASM syndrome accounted for only 0.7% of BA patients, and other major abnormalities accounted for 15.4% in Taiwan. It was rare to see BA with polysplenia in our data. This result is similar to the BASM incidence rate reported by Yang et al.<sup>16</sup> Furthermore, our records showed that the BASM deformity rate was much lower than that in the Taiwan report. At same time, the incidence rate of other associated malformations was also lower compared with that in the other medical center report.

There were many other malformations detected in addition to the polysplenia, including laterality anomalies, cardiac anomalies, and pancreatic anomalies. The laterality anomalies include situs inversus, intestinal malrotation, and intra-abdominal vascular anomalies including absent/interrupted inferior vena cava and preduodenal portal vein.<sup>17</sup> The Canada research through hierarchical cluster analysis on 328 cases of BA with deformity found that a large proportion have only congenital cardiac disease and another large proportion have a constellation of findings all marked by intra-abdominal vascular abnormalities and features consistent with disordered laterality, and the authors recommended that BASM be amended to "biliary atresia structural malformation."<sup>18</sup> Congenital cardiac malformations included ASD and VSD were identified as the most common deformity in our study, and these results are somewhat supportive of their suggestion.

The different BASM ratio may present a different disease process during bile duct development or the role of viruses. In isolated-type BA, the pathological obliterative process may begin later (perhaps in the perinatal period) than it does in those with associated malformations origin (perhaps in the embryonic phase).<sup>19</sup> BA has several possible etiologies, including genetic predisposition, viral infection, and dysregulation of immunity. Genes such as *CFC1*, *ICAM1*, and *VEGF* were found to have variable polymorphism frequency in patients with BA. The role of viral infection in human BA has also been investigated, although viral infection is unlikely to be the specific reason.<sup>20</sup> There are several hypotheses for the etiology of BA, in that during the

embryonic period or perinatal period, viral infection leads to BA in children with genetic susceptibility.<sup>21</sup> Clinically, BA infants with cytomegalovirus infection seem to have severe clinical outcomes, with lower rates of jaundice clearance and higher rates of cholangitis and liver fibrosis.<sup>1</sup> Given that the incidence of BA-associated malformations is lower in our study, it is possible that viral infection is the more common reason inducing BA in China. We need to verify the role of cytomegalovirus and other virus infection situations in BA patients from this group.

The general consensus is that patients who have BA with associated malformations might have poorer prognosis, and patients with associated heart malformations were more likely to suffer from hepatopulmonary syndrome and had higher rates of mortality after undergoing Kasai portoenterostomy.<sup>22</sup> Our clinical data showed that BA with associated malformations might indeed affect the implementation of the Kasai procedure. Compared to patients who have BA with associated malformations, the proportion of patients with isolated BA who did not receive Kasai operation was relatively lower (75.57% vs. 69.23%), indicating that associated malformations might influence the clinical management process; however, the difference did not achieve statistical significance. The reason may be that parents usually chose not to accept Kasai portoenterostomy when they are informed of the presence of associated malformations. Controversy has centered on the effects of malformations on clinical outcomes. A Canadian study showed that no significant difference in post-Kasai native liver survival was observed when BA patients with congenital abnormalities were compared to patients with isolated BA. However, studies in the United States and England have demonstrated poorer outcomes among BASM patients. Several studies have also pointed out that malformations were not a contraindication for liver transplant, and that they had no significant association with prognosis. Polysplenia or complex heart disease did not reduce transplant-free liver survival time after Kasai operation. Further studies are necessary to compare the outcomes of patients with or without malformations.

In conclusion, BA-associated congenital malformations were not rare in our study, with cardiac malformations being identified as the most common anomaly. However, there are fewer spleen anomalies noted in our cohort compared with those reported in the literature. Both the incidence and type of extrahepatic anomalies of BA in mainland China were different from those reported in Western countries, which may suggest different genetic and environmental risk factors for BA. This information may be helpful in preoperative counseling.

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