The Assessment and Management of Biliary Atresia in Hawai‘i, 2009-2023

Sneha A. Singh MD; Kalpana K. Balaraman MA; Madeline I. Johnson BA; Venkataraman Balaraman MD; Devin P. Puapong MD; Sidney M. Johnson MD; Benjamin D. Tabak MD; Russell K. Woo MD

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Abstract

Although biliary atresia (BA) is a rare neonatal disorder, it remains the leading cause of pediatric end-stage liver disease. Early diagnosis of BA and treatment with the Kasai procedure can significantly reduce the need for pediatric liver transplant. Current data suggests that performing the Kasai procedure at 30-45 days of life is associated with longer native liver survival rates and reduction of the need for liver transplant. The incidence rate of BA in the state of Hawai‘i is nearly double the incidence rate in the continental US. International studies have demonstrated that screening programs for BA reduce the age at diagnosis and treatment. However, there has been no statewide analysis on the ages at diagnosis or at Kasai, nor does a statewide screening program for BA exist. The purpose of this study is to review the age of diagnosis and treatment of BA to determine if the current practice in Hawai‘i is in line with the published data. A retrospective chart review of all patients diagnosed with BA at the state's primary children's hospital was performed (2009-2023) and 19 patients who underwent the Kasai procedure were identified. The mean age at diagnosis is 71.4 days (n=19) and the mean age at Kasai procedure is 72.0 days (n=19). Both the average age at diagnosis and treatment for BA in Hawai‘i is significantly higher than published data suggesting best outcomes at 30-45 days of life. This review suggests that the implementation of a statewide screening program for BA in Hawai‘i is warranted.

Keywords

Biliary Atresia, Kasai Procedure, Liver transplant

Abbreviations & Acronyms

BA = biliary atresia
HPH = Hawai‘i Pacific Health
SCC = stool color cards

Introduction

Biliary atresia (BA), a rare neonatal disease affecting the liver, is the leading cause of pediatric end-stage liver disease.[1-3] BA occurs when ascending obstruction of the biliary tree impedes bile flow and, if left untreated, eventually leads to biliary cirrhosis.[2,3] This disease generally manifests in the first few weeks of life.[1,2,4] It is characterized by acholic stool, dark urine, and jaundice.[1,5,6] The diagnosis of BA is generally made by an operative cholangiogram and liver biopsy only after a child with suspected BA is referred for subspecialty care. Intraoperative cholangiogram demonstrates inadequate patency of the biliary tree. Liver biopsy shows histologic evidence of biliary obstruction and bile duct proliferation. The primary treatment is the Kasai hepatoportoenterostomy. This surgery, developed by Dr. Morio Kasai from Japan, involves resection of the atretic biliary tree which is not effectively draining bile from the liver.[7] A loop of jejunum is then anastomosed to the portal plate of the liver employing a Roux-en-Y reconstruction.[7] This loop of jejunum then serves to drain bile from the liver into the alimentary tract.[7] For those children who experience persistent biliary obstruction after the Kasai procedure, a liver transplant is a potential rescue therapy.[1,2,6] Studies have shown that performing the Kasai procedure earlier in life is associated with a longer preservation of native liver function and improved overall outcomes.[1,2,8] Many patients with biliary atresia will undergo a liver transplant regardless of whether a Kasai procedure was performed. However, a successful Kasai procedure can delay or negate the need for liver transplant.[1,5,6] Prolonged native liver survival allows children to survive to an age at which a larger donor base is available for liver transplant.

Recent US census data demonstrates an incidence of BA of 6.5 to 7.5 cases per 100 000 live births in the continental US versus 10.1 cases per 100 000 live births in the state of Hawai‘i.[9] This disease shows a higher incidence in Asian and Pacific Islander populations compared to other ethnic groups that make up the US population.[9,10] Compared to the continental US, Asian and Pacific Islander ethnic groups make up a significant portion of the population in Hawai‘i.[9,10]

Early diagnosis and surgical treatment of biliary atresia has been shown to directly affect patient outcomes. Infants with BA typically present with symptoms of direct hyperbilirubinemia including jaundice and acholic stools due to poor drainage of bile from the liver through the atretic biliary tree. Non-cholestatic jaundice is commonly present at birth or shortly after birth in many term infants, often making it challenging to distinguish biliary atresia in early infancy.[1,6] As a result, the diagnosis of biliary atresia is often delayed. The previously accepted optimal timeframe for surgical intervention for biliary atresia was 60 days.[11] Recent data suggests that intervening before 30 days

of life provides superior outcomes. A Canadian study of 349 patients identified those who received the Kasai procedure before 30 days, between 30 and 90 days, and those greater than 90 days and reported native liver survival of 49%, 36% and 23% respectively.[12] A French study with a total of 743 patients, 695 of whom underwent the Kasai procedure, reported similar trends of increasing age of surgery associated with decreased rates of native liver survival.[8] They additionally detail that if every patient in their study underwent the Kasai procedure earlier than 46 days of life, 5.7% of all liver transplants before the age of 16 could be spared.[8] Both studies commented on the difficulty of early diagnosis and how it hindered a timely surgery. Both studies noted that the benefit of performing the Kasai procedure before 30-45 days of life is longer native liver survival rate.[8,11,12] Therefore, early diagnosis is not a challenge unique to Hawai‘i, but there is compelling data to suggest that every effort should be made to address the timeliness of diagnosis. The aim of this study is to review the most current data regarding the age at diagnosis, age at surgery, and overall outcomes of children with BA in the state of Hawai‘i to evaluate if the current practices provide the best long-term outcomes as suggested by the published data. This information could be used to inform the need for the development of a screening method to facilitate earlier diagnosis of BA in Hawai‘i.

Methods

The study team conducted a retrospective review of the electronic medical records of all patients diagnosed with BA treated at the primary children's hospital in Hawai‘i between January 1, 2009, and January 31, 2023. The study was submitted for regulatory review (Study No. 2019-045) by the Hawai‘i Pacific Health Research Institute and was approved under "exempt" status. In Hawai‘i, a single pediatric surgery group is responsible for care across the island chain and throughout all the major hospitals on O‘ahu. Over the last 15 years, it has been the group's standard practice to refer all patients with suspected BA to the state's primary children's hospital for evaluation, diagnosis, and treatment. All patients treated at the primary children's hospital in Hawai‘i with the diagnosis of BA between 2009 and 2023 were included in the study. The charts were extracted using a key word search "biliary atresia" as well ICD code Q44.2 and CPT code 47701 (portoenterostomy) for Kasai procedure in the electronic medical record. This included both inpatient and outpatient records. There were no exclusion criteria for the initial data collection. This data was used to determine the incidence rate of BA in Hawai‘i for the study period. Primary analysis was performed to look at the average ages at diagnosis and at Kasai procedure. Therefore, at this stage, all patients without a Kasai procedure were excluded. The secondary analysis was performed by dividing the resulting cohort into 2 groups based on patients who retained their native liver (ie, did not require a transplant) and those who required a liver transplant following the Kasai procedure. Patient charts were excluded again from the remainder from the secondary analysis due to missing information regarding native versus transplanted liver status. The purpose of the secondary analysis was to determine if the native liver group had a significantly lower age at diagnosis and treatment since published data suggests that the younger the patient is at the Kasai procedure, the longer they can retain their native liver.[8,11,12] Descriptive statistics were used to analyze the patient cohort. Statistical analysis using a two-sample T test through RStudio version 2023.06.1+524 (Posit Software, Boston, MA)[13] was used to compare the patient's mean ages at diagnosis and at Kasai procedure based on the native vs transplant liver status.

Results

Twenty-one patients with the diagnosis of BA were identified. Two patients did not undergo Kasai procedure. These patients were referred out of state for primary liver transplant and therefore not included in the statistical analysis. The primary analysis was conducted based on the remaining 19 patients. **Table 1** reports all the cases used in the statistical analysis. Of the 19 patients who underwent the Kasai procedure, 16 had data regarding native versus transplanted liver status. Three patients were lost to follow up and therefore did not have information regarding their liver status. The 16 identified patients are followed yearly by the hepatology clinic at the primary childrens' hospital in Hawai‘i. Twenty-one biliary atresia cases amongst a total of 166 410 live births during the study resulted in an incidence of 11.4 cases per 100 000 live births.[14] The live birth rate was calculated from Hawai‘i census data between the years 2009-2023. From the primary analysis of the 19 patients who underwent the Kasai procedure, the mean age at diagnosis was found to be 71.4 days (n=19). The mean age at the Kasai procedure was 72.0 days (n=19). The median and interquartile ranges (IQR) were also calculated. The median age of diagnosis was 69 days with an IQR of 10.5. The median age at Kasai procedure was 71 days with an IQR of 9.5. In the secondary analysis for the native liver group, the mean age of diagnosis was 67 days (n=16) while the mean age of diagnosis for the transplant group was 78.2 days (n=16). There was no statistically significant difference between the 2 groups (P=.34). Similarly, the mean age at the Kasai procedure for the native liver group was 67.7 days and 78.5 days for the transplant group. Again, there was no statistically significant difference between the two groups (P =.34). **Table 2** reports the descriptive statistics all cohorts. **Figure 1** highlights the variability in the native liver group with most patients receiving their diagnosis after 60 days of life. **Figure 2** highlights the similar variability in the age at Kasai procedure among the native liver group. Of note, the mean age of diagnosis and surgery within the 2 study groups are often the same. BA diagnosis requires a surgical procedure (liver biopsy and intraoperative cholangiogram) and once diagnosed, the Kasai procedure is done shortly after, often on the same day. Of the 16 patients included in the secondary analysis, 6 subsequently underwent liver transplant. Of the 10 remaining children with

a native liver, 1 child currently under the age of 5 years with surviving native liver could not be included in 5-year native liver survival rate calculation. Five-year native liver survival percentage was 60% (9 out of 15). In the overall data, there was a notable outlier who received the Kasai procedure at 128 days of life and subsequently received a liver transplant. Removing the outlier from the mean age at surgery still results in a value above 60 days.

Table 1. Biliary Atresia Patients with Kasai Procedure, Hawai'i 2009-2023

Patient Number	Diagnosis Age (days)	Kasai Age (days)	Current Age (years)	Liver Status	Transplant Age (days)
1	66	68	12	Native	N/A
2	54	54	7	Native	N/A
3	64	64	9	Native	N/A
4	69	69	12	Native	N/A
5	69	71	11	Native	N/A
6	76	76	14	Native	N/A
7	75	75	7	Native	N/A
8	70	71	4	Native	N/A
8	77	79	10	Native	N/A
10	50	50	11	Native	N/A
11	69	69	7	Transplant	260
12	69	71	9	Transplant	2037 (5Y)
13	128	128	6	Transplant	269
14	62	62	8	Transplant	667
15	73	73	5	Transplant	180
16	68	68	10	Transplant	305
17	77	77	1.5	Unknown	Unknown
18	82	84	10	Unknown	Unknown
19	58	58	0.75	Unknown	Unknown

N/A = not applicable, 5Y = 5 years of age
Note: all patients used in primary and secondary analysis with diagnosis age, Kasai age, and liver status noted.

Table 2. Descriptive Statistics of All Patients with Kasai Procedure in Accordance with Liver Status, Hawai'i 2009-2023

	Mean	Median	Standard Deviation	Q1	Q3	IQR
All Patients with Kasai Procedure Descriptive Statistics (n=19)						
Diagnosis Age (days)	71.4	69.0	15.9	65.0	75.5	10.5
Kasai Age (days)	72.0	71.0	16.0	66.0	75.5	9.5
Native Liver Descriptive Statistics (n=10)						
Diagnosis Age (days)	67.0	69.0	9.0	64.5	73.6	9.3
Kasai Age (days)	67.7	70.0	9.4	61.5	74.0	12.5
Transplant Liver Descriptive Statistics (n=6)						
Diagnosis Age (days)	78.2	69.0	24.7	68.3	72.0	3.8
Kasai Age (days)	78.5	70.0	24.5	68.3	72.5	4.3

IQR = interquartile range, Q1 = First Quartile, Q3 = Third Quartile

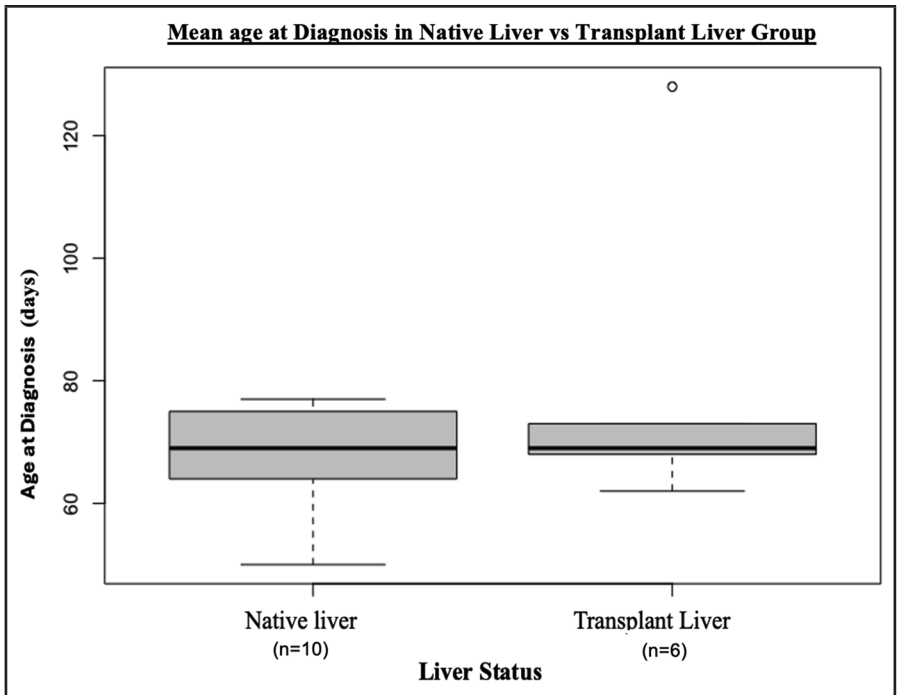

Figure 1. Box Plot of Mean Age at Biliary Atresia Diagnosis Among Native Liver and Transplant Groups Reflecting the Variability in the Mean

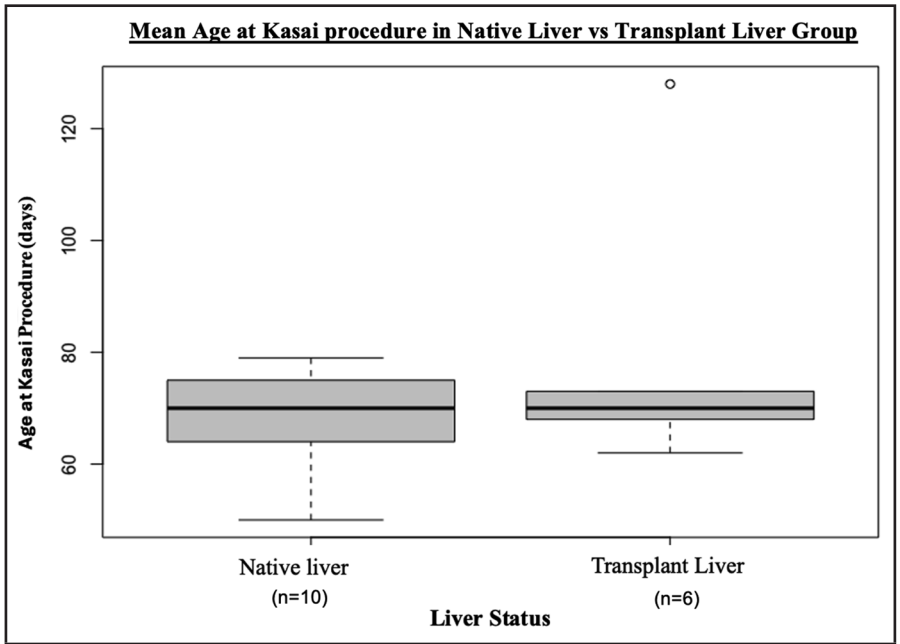

Figure 2. Box Plot of Mean Age at Kasai Procedure Among Native Liver and Transplant Groups Reflecting the Variability in the Mean

Discussion

The goal of this study was to determine if the current practice surrounding treatment of BA in Hawai'i is in line with the most recently published studies regarding best outcomes. Though the sample size identified in this study was small, it highlights an important opportunity for improvement. Historically, studies report the goal has been to have patients undergo the Kasai procedure for BA at less than 60 days of life, with worse outcomes noted after greater than 90 days of life.[11] More recent studies suggest that even earlier intervention with the Kasai procedure performed between 30-45 days of life results in longer native liver survival.[11] The results of this study show that, on average, patients in Hawai'i underwent the Kasai procedure at 72.0 days of life with the median age of at 71 days. None of the patients included in the data set were diagnosed with BA before 45 days of life. This is higher than published data from the continental US, which reports the Kasai procedure being performed at a median age of 63 days of life.[15] Additionally, the secondary analysis shows that patients in the transplant group tended to be older at the time of procedure with less variability in age range, though these results were not statistically significant. There was one outlier at 128 days noted. Even when accounting for the outlier, the transplant group still underwent the Kasai procedure in the 60-70 day of life range, versus the native group who underwent the Kasai procedure in the 50-60 day of life range. The youngest patient who was included in the 5-year native liver survival rate received the Kasai procedure at 50 days of life and still retains his native liver now at 11 years old. Although this observation was not statistically significant, it does correlate with published data which show better outcomes the younger the Kasai procedure is performed.[8,11,12] The data in this study suggest that the age of diagnosis and at Kasai procedure in Hawai'i is not congruent with published studies reporting better outcomes with intervention under 30-45 days of life.[11]

There were several limitations in this study, the most prominent being a small sample size. The availability and access to the electronic medical records as well as the practice pattern of the pediatric surgeon group in Hawai'i determined the years included in the study period. It would be useful to include data prior to 2009 to increase the sample size. However, prior to 2009 not all patients were centrally referred within the state. Additionally, the data collected through the state's primary children's hospital should cover all cases of BA throughout the island chain, but there is a chance of non-reported cases and of mis-diagnosed cases. The data collected here also did not include cases at other hospitals in the state that provide pediatric care. However, it is unlikely that a case was diagnosed and treated elsewhere in the island chain given the standard practice of the pediatric surgeons group. There is a chance that children born with BA in Hawai'i may have been diagnosed and treated off-island. This would falsely decrease the reported incidence rate in this study. It is impossible to know how many cases may have moved off island. Finally, given the unique nature of delivering health care throughout an island chain, there will be unavoidable delays in diagnosis and surgery. These variables all skew Hawai'i data towards a higher reported age at diagnosis and at Kasai procedure. Still, the benefit of diagnosing BA and performing the Kasai procedure before 30- 45 days of life is clear. Hawai'i would benefit from making every effort to reduce both the age of diagnosis and age at Kasai procedure.

A major obstacle to decreasing the age at which patients receive the Kasai procedure is early diagnosis. The earliest presenting symptom, jaundice, is often associated with much more common and benign processes, and BA is overlooked. Furthermore, most well child visits are spaced out in such a way that the optimal time to make the diagnosis is often missed. Because of disease rarity and lack of an easy biomarker, screening for BA is not often included in routine newborn screening. Without a screening program, pediatricians must have a high index of suspicion for BA and then refer patients for formal subspecialty evaluation, diagnosis, and treatment.

There are several nations that have successfully implemented screening programs for BA. Taiwan was the first country to implement a nationwide screening program in 2004 utilizing stool color cards (SCC). Parents use the SCC to identify abnormal stool color and any potential cases are reported to a national registry.[16] The follow up studies to the screening program reported that the sensitivity of diagnosing BA at <60 days was 72.5% in 2004 and increased to 97.1% in 2005.[16] Additionally, the rate of Kasai at <60 days was 60% in 2004 which increased to 74.3% in 2005.[16] In the 5 year follow up, Kasai procedure at >90 days was non-existent.[1] Another example is data from British Columbia, Canada, which reports an incidence rate of BA that is 1.5 times larger than the rest of the country.[17] A large scale prospective study in British Columbia in 2014 reported a decrease in the age of diagnosis with the distribution of the SCC.[1]

In addition to the SCC reported in these studies, there are other demonstrated and effective ways to remove of the obstacle of early diagnosis with user-friendly screening tools. One screening tool option is a smartphone application to assist with early diagnosis. In 2014, Johns Hopkins released the PoopMD©(2015) application with a color recognition software based on the Taiwan stool color card images.[1] These were converted to a 16-base color pallet using RGB (red, green, and blue) digital photo hex codes and thereby allow accurate identification of acholic stools with reported 100% correct identification of acholic stools and a 0% false negative rate.[1] Japan released a similar application which uses both RGB and HSV (hue, saturation, and value) to identify acholic stools.[1] This study reported a 100% sensitivity and specificity for identifying acholic stools based off 40 unique photos.[1] Italy released another application in 2021 using similar image identification software based on Japanese 7 stool color

photo panels and 160 unique photos with no reported false negatives.[1] There have not been any larger scale studies to date using applications alone.

Another proposed early diagnostic tool is fractionated bilirubin as a screening adjunct for the newborn screening panel. This was first suggested in 1998 in the United Kingdom. In a follow-up prospective study, a total of over 27 000 neonates were tested using a conjugated bilirubin cutoff above 18 μmol/l (0.2 mg/dl) with 107 identified above the cutoff and a resulting 11 patients with confirmed liver disease.[18] A US based study published in 2020 including over 120 000 newborns used a 2-stage screening of direct bilirubin within the first 60 hours of life and before the 2 week well child visit. The study reports that 7 infants were identified with BA and their age of surgery was significantly younger than prior to the implementation of the screening tool: 36 days vs 56 days age at Kasai procedure.[19] Overall, several diagnostic tools exist with validated results and may be solutions to overcoming the obstacle of early diagnosis. There is extensive room for further research in which of these previously verified methods would be suitable for the Hawai'i population and which would be most effective in reducing the age of diagnosis and at Kasai procedure.

Conclusion

BA carries significant morbidity and mortality for the newborn population. It is the leading cause of newborn liver transplant worldwide.[1] The incidence of BA in Hawai'i is nearly double that of the continental US, and the incidence rate reported in this study aligns with that trend. The study team concluded that the age of diagnosis and age at Kasai procedure were outside the optimal window as reported in several studies to be less than 30-45 days of life.[8,11,12] A major obstacle in delivering necessary care to BA patients in this optimal time frame is early diagnosis. Given these findings, the study team recommends further research into the development of a statewide screening program to facilitate the earlier diagnosis and treatment of BA in Hawai'i.

Conflict of Interest

None of the authors identify a conflict of interest.

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Authors' Affiliations:
- General Surgery, Tripler Army Medical Center, Honolulu, HI (SAS)
- John A. Burns School of Medicine, University of Hawai'i, Honolulu, HI (KKB, MIJ, VB)
- Pediatric Surgery, Kapi'olani Medical Center for Women and Children, Honolulu, HI (DPP, SMJ, BDT, RKW)

Corresponding Author:
Russell K. Woo MD; Email: russell.woo@hphmg.org

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