นิพนธ์ต้นฉบับ • Original Article

การประเมินภาวะท่อน้ำดีอุดตันในทารก: ผลวิเคราะห์จากการตรวจสแกนตับและทางเดินน้ำดีใน โรงพยาบาลศรีนครินทร์ในช่วงปี พ.ศ. 2548 – 2557

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หน่วยเวชศาสตร์นิวเคลียร์ ภาควิชารังสีวิทยา คณะแพทยศาสตร์ มหาวิทยาลัยขอนแก่น

Evaluation for Biliary Atresia: Analysis of Hepatobiliary Scintigraphy in Srinagarind Hospital from 2005-2014

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หลักการและวัตถุประสงค์ ภาวะท่อน้ำดีอุดตันในทารก (biliary atresia: BA) เป็นความผิดปกติแต่กำเนิดที่ร้ายแรงที่จำเป็นต้องให้การวินิจฉัยและรักษาอย่างรวดเร็ว การตรวจสแกนตับและทางเดินน้ำดี (hepatobiliary scintigraphy: HBS) เป็นการตรวจลำดับแรกๆในผู้ป่วยกลุ่มนี้ การศึกษานี้มีเป้าหมายเพื่อประเมินว่ามีผู้ป่วยเป็นสัดส่วนเท่าใดที่ได้รับการตรวจ HBS ที่อายุเกิน 60 วัน และประเมินปัจจัยเกี่ยวกับระยะทางว่ามีผลต่อความล่าช้าในการได้รับการตรวจวินิจฉัยหรือไม่ และวิเคราะห์ผลจากการตรวจ HBS การทำงานของตับ และประโยชน์ของการถ่ายภาพที่ 24 ชั่วโมง

วิธีการศึกษา เก็บข้อมูลจากการตรวจ HBS ตั้งแต่ปี 2548 ถึง 2557 ทำการประมาณระยะทางระหว่างบ้านและโรงพยาบาล ประเมินว่ามีสารเภสัชรังสีออกมาในลำไส้หรือไม่ และประเมินการทำงานของตับจากลักษะของภาพสแกนโดยให้คะแนนแบบกึ่งเชิงปริมาณ

ผลการศึกษา จากทารก 491 มีร้อยละ 64 ได้รับการตรวจ HBS ที่อายุเกิน 60 วัน (มัธยฐาน 71 วัน) ความล่าช้าในการได้รับการตรวจนี้คงที่ตลอด 10 ปี ไม่พบว่ามีความสัมพันธ์ระหว่างระยะห่างจากโรงพยาบาลและอายุที่ได้รับการตรวจ (r = 0.0784) แต่ผู้ที่อาศัยอยู่ในตัวอำเภอเมืองขอนแก่นมีแนวโน้มที่จะได้รับการตรวจเร็วกว่าผู้ที่ไม่ได้อยู่ในเขตนี้แต่ไม่พบนัยสำคัญทางสถิติ (มัธยฐาน 64 วัน เทียบกับ 71 วัน, p=0.09) การตรวจเพิ่มที่ 24 ชั่วโมงมีประโยชน์น้อย โดยมีผู้ป่วยเพียงร้อยละ 0.86 เท่านั้นที่พบว่ามีสารเภสัชรังสีออกมาในลำไส้ที่ 24 ชั่วโมง

สรุป ทารกที่สงสัยว่าเป็น BA ที่ได้รับการตรวจ HBS ล่าช้ามีสัดส่วนที่สูงตลอดระยะเวลา 10 ปีที่ผ่านมา ไม่มีความ

Background and Objectives: Biliary atresia (BA) is a serious congenital condition that needs prompt diagnosis and treatment. Hepatobiliary scintigraphy (HBS) is often used as the initial imaging test for diagnosis. This study aims to determine the proportion of patients receiving HBS later than 60 days of age, assess relationship between distance from hospital and age at HBS, describe HBS findings regarding positivity of scans, degree of liver function and value of 24-hour imaging.

Methods: Information of HBS during 2005-2014 was collected. Distance from hospital was estimated. Presence of intestinal activity was visually determined. Liver function was semi-quantitatively scored.

Results: From 491 infants, 64% was examined when older than 60 days of age (median 71 days). This delay has remained stable during the past decade. No correlation was found between distance from hospital and age at HBS (r = 0.0784). There was a trend that patients living in the same district as our center would be evaluated earlier (median 64 vs. 71 days, p=0.09). The 24-hour image had minimal value with only 0.86% revealing intestinal radiotracer activity which the initial first-day image did not.

Conclusion: Proportion of infants suspected of BA receiving delayed evaluation has remained consistently high over the past decade. No relationship between

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สัมพันธ์ระหว่างระยะห่างจากโรงพยาบาลศรีนครินทร์กับอายุที่ได้รับการตรวจ ควรมีการศึกษาไปข้างหน้าเพื่อประเมินหาปัจจัยที่ทำให้การตรวจล่าช้าเพื่อปรับปรุงนโยบายและระบบการส่งต่อผู้ป่วย

distance from tertiary care center and age at HBS was found. Additional prospective studies should be done to assess for factors that delay access to medical care and guide health policy.

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Introduction

Biliary atresia (BA) is a potentially fatal congenital condition that needs prompt diagnosis and treatment. Its incidence ranges from 5.3 to 7.4 per 100,000 live births in the Caucasian population[1–4] but has been found to be higher in Asians with a reported incidence of up to 10 and 20 per 100,000 live births in Japan[5] and Taiwan, respectively[6]. BA is the congenital obstruction of the biliary drainage system,[7] its exact pathophysiology has still not yet been clearly elucidated[8]. If it is not promptly treated, patients will develop progressive liver damage leading to cirrhosis, liver failure, and death. The treatment of BA is hepatic portoenterostomy or Kasai operation which allows direct biliary drainage from the liver into the small intestine[9]. The patient's age at the time of operation is of paramount importance with the majority of studies reporting that patients operated on before two months of age have better success rates than patients treated later[10–23]. Even after successful Kasai operation, a considerable portion of patient will eventually have to undergo liver transplantation[19, 24]. Clinical features alone cannot reliably differentiate between BA and other causes of icterus[25]. Intraoperative cholangiography is the gold standard for diagnosis but is an invasive procedure. Non-invasive imaging such as ultrasonography (US), and magnetic resonance cholangiography (MRCP) have been used,[26] however, the imaging modality that has most long been used and studied is hepatobiliary scintigraphy (HBS) which utilizes technetium-99m-labeled IDA radiopharmaceuticals. Visualization of intestinal radiopharmaceutical activity effectively excludes BA. A systematic review found that HBS has 98.7% sensitivity and 70.4% specificity for differentiating BA from neonatal hepatitis.[27] Because of its almost perfect sensitivity, HBS is one of the initial tests used for exclusion of BA, and can be viewed as a "gate keeper" test before further invasive investigations. Late referrals have long been a problem even in developed countries with most studies finding that approximately half of patients receive the Kasai procedure later than two months of age[14, 20, 22, 23, 28, 29]. The objectives of this retrospective study are to determine the proportion of patients who receive HBS when older than 60 days of age, to evaluate the trend over a period of 10-years, to determine the degree of liver function at the time of HBS, to assess whether distance from hospital is related to delayed HBS, and to assess the value of 24-hour imaging.

Materials and Methods

Patients

This study was approved by the institutional review board. From January 2005 to December 2014, information of infants with neonatal jaundice sent for HBS at the Division of Nuclear Medicine, Department of Radiology, Khon Kaen University: a tertiary care university hospital in northeast Thailand was reviewed. Patients sent for HBS for reasons other than for evaluation for BA were excluded. Collected data include sex and age at the time of HBS. To gauge the distance from the patient's residential area to our center, the district and province of the patient's address was entered into Google Maps and distance to our hospital was calculated.

Hepatobiliary scintigraphy

Imaging protocol. Patients fasted for four hours. A 0.05 mCi/Kg dose of ^{99m}Tc-disofenin (diisopropyl iminodiacetic acid; DISIDA) was administered intravenously and anterior static planar images were

acquired every 5-10 minutes for the first hour and every 30-60 minutes thereafter depending on the availability of the gamma camera. The early images were checked by the Nuclear medicine physician in charge and was stopped when definite radiopharmaceutical activity was seen in the bowel. If bowel activity was not demonstrated, the images would be acquired for up to 6 hours on the first day of the scan. The 24-hour delayed imaging was optional depending on the judgement of the nuclear medicine physician, and was often not done in patients whose liver function was so poor that delayed imaging was highly unlikely to be of benefit. Lateral images were obtained to differentiate between gall bladder activity and activity in the kidney.

Image interpretation. The following was examined: presence or absence of intestinal radiopharmaceutical activity, presence of absence of activity in the gall bladder, time of the last image of the first day, and whether or not a 24-hour image was obtained. The degree of liver function was determined in three domains and semi-quantitatively scored as 0, 1, or 2 for each domain (Table 1). The scores of the three domains were summed. A summed score of 0 indicates normal liver function. Scores of 1 to 2, 3 to 4, and 5 to 6 represent mild, moderate, and severe impairment of liver function, respectively.

Statistical analysis

Patient characteristics are described as mean, SD, median, range, and percentage. Normal distribution of continuous data was tested by Shapiro-Wilk test. Continuous variables as well as the ordinal variable—the liver function scores were compared using the Wilcoxon–Mann–Whitney test. Proportions were compared using z-test for proportions. The correlation between distance from hospital and age at HBS was assessed using Pearson product-moment correlation coefficient. Analysis was done using Stata version 10.

Results

From January 2005 to December 2014, there were 491 infants suspected of having BA sent for HBS at our institute. Patient characteristics as well as HBS findings are listed in Table 2. The cohort consists of significantly more males than females. Almost all patients are from the northeast part of Thailand, with 16 patients from our neighboring country Lao PDR.

Age at the time of hepatobiliary scintigraphy

Patients sent for HBS range from 8 to 789 days of age. The age distribution is positively skewed with a median of 71 days. Sixty-four percent of patients received HBS after the age of 60 days. The proportion of patients whom received delayed diagnostic evaluation has been consistently high during the past 10 years as shown in Figure 1, exceeding 70 percent in some years.

Relationship between distance and age at hepatobiliary scintigraphy

There was no significant difference in distance from our center between patients examined not later than 60 days of age and those examined after 60 days of age (Table 2). Even after excluding clear outliers, no correlation between distance and age at HBS was found (Pearson r = 0.0789) as shown in Figure 2. Since the referral system in Thailand requires that patients be transferred from district hospitals to provincial hospitals and then to university hospitals as the final tier, thus the factor of district of residence was explored as a potential determinant of age at HBS with the hypothesis that patients living near provincial hospitals and patients living in the same district as our center should receive faster referral than patients living in the more peripheral districts. However, as shown in Table 3, there was no difference in age between patients living in Khon Kaen province and other provinces, neither was there any significant difference between patients living in the main city districts which have direct access to provincial hospitals and those living in peripheral districts. There was a trend that patients living in Khon Kaen city district received earlier HBS at a median age of 64 days compared with patients living elsewhere which received HBS at a median age of 71 days. This difference, however, did not reach statistical significance (p = 0.09).

Intestinal radiotracer activity and liver function

Overall 193 patients had definite intestinal radiotracer activity thus excluding biliary atresia. Intestinal radiotracer activity was not demonstrated in the remaining 298 patients (Table 2). The proportion of patients with present intestinal radiotracer activity was significantly lower ($p = 0.03$) in patients aged > 60 days (35.8%) than patients aged ≤ 60 days (45.5%). Liver function was semi-quantitatively scored. In this cohort only 9.57% of patients had normal liver function (score 0), and 27.5%, 28.5%, and 34.4% had mildly impaired (score 1 and 2), moderately impaired (score 3 and 4), and severely impaired (score 5 and 6) liver function, respectively (Table 2). As expected, the more severe the impairment of liver function, the less likely there is to be radiotracer excretion into the bowel with almost 90% of patients with normal liver function having intestinal activity compared with only about 10% in patients with liver function score of 6 (Figure 3). Patients with intestinal activity had significantly better liver function score than those that displayed no intestinal activity (Table 4). The value of 24-hour delayed imaging in this study is very limited. Among 194 patient with non-demonstrable intestinal activity on the first day, 116 underwent 24-hour delayed imaging of which only one (0.86%) demonstrated intestinal activity.

Discussion

This study identified a large cohort of infants suspected of having BA whom were sent for evaluation with HBS. The main objective was to determine the proportion of patients who underwent HBS later than 60 days of age which is the threshold for good outcome from Kasai operation. Results show that two-thirds of patients in this cohort received HBS later than 60 days of age, which placed them with an increased risk of poor outcome in cases that BA was ultimately present and Kasai operation was surely delayed. In order for patients to be able to receive Kasai operation within 60 days of age, results of diagnostic procedures should be available before that time point. Further analysis of the present results showed that if a cutoff age of 50 days at time of HBS was used (to allow time for preoperative preparation), only 23% would receive HBS at age ≤ 50 days. The median age at HBS was 71 days which compared poorly to previous studies which found that patients received Kasai operation at a median age of approximately 50 to 60 days[14, 20, 22, 23, 28, 29]. However, this finding is not isolated to this present study as previous studies describing HBS in neonatal jaundice reported that the average or median age at the time of HBS ranged from 31 to 117 days[30, 31]. Variations of the age at HBS were present across studies; studies done in developed

Table 1 Determination of liver function by hepatobiliary scintigraphy

Domain	Score 0	Score 1	Score 2
Cardiac blood pool	persists for less than 10 minutes	persisted for more than 10 minutes but progressively became less intense as time passes	constantly persists throughout the study without decreasing activity with time
Hepatic uptake of DISIDA*	clearly much more intense than cardiac blood pool activity and soft tissue activity	only slightly more intense than the cardiac blood pool and soft tissue background	equal to the cardiac blood pool with much soft tissue background activity
Renal excretion of DISIDA	only minimal radiotracer activity excreted via the kidneys	increased renal excretion but hepatic activity was greater or comparable to that of the activity in the kidneys and urinary bladder	renal excretion is the predominant route of radiotracer excretion

*DISIDA = diisopropyl iminodiacetic acid

Table 2 Patient characteristics, comparing patients receiving HBS at age ≤ 60 days with those receiving HBS after 60 days of age.

	All patients		Age ≤ 60 days		Age > 60 days		
		Percent		Percent		Percent	p value
Number	491	100.00	178	36.25	313	63.75	
Male	282	57.43*	107	60.11**	175	55.91†	
Age at HBS (days)							
Mean ± SD	87 ± 64		44 ± 12		112 ± 68		
Median	71		46		92		
Range	8 – 789		8 – 60		61 – 789		
Distance (km)							
Mean ± SD	140 ± 82		134 ± 79		144 ± 84		0.4097
Median	126		123		126		
Range	3 – 645		7 – 442		3 – 645		
Liver function score							
Mean ± SD	3.37 ± 1.95		3.07 ±1.98		3.55 ± 1.92		0.0236
Normal function (score 0)	47	9.57	25	14.04	22	7.03	
Mildly impaired (score 1, 2)	135	27.49	49	27.53	86	27.48	
Moderately impaired (score 3, 4)	140	28.51	57	32.02	83	26.52	
Severe impaired (score 5, 6)	169	34.42	47	26.40	122	38.98	
Intestinal radiotracer activity							
Present	193	39.31	81	45.51	112	35.78	0.0338
Absent	298	60.69	97	54.49	201	64.22	
Gall bladder activity							
Present	98	19.96	40	22.47	58	18.53	0.2937
Absent	393	80.04	138	77.53	255	81.47	

* p-value 0.0006; ** p-value 0.0035; † p-value 0.0183

countries tended to report earlier diagnostic evaluation [32–40] than studies from developing countries[31, 41–44]. Even among patients in the same country, there is still considerable variation of the age at diagnosis; studies from India report average or median age ranging from 50 to 117 days [31, 41, 44, 45], while studies from Thailand report approximately between 57 to 89 days[46–48]. HBS for diagnosis of BA is universally considered to be urgent. At our institute, patients will be scanned at the earliest possible date provided that they have been prescribed phenobarbital for 5 days. The waiting time is thus usually no longer than one week. Factors related to access to medical care were analyzed as there are only a few centers in northeast Thailand equipped with nuclear medicine imaging service, and capability to perform pediatric surgery; patients in the northeast region of Thailand may need to travel up to 300 kilometers to receive evaluation and treatment. Even so, no relationship was found between distance to hospital and age at the time of HBS. There was however, a trend that patients living immediately in the Khon Kaen city district which is closest in proximity to our center would receive HBS at an earlier age than patients living elsewhere. Because the fact that BA needs to be promptly treated and a large proportion of patients have delayed diagnosis, some reports have suggested that abdominal ultrasound should be used as the initial test for evaluation since the triangular cord sign is very specific for BA[36, 49] and HBS is used only in patients whom ultrasound is non-diagnostic. The present results confirm that even in patients aged over 60 days, HBS showed intestinal activity in about 35% thus excluding BA and preventing further invasive investigations. The present results revealed that 24-hour delayed image

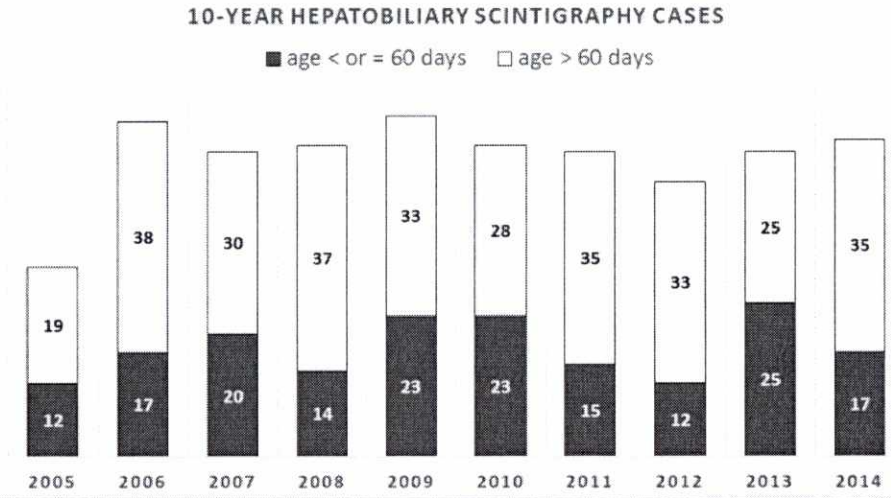
Table 3 Relationship between area of residence and time to HBS

	Khon Kaen province	Other provinces	p-value
Number	100	391	
Age (days)			0.2913
Mean ± SD	82 ± 66	88 ± 63	
Median	68.5	73	
	Main city districts	**Peripheral districts**	**p-value**
Number	127	364	
Age (days)			0.3512
Mean ± SD	87 ± 79	87 ± 56	
Median	71	70	
	Khon Kaen city district	**All others**	**p-value**
Number	31	460	
Age (days)			0.0922
Mean ± SD	68 ± 28	88 ± 66	
Median	64	71	

Table 4 Comparison of liver function impairment between patients with present and absent intestinal radiotracer activity

	Present intestinal activity	Absent intestinal activity	p-value
Total	193	298	
Normal (%)	42 (21.8)	5 (1.7)	
Mildly impaired (%)	80 (41.4)	55 (18.4)	
Moderately impaired (%)	48 (24.9)	92 (30.9)	
Severely impaired (%)	23 (11.9)	146 (49.0)	
Liver function score (mean ± SD)	2.14 ± 1.76	4.17 ± 1.63	<0.0001

proved to be of minimal value with only 1 patient from 116 who demonstrated bowel activity in the delayed image which was not seen on the first day. The remaining 115 revealed no bowel activity at the end of the first day and the 24-hour delayed image. This is likely because the radiopharmaceutical Tc-99m DISIDA used in this study has a lower hepatic extraction fraction than other radiopharmaceuticals such as Tc-99m BrIDA. A previous study found similar findings and has concluded that imaging up to 6 hours of the first day is sufficient[50]. Semi-quantitative scoring of liver function provided a simple method for gauging the level of hepatic impairment and revealed that the more severe the impairment, the less proportion of patients had intestinal activity, regardless of the cause of dysfunction. The fact that the proportion of patients receiving delayed diagnostic evaluation has remained high over the past 10 years possibly reflects the difficulty of clinical detection of patients with possible biliary atresia. This problem needs to be dealt with at the level of healthcare policy. Referral of patients suspected of having BA should be expedited, with patients sent directly to centers capable of performing HBS, pediatric ultrasound, and pediatric surgery. A fast track channel should be available at the imaging center. Improved communication between health care centers would allow proper patient preparation such as premedication with phenobarbital. The diagnostic accuracy of HBS was not determined since a myriad of studies have already elucidated the diagnostic performance of HBS as a test with almost perfect sensitivity and reasonable specificity. Limitations of this study is due to the



	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014
Number	31	55	50	51	56	51	50	45	50	52
Median age at HBS (days)	66	73	72	82	71	64	78.5	73	62	72
Age at HBS > 60 days (%)	61.3	69.1	60.0	72.6	58.9	54.9	70.0	73.3	50.0	67.3

Figure 1 Number of hepatobiliary scintigraphy performed from 2005 to 2014, with median age when HBS was performed and percentage of patients receiving HBS later than 60 days of age.

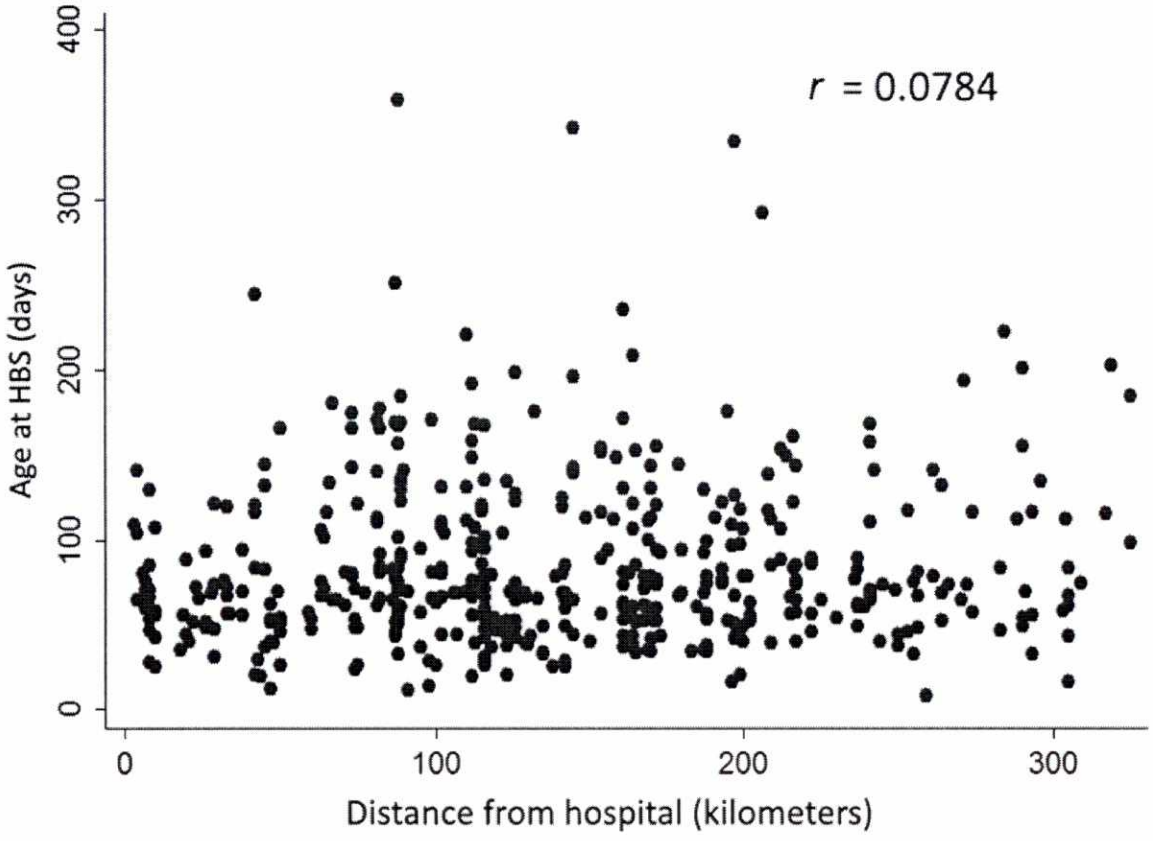


Figure 2 Scatter plot of the relationship between the distance from the patients' home to our center, and age of the patients on the day HBS was performed.

retrospective nature so factors that influence the age at HBS could not thoroughly be investigated. The district of residence is only a crude estimate of the patients' proximity from our center as some patients may live in different areas from what was stated in their medical record.

Conclusion

The proportion of infants suspected of having biliary atresia whom receive delayed HBS has remained consistently high with about two-thirds evaluated at age over 60 days. There was a trend that patients living immediately in the same district as our center had earlier access to HBS. Additional prospective studies should be done to assess for factors that may delay access to medical care. Policies should focus on screening, case finding, and expediting diagnosis and treatment of infants suspected of having biliary atresia to optimize therapeutic outcome.

Conflicts of interest

The authors declare no conflict of interest. No funding was received for conducting this study.

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