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Differentiation of Biliary Atresia from the Intrahepatic Etiology of Infantile Cholestasis with Alagille Criteria

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Abstract

Background: Biliary atresia (BA) is an important etiology of liver disease in pediatric patients which manifests as extrahepatic cholestasis. Alagille criterion is a combination of noninvasive findings for the diagnosis of BA. In this regard, the current retrospective study aimed to evaluate the diagnostic accuracy of Alagille criteria for BA.

Methods: This cross-sectional study was conducted in Ghaem Hospital, affiliated to Mashhad University of Medical Sciences during 2009-2014. All infants less than 2 years old with cholestasis referred to the pediatric gastrointestinal ward were included in this study. Alagille criteria were evaluated for each patient, and BA was confirmed with intraoperative cholangiography. Finally, sensitivity, specificity, and positive and negative predictive values of Alagille criteria were determined according to the final diagnosis.

Results: In general, 92 patients were included in this study. The male-to-female ratio and the mean age of patients were 54/38 and 42±5 days (ranging between 1 and 5 months), respectively. There was a significant difference between the two groups in terms of gender, onset time of jaundice, and the presence of the acholic stool (P=0.02, 0.04, and 0.005, respectively). Eventually, the acholic stool had the highest sensitivity, specificity, and positive and negative predictive values.

Conclusion: Based on the findings, the presence of the acholic stool was the most valuable criterion for the diagnosis of BA among all Alagille criteria.

Key Words: Acholic Stool, Alagille Criteria, Biliary Atresia, Cholestasis, Infantile Liver Disease, Intrahepatic Etiology, Non-invasive Diagnostic Approaches, Pediatrics.

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1- INTRODUCTION

Biliary atresia (BA) is considered as an essential etiology of the liver disease in pediatric patients that manifests as progressive extrahepatic cholestasis (1, 2) and is the most common cause of liver transplantation in children (3).

The differentiation of BA from the other causes of infantile cholestasis is critical because an early surgical intervention, which is known as 'Kasai portoenterostomy', can help in preventing the worsening of the liver disease during the first 60 days of life and delays the need for liver transplantation (4).

Age at the time of Kasai portoenterostomy is the most important prognostic factor in patients with BA (4, 5). Untreated patients with BA can become complicated with cirrhosis within the first year of life (6).

Although multiple clues exist for the suspicion of BA, including clinical findings, biochemical markers, ultrasound data, hepatobiliary scintigraphy, magnetic resonance cholangiopancreatography, and histopathological findings, there is no single criterion for the differentiation of BA from the intrahepatic etiologies of infantile cholestasis. The current strategy for the definitive diagnosis of BA is intraoperative cholangiography, which is possible during surgical intervention (7).

Accordingly, there is a need for high specificity screening methods regarding distinguishing BA from the other causes of intrahepatic cholestasis. In this respect, a combination of findings has been proposed in Alagille criteria, including birth weight, onset time of jaundice, stool color, and the size and consistency of the liver (8).

Thus, the current retrospective study sought to evaluate the Alagille criteria for differentiating BA from intrahepatic cholestasis in the infancy period.

2- MATERIALS AND METHODS

2-1. Design and participants

This cross-sectional retrospective study was performed in Ghaem Hospital, affiliated to Mashhad University of Medical Sciences during 2009-2014. This research was approved by the Ethical Committee of Mashhad University of Medical Sciences. The participants included 92 infant patients referred to the pediatric gastrointestinal ward of the hospital.

2-1.1. Inclusion and exclusion criteria

All infants less than 2 years of age with cholestasis, referred to the pediatric gastrointestinal ward, were included in the present study. The exclusion criteria were patients with choledochal cysts, bile ducts perforation, incomplete records, and no definitive diagnosis.

2-2. Procedure

Demographic information, initial complaint, clinical signs, laboratory findings, histopathological result, liver biopsy, and intraoperative cholangiography findings were recorded for each patient. Alagille criteria including birth weight, onset time of jaundice, stool color, liver size, and consistency were evaluated for each patient. According to these criteria, the patients were divided into intrahepatic and extrahepatic cholestasis (BA) groups.

The final diagnosis for each patient was recorded, and BA was confirmed with intraoperative cholangiography. Each intrahepatic cause of cholestasis was diagnosed according to specific diagnostic tests.

2-3. Data Analysis

Data were analyzed with SPSS, version 11. Descriptive data were expressed as the mean ± standard deviation or number (percentage). In addition, the Chi-square test was used to evaluate the relation

between qualitative and quantitative variables, and P-value <0.05 was considered as the significance level. Eventually, the sensitivity, specificity, and positive and negative predictive values of Alagille criteria were determined according to the final diagnosis.

3- RESULTS

In general, 92 patients were included in this study. The male-to-female ratio and the mean age of patients were 54/38 and 42±5 days (in the range of 1-5 months), respectively. The basic characteristics of patients are summered in **Table 1**.

Table-1: Basic Characteristics of Patients

Variable		Frequency (%)
Age (Mean ± SD), day		42±5
Gender (Male/female)		54/38 (58.7/41.3)
Etiology of cholestasis	Biliary atresia	33 (35.9)
	Idiopathic neonatal hepatitis	15 (16.3)
	Chromosomal disorder	14 (15.2)
	Infections	1 (1.1)
	Metabolic hepatopathy	22 (23.9)
	Others	7 (7.6)

Note. SD: Standard deviation.

Alagille criteria according to intrahepatic or extrahepatic causes are provided in **Table 2**. There was a significant difference between the two groups regarding gender, onset time of jaundice, and presence of the acholic stool (P=0.02, 0.04, and 0.005, respectively).

Table-2: Alagille Criteria According to Intrahepatic or Extrahepatic Causes

Variable		Intrahepatic Cholestasis (%)	Extrahepatic Cholestasis (%)	P-value
Gender (M/F)		39/19 (67.2/32.8)	15/19 (44.1/55.9)	0.02
Birth weight	< 2500 gr	16 (30.2)	6 (18.2)	0.2
	2500-4000 gr	35 (66)	27 (81.8)	
	>4000 gr	2 (3.8)	0	
Onset time of jaundice	< 2 week	37 (64.9)	26 (83.9)	0.04
	> 2 week	20 (35.1)	5 (16.1)	
Stool color	Bright	27 (64.3)	26 (92.9)	0.005
	Normal	15 (35.7)	2 (7.1)	
Size and consistency of the liver	Large Firm	32 (58.2)	25 (75.8)	0.07
	Normal	23 (41.8)	8 (24.2)	

Sensitivity, specify, and positive and negative predictive values were determined for each of the Alagille criteria (**Table 3**). The presence of the acholic stool had the highest sensitivity, specificity, and positive and negative predictive values.

Table-3: Sensitivity Specificity, Positive Predictive Value, and Negative Predictive Value for Each of the Alagille Criteria

Alagille Criteria	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
Birth weight	85%	33%	46%	77%
Onset time of jaundice	16%	35%	20%	58%
Color of stool	93%	64%	50%	88%
Size and consistency of liver	75%	58%	43%	74%

Based on the results, the presence of all Alagille criteria together had sensitivity, specificity, and positive and negative predictive values of 12, 91, 50, and 60% for the diagnosis of extrahepatic cholestasis, respectively.

4- DISCUSSION

Our study had some important findings. First, the infant's stool color had a high sensitivity for diagnosis of BA. In addition, the results of the current study showed that the presence of all Alagille criteria while having high specificity for the diagnosis of BA was not extremely sensitive indicating that the false negatives of the test are high and should be considered when making treatment decisions. There were few false positive results if all of the Alagille criteria together were present in a patient; so simultaneous presence of all Alagille criteria can be used as a tool for selection of patients as an appropriate candidate for intraoperative cholangiography.

Positive predictive value of each criterion was very low, similar to the presence of all of them. Although, the negative predictive value of each criterion was higher than the positive predictive value but it is not considerably high; so physicians cannot use it as a tool for rollout non BA etiology of neonatal cholestasis. Both positive and negative predictive values for presence of all criteria were very low. So the probability that patients with a positive screening test truly have BA is relatively low, similar to the probability that patients with a negative screening test truly don't have BA.

Among Alagille criteria, stool color had few false negative results, thus fewer cases of BA are missed; and so it can be used as a screening tool for diagnosis of BA. As we know, BA is a progressive disease and stool color may change from green to acholic during time. Two patients with BA, in our study with pigmented stools, were very young and so the diagnosis may have caught the disease early in its course. Lee and Chai, studying 146 infants with neonatal cholestasis of which 35 had BA, found stool color to be highly sensitive in BA (83%) but with less specificity (51%). They observed two patients with pigmented stools that become alcoholic later in the course of disease (9). Based on the report by Liu X et al., the sensitivity, specificity, and positive and negative predictive values of stool color for BA were 93.9, 59.8, 54, and 95%, respectively (10). In some countries there are universal screening programs using stool color cards (1, 11-15).

Occurrence of jaundice in infants <2 weeks was significantly higher in extrahepatic etiology (p=0.04). In a case-control study, the age at the onset of jaundice in patients with intrahepatic cholestasis was more than BA (16). Based on the findings of another study, there was no statistically significant difference in the age of the BA and non-BA groups at the onset of jaundice (2), although most studies had opposite results about age at the onset of jaundice (17, 18) . This

difference may be due to concurrency of physiologic jaundice with pathologic etiologies of jaundice, so it is difficult to determine accurate onset of jaundice.

In the present study, a significant difference was found between BA and intrahepatic cholestasis groups in terms of gender so that the rate of girls in the BA group was higher. Although Poddar et al. indicated that the percentage of boys in both BA and non-BA groups was higher than that of the girls (5), the results of the present study revealed that the presence of large and firm livers offers the possibility of BA, which is compatible with the findings of other studies (2, 14, 19).

Over the past few decades, extensive effort has been made to recognize BA using non-invasive methods. Several studies have previously reported the effectiveness of each of the applied parameters (13, 15, 20). It is believed that improving non-invasive diagnostic approaches is highly important, especially in the infancy period. El-guindi et al. presented a twelve-point scoring system according to clinical, laboratory, sonographic, and histopathological parameters that had high sensitivity and specificity for the diagnosis of BA from other causes (100%) (21). The results of this evaluation system were highly valuable. In comparison to this scoring system, Alagille criteria is a non-invasive method in order to identify patients with a high probability of BA.

In this study we evaluated the diagnostic accuracy of Alagille criteria for diagnosis of BA.

4-1. Limitations of the study

Our study had some limitations which may affect the interpretation of our results including the single-center design and the inclusion of a small number of patients. Therefore, we suggest multicenter studies with larger sample sizes for future research.

5- CONCLUSION

Overall, it seems that the presence of acholic stool, among all Alagille criteria, is the most valuable criterion for the diagnosis of BA.

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