

## The Value of <sup>99m</sup>Tc-EHIDA Hepatobiliary Scintigraphy with Different Liver/Kidney Ratio in the Distinguish of Infant Persistent Jaundice

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### Abstract

**Objective:** To evaluate the value of <sup>99m</sup>Tc-EHIDA hepatobiliary scintigraphy with different Liver/Kidney ratio (LKR) in the distinguish of infant persistent jaundice.

**Methods:** A total of 128 patients with infant persistent jaundice (45 females, with a mean age of 45.9 ± 23.4 d) underwent hepatobiliary scintigraphy were analyzed retrospectively. All patients were underwent to detecting their level of glutamyl transpeptidase (γ-GT) before hepatobiliary scintigraphy. We drawn the outline of same size region of interest in the near right of liver (L) edge and left kidney (K) at the ten minutes of hepatobiliary scintigraphy and calculated the ROI of liver to kidney ratios. The receiver operating characteristic (ROC) curve was used to analyze the threshold and calculate the sensitivity and specificity of γ-GT.

**Results:** The sensitivity, specificity and accuracy of hepatobiliary scintigraphy in the diagnosis of biliary atresia (BA) was 91.4% (32/35), 83.8% (78/93) and 85.9% (110/128), respectively. The LKR of (BA) group were slightly higher than infantile hepatitis syndrome (IHS) group ( $t_{2.23P}<0.05$ ). The LKR of between BA and IHS have no statistics significance ( $P>0.05$ , 1.17, 1.29, respectively). The AUC of serum γ-GT in diagnosis of BA is 0.87 according to the ROC curve, and the sensitivity and specificity of BA is 0.91 and 0.71, respectively. The accuracy of both methods was 91.5% when the LKR and γ-GT were combined to diagnosing the BA.

**Conclusions:** The <sup>99m</sup>Tc-EHIDA dynamic hepatobiliary scintigraphy has unique advantages in the differential diagnosis of persistent jaundice in infants. The comprehensive analysis of LKR combined with serum γ-GT can obvious improve the diagnosis value for persistent jaundice in infants.

**Keywords:** <sup>99m</sup>Tc-EHIDA; Hepatobiliary scintigraphy; Liver/kidney ratio; Persistent jaundice; Biliary atresia

**Abbreviations:** LKR: Liver/Kidney Ratio; BA: Biliary Atresia; IHS: Infantile Hepatitis Syndrome; γ-GT: Glutamyl Transpeptidase; ROC: Receiver Operating Characteristic

### Introduction

Persistent jaundice of infants usually occurs between after birth 2 days and 50 days, which is a common disease in neonates [1]. The two major pathogenesis of persistent jaundice in infants are biliary atresia (BA) and infantile hepatitis syndrome (IHS), which clinical manifestations are very similar so that it is difficult to differential diagnosis. However, the therapeutic schedule and disease prognosis of the two type patients were completely different, the former was treated with surgery, while the latter was treated with internal medicine medications to declining bilirubin [2]. Therefore, it is pretty important to being accurate differential diagnosis the two type patients. The aim of this paper is to analyze the value of <sup>99m</sup>Tc-EHIDA hepatobiliary scintigraphy with different liver/kidney ratio (LKR) and glutamyl transpeptidase (γ-GT) in persistent jaundice of infants.

### Materials and Methods

#### Patients

We retrospectively analyzed the hospitalized 128 infants with persistent jaundice and have accepted <sup>99m</sup>Tc-EHIDA hepatobiliary scintigraphy in June 2015 to April 2016. The selected patients included 83 males and 45 females, the age are between 20 days to 197 days, average 45.9 ± 23.4 days. All patients were identified diagnosis by making surgery and pathology or clinical treatment and follow-up at least 6 months. All patients have been underwent the test of serum bilirubin and γ-GT before hepatobiliary scintigraphy.

#### Hepatobiliary scintigraphy

**Imaging apparatus:** Double probe SPECT was produced by USA GE company Infinia Hawkeye 4; Photographic developer: <sup>99m</sup>TcO<sub>4</sub> (Beijing atomic high-tech Co. LTD, purity>95%), EHIDA (Jiangsu Institute of Atomic Medicine Jiangyuan Pharmaceutical Factory provided), dose of per patients 1.11~7.4 MBq/kg; The patient was required abrosia about 4 to 6 hours before examination and made the children sleeping using diazepam 15 minutes before the examination. The position was supine position. Immediately continuous collection

of anterior abdominal dynamic image after intravenous photographic developer, the imaging was collected as 20 frames, 1 frame/min. If the bowel can see distribution of radioactivity, the scan will be stopped. Otherwise, continue to collecting the static imaging of abdomen in 1 hour, 2 hour, 6 hour, respectively. Even extended to 24 hours.

### Imaging analysis

The image was analysed independently by two senior nuclear medicine physicians. If there isn't radioactive distribution in abdomen, the patient will be considered as BA. If not, the patient will be regard as IHS. We have drawn the outline of same size region of interest in the near right of liver (L) edge and left kidney (K) at the imaging of ten minutes of dynamic hepatobiliary scintigraphy and calculated the ratio of liver to kidney region of interest.

### Statistical analysis

The measurement data is showed with standard and deviation. Independent sample t-test was used to contrast for between groups data, and the diagnostic efficacy were evaluated with hepatobiliary scintigraphy LKR for BA. Besides, the value of  $\gamma$ -GT with ROC curve were analyzed and calculated the cutoff vauue and sensitivity and specificity, respectively. The significance level was 0.05 of the P analysis values. The SPSS version 20.0 was used to analyzing our data.

## Results

### Imaging results

By clinically diagnosed, we confirmed 35 patients of BA and 93 of IHS. 32 patients of BA group were not found imaging distribution at the abdomen in 24 hours, we renamed as group of BA I. Another patient of BA group can fund little imaging distribution at the abdomen in 24 hours, we renamed as group of BA II. In the IHS group, 15 patients abdomen had not radioactivity distribution in abdomen, we renamed as IHS I. It was renamed as IHS II that have 78 patients abdomen were found little radioactivity in the IHS group. The sensitivity, spcitivity and accuracy of hepatobiliary scintigraphy for BA is 91.4% (32/35, 83.8% (78/93 and 85.9% (110/128, respectively).

### The LKR and $\gamma$ -GT in the groups of between BA and HIS

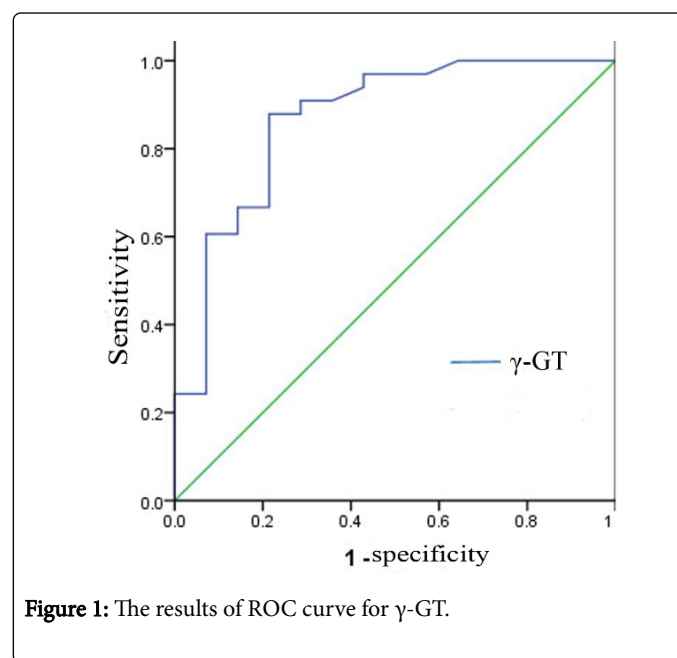
The LKR of BA group were slightly higher than IHS group ( $t=2.23, P<0.05$ ). However, The LKR of BA I group were obviously higher than IHS I group ( $t=3.62, P<0.05$ ). The LKR of between BA I and BA II and between HIS I and IHS II have no statistics significance ( $P>0.05, t=1.17, 1.29, respectively$ ) (Table 1). The level of  $\gamma$ -GT in the BA group was slightly higher than IHS, IHS I and IHS II (all  $P<0.05, respectively$ ). The level of  $\gamma$ -GT between BA I and BA II have no statistics significance ( $P>0.05, t=1.62, respectively$ ). The level of  $\gamma$ -GT between IHS I and IHS II have no statistics significance ( $P>0.05, t=1.62, respectively$ ) (Table 1).

### The results of ROC curve for $\gamma$ -GT

According to the ROC curve (Figure 1) showed the area under curve is 0.87. The sensitivity and specificity of  $\gamma$ -GT for BA is 91%, 71% when the value of cutoff is 192.5  $\mu$ l, respectively. The combination of the two methods to diagnose BA. The accuracy of both methods was 91.5% when the LKR and  $\gamma$ -GT were combined to diagnose the BA.

Groups	No. of patients (n)	LKR	$\gamma$ -GT
BA	35	1.26 $\pm$ 0.32	459.59 $\pm$ 352.01
BA	32	1.61 $\pm$ 0.28	486.58 $\pm$ 359.35
BA	3	1.17 $\pm$ 0.22	198.67 $\pm$ 5.51
IHS	93	1.16 $\pm$ 0.29	316.02 $\pm$ 263.73
IHS	15	1.06 $\pm$ 0.24	158.57 $\pm$ 131.43
IHS	78	1.18 $\pm$ 0.36	337.33 $\pm$ 284.18

**Table 1:** The LKR and  $\gamma$ -GT in the groups of between BA and IHS.



**Figure 1:** The results of ROC curve for  $\gamma$ -GT.

## Discussion

The BA and IHS are common etiology of persistent obstructive jaundice in infancy. However, the treatment principle and prognosis are completely different for BA and IHS [1]. Therefore, the accurate judgment for etiology is very important to improving the prognosis and survival rate of patients. The value is limited of conventional biochemical test because of its most results are the same. Cholangiography or percutaneous transhepatic cholangiography have a big clinical value, but their results reliability are being easy interference by bilirubin and the operation has certain risks for children. Recently, the hepatobiliary scintigraphy was considered as a safe, simple and effective non-invasive examination methods. However, according to some studies' results found that the diagnostic efficiency of hepatobiliary scintigraphy BA is inconsistent.

Chatzioannou et al. [2] reported that the sensitivity of hepatobiliary scintigraphy for BA was 100%, the specificity was 64.3%, and the accuracy was 85.6%. Besides, Norman et al. [3], thought that the sensitivity, spcitivity and accuracy of hepatobiliary scintigraphy for BA is 100%, 49.3% and 60.5% respectively. Ours study suggested that the sensitivity, spcitivity and accuracy of hepatobiliary scintigraphy for BA is 91.4%, 83.8% and 85.9, respectively. Meanwhile, ours conclusions are consistent with above two research's results. Besides,

the accuracy of both methods was 91.5% when the LKR and  $\gamma$ -GT were combined to diagnose the BA. Stipsanelli et al. [4] analyzed the diagnostic value of hepatobiliary scintigraphy with liver to heart ratios to distinguishing biliary atresia in infants. In this study, another index of hepatobiliary scintigraphy LKR were also assessed and was found to be different in the BA group and the IHS group for differential diagnosis in infants with persistent jaundice.

Patients with BA in age of 3 months have adequate liver reserve and the liver have stronger uptake ability for photographic developer and the rate of hepatocyte scavenging photographic developer was relatively stable, and the developer will continue remaining in liver [5]. So we couldn't find the radioactivity distribution in abdomen at 24 hours, and the kidney will be uptake the developer stronger. The ability of liver will decline for uptake the developer and the time of scavenging and passing bile duct will even more, when the liver functional damage of the patients with IHS. We couldn't find radioactivity distribution in biliary system, and the only discharge path is the kidney at this moment. Therefore, the contrast between liver and kidney in BA is even stronger than IHS. Shan et al. [6] suggested that 70% patients with IHS have kidney uptake radioactivity becoming stronger, and all patients' liver absorbed the developers are poor.

In our study, we found 15 patients of false positive, it maybe that the severely damaged hepatocytes are slower to clear and remove developer, and the abdomen has a few radioactivity and even has no radioactivity. Hence, if the abdomen can see radioactive distribution, we will exclude the patient as BA. But, if not, we cannot exclude the patient as IHS [7].

The  $\gamma$ -GT is produced by the mitochondria of hepatocytes and is confined to cytoplasm and epithelial cells of intrahepatic bile duct. When the intrahepatic or extrahepatic duct was obstructed, the  $\gamma$ -GT excretion is blocked, and the longer the blocking time and the greater the degree of obstruction, the greater the increasing of the  $\gamma$ -GT is [4]. In our study, it has certain significance of  $\gamma$ -GT for differential diagnosis of BA, and the level of  $\gamma$ -GT with BA group is higher than IHS group. Meanwhile, the sensitivity and specificity of  $\gamma$ -GT for BA is 91% and 71% when the value of cutoff is 192.5  $\mu$ /l, respectively. It shows that the sensitivity of  $\gamma$ -GT is high, but the specificity slightly lower. Rendón-Macías et al. [8] concluded that the  $\gamma$ -GT had all increased in various degrees at the BA and IHS. At the same time, in

the condition that the intestinal tract does not develop, they will consider as BA when they  $\gamma$ -GT more than 150  $\mu$ /l; whereas they will consider as IHS. The sensitivity of this method to diagnose biliary atresia was 91.7% and specificity was 88%. The BA and IHS may be different manifestations of the same disease changing. Some patients with IHS will develop to BA when their condition becoming worse.

## Conclusions

The 99mTc-EHIDA dynamic hepatobiliary scintigraphy has unique advantages in the differential diagnosis of persistent jaundice in infants. The comprehensive analysis of LKR combined with serum  $\gamma$ -GT can obviously improve the diagnosis value for persistent jaundice in infants.

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