Rapid Diagnosis of Biliary Atresia in Infants, a Multicenter Retrospective Analysis

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Abstract

Background: Although the laboratory and imaging examinations of Biliary atresia (BA) has improved, some patients have not received timely diagnosis and treatment.

Methods: 200 infants with BA and intrahepatic cholestasis(IC) from three centers were included in this study. Before an operation, the stool color and liver function were compared in infants with BA and IC within 90 days.

Results: There were 115 patients with BA and 85 patients with IC seeing doctors within 90 days of age. The incidence rate of clay-colored stool, light-colored stool, and normal stool in the two groups was 58.3% *vs.* 17.7%, 39.1% *vs.* 65.9%, and 2.6% *vs.* 16.5%, and the difference was statistically significant (P<0.001). Compared with IC, the direct bilirubin (Dbil) and gamma glutamine transpeptidase (GGT) of BA was higher (P_{Dbil} =0.022, P_{GGT} <0.001). According to ROC curve analysis, combined clay-colored stool, Dbil>75.3 umol/L and GGT>252 U/L, BA was diagnosed (AUC=0.911; 95% CI, 0.870 to 0.952), with the sensitivity of 88.7% and specificity of 80.0% was better than the single diagnosis (P<0.001).

Conclusion: For infants within 90 days of age, stool color, Dbil, and GGT are simple and effective diagnostic indicators in BA.

Background

Biliary atresia (BA), a disease of unknown etiology, often involves intrahepatic and extrahepatic bile ducts, causing progressive fibrosis and inflammation of the intrahepatic and extrahepatic bile ducts, leading to hepatic fibrosis and bile duct obstruction eventually[1, 2]. BA can progress to cirrhosis, liver failure, and eventually death without being treated timely and effectively. Even if the bile drainage in patients is regained through Kasai surgery procedure, the disease will continue, and 75% of patients will eventually require liver transplantation[3]. Kasai surgery enables partial infants with BA to obtain bile drainage and prolong the survival time of the autologous liver. The operative time of Kasai surgery is usually within 90 days of birth, and the effect of bile drainage in Kasai surgery after 90 days of birth is reduced[4, 5]. At present, more and more laboratory and imaging examinations are applied for BA diagnosis. However, not all medical institutions have detective conditions completely. Some infants still miss the best time for surgery due to the late consultation or repeated consultation to several hospitals. Therefore, it is important to explore a simple and effective BA diagnosis for obtaining early treatment in infants[6].

Methods

General information in the patient

In this multicenter retrospective analysis, the clinical data from 248 infants with BA and intrahepatic cholestasis(IC) were collected in the First Affiliated Hospital of Guangxi Medical University, Hainan Women and Children's Medical Center and Hainan General Hospital from January 2017 to December 2019. Five cases were excluded due to preoperative complicated pneumonia and septicemia. Forty-three of the 248 infants with BA and IC (17.3%) were excluded due to older than 90 days at the consultation time. A total of 200 infants are involved in the study, as shown in Figure 1.

Inclusion and exclusion criteria

Inclusion criteria: (1) Infants with BA and IC admitted to the First Affiliated Hospital of Guangxi Medical University, Children's Hospital of Fudan University at Hainan, and Hainan General Hospital from January 2017 to December 2019; (2) A baby who has been treated by surgery; (3) Whether or not undergone conservative treatment (including steroid hormones, ursodeoxycholic acid, liver protection) before surgery.

Exclusion criteria: (1) Infants with severe infections in other parts of the body before operation; (2) Infants older than 90 days at the operative time.

Preoperative treatment, surgical procedures, and the diagnostic gold standard

Before the operation, the patients were routinely given liver protection therapy, including reduced glutathione, ademetionine, compound glycyrrhizin, et al. BA was confirmed through intraoperative biliary tract exploration and cholangiography. The morphology of the gallbladder and extrahepatic bile duct was fibrotic, or the left and right hepatic ducts and common bile ducts were not shown after contrast agents were injected into the gallbladder, confirming the diagnosis of BA. During the operation of BA, hepatic fiberboard resection and Roux-en-Y portoenterostomy were adopted, while patients with IC had cholecystostomy with an indwelling drainage tube at the bottom of the gallbladder.

Observation indicators and grouping

Patients can be divided into BA and IC groups according to the intraoperative results of bile duct exploration and cholangiography. Two groups were compared before surgery on whether patients had conservative treatment (including steroid hormones, ursodeoxycholic acid, and liver protection), stool color (including three colors: clay-colored stool, light-colored stool, and normal stool), and liver function (including total bilirubin [Tbil], direct bilirubin [Dbil], gamma glutamine transpeptidase [GGT], total bile acid [TBA], alanine aminotransferase [ALT], aspartate aminotransferase [AST] and alkaline phosphatase [ALP]).

Statistical analysis

The statistical efficacy of this diagnostic test was estimated before statistical analysis. The study achieved statistical efficacy at 93% and 5% significance level in diagnostic tests with the assumption of the area under the curve (AUC) was at least 0.64. In this study, GGT and ALP had some missing values which could be filled multiply through the fully conditional specification. The robustness of the multiple imputation results was tested by sensitivity analysis. Disease diagnosis, stool color, Tbil, Dbil, GGT, TBA, ALT, AST, and ALP were included in the model to fill missing values that were supposed to miss at random. In this study, comprehensive values of 20 fillings were calculated with Rubin's rule.

Each indicator was reported with descriptive statistics. The comparison of continuous variables was explored with Student's t-test. The comparison of categorical variables was explored with χ^2 test and Cochran-Mantel-Haenszel test. The other two groups were combined to evaluate the stool rate ratio, and the results were point estimation and 95% confidence interval (CI). The relationship between liver function and age was analyzed by a linear regression model. The receiver operating characteristics (ROC) curve was adopted to determine the cut-off values of the continuous variables, which were selected with the Youden index. All tests were bilateral with a statistically significant difference ($P<0.05$). All statistics were analyzed with SAS 9.4 software.

Results

General information about the subjects

Of the 248 infants with BA and IC, 43 cases (17.3%) were older than 90 days for consultation in the hospital. Of the 200 infants, 115 cases (57.5%) had BA, and 85 cases (42.5%) had IC for consultation within 90 days. BA group had 59 males (51.3%) and 56 females (48.7%). IC group had 62 males (72.9%) and 23 females (27.1%).

Comparison of Stool color between BA and IC

The incidence rate of clay-colored stool, light-colored stool, and normal stool in the BA group and the IC group was 58.3% *vs.* 17.7%, 39.1% *vs.* 65.9%, and 2.6% *vs.* 16.5%, with statistically significant differences ($P<0.001$). The incidence of clay-colored stool in the BA group is 2.3 times higher than IC group (rate ratio, 3.3; 95% CI, 2.0 to 5.4), the rate ratio of light-colored stools is 0.59 (95% CI, 0.45 to 0.78), and the rate ratio of normal stools is 0.16 (95% CI, 0.05 to 0.53), as shown in Table 1 and Figure 2.

Table 1
Comparison of stool color and liver function between BA and IC

Characteristics	**BA group (115)**	**IC group (77)**	***P* values**
liver function			
Tbil	168.9±47.5	163.7±66.7	0.542
Dbil	117.9±34.1	104.2±46.4	0.022
GGT	643.9±444.3	183±173.7	<0.001
TBA	143.8±38	140.6±73.4	0.717
ALT	134.8±96.4	171.9±131	0.029
AST	215.7±150.4	245.1±168.4	0.195
ALP	588.2±441.7	564.8±213.5	0.621
stool color			
Clay-colored stool	67(58.3%)	15(17.7%)	<0.001
Light-colored stool	45(39.1%)	56(65.9%)	
Normal stool	3(2.6%)	14(16.5%)	

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BA, biliary atresia; Dbil, direct bilirubin; GGT, gamma glutamine transpeptidase; IC, intrahepatic cholestasis; TBA, total bile acid; Tbil, total bilirubin.

Comparison of liver function between BA and IC

There were 103 infants (89.6%) with BA receiving conservative treatment before surgery, while 77 (90.6%) infants with IC receiving conservative treatment before surgery, with a difference of -1 percentage points (95% CI, -9.4–7.3%; *P*=0.812). Dbil of BA and IC groups were 117.9±34.1 umol/L *vs.* 104.2±46.4 umol/L with the mean difference (13.8 umol/L; 95% CI, 2.0 to 25.5 umol/L; *P*=0.022) was statistically significant. GGT of the two groups was 643.9±444.3 U/L *vs.* 183.0±173.7 U/L with the mean difference (406.9U/L; 95% CI, 371.0 to 550.8 U/L; *P*<0.001) was statistically significant. ALT of the two groups were 134.8±96.4U/L *vs.* 171.9±131U/L with the mean difference (-37.2 U/L; 95% CI, -70.4 to -3.9 U/L; *P*=0.029) was statistically significant. There is no statistically significant difference in Tbil, TBA, AST, and ALP between the two groups, as shown in Table 1 and Figure 2.

The relationship of Dbil, GGT, ALT, and age

Figure 3 shows no significant change (R^2=0.030, *P*=0.063; R^2=0.005, *P*=0.508) in Dbil of the BA group and IC group with the increase of age. GGT increases in the BA group (R^2=0.106, *P*<0.001), but the IC group has no significant change (R^2=0.007, *P*=0.935) with the increase of age. ALT of the BA group and IC group shows no significant change (R^2=0.003, *P*=0.532; R^2=0.024, *P*=0.153) with the increase of age.

Combined diagnosis of BA with single factor and multi-factor

Dbil=75.3 umol/L (area under the curve [AUC]=0.642) was cut-off as a diagnostic criterion according to ROC curve analysis, with a sensitivity of 94.8% and specificity of 34.1%. GGT=252 U/L (AUC=0.885) was cut-off as a diagnostic criterion, with a sensitivity of 79.1% and specificity of 85.9%. clay-colored stool (AUC=0.727) was cut-off as a diagnostic criterion, with a sensitivity of 58.3% and specificity of 82.4%. ALT=158U/L (AUC=0.569) was cut-off as a diagnostic criterion, with a sensitivity of 77.4% and specificity of 43.5%. The diagnostic value of ALT was not high. Combining stool color, Dbil and GGT diagnosis of BA (AUC=0.911; 95% CI, 0.870 to 0.952), with a sensitivity of 88.7% and specificity of 80.0%, are better than the single diagnosis by ROC curve (*P* <0.001), as shown in Table 2 and Figure 4.

Table 2
ROC curve analysis

Value	Cut-off	AUC	Sensitivity	Specificity
Dbil(ROC1)	75.3umol/L	0.642	94.8%	34.1%
GGT(ROC2)	252U/L	0.885	79.1%	85.9%
Stool color(ROC3)	Clay-colored stool	0.727	58.3%	82.4%
Model		0.911	88.7%	80.0%

The model is combining stool color, Dbil and GGT diagnosis of BA. Dbil, direct bilirubin; GGT, gamma glutamine transpeptidase.

Red curve (ROC1) show diagnostic accuracy of BA basing on Dbil (AUC=0.642). Green curve (ROC2) show diagnostic accuracy of BA basing on GGT (AUC=0.885). Brown curve (ROC3) show diagnostic accuracy of BA basing on stool color (AUC=0.727). Blue curve show combining stool color, Dbil and GGT diagnosis of BA (AUC_{model}=0.911; 95% CI, 0.870 to 0.952), with a sensitivity of 88.7% and specificity of 80.0%, are better than the single diagnosis by ROC curve (*P* <0.001). AUC, area under the curve; BA, biliary atresia; Dbil, direct bilirubin; GGT, gamma glutamine transpeptidase; IC, intrahepatic cholestasis.

Sensitivity analysis

The mean GGT of the two groups were 643.9 U/L *vs.* 180.1 U/L before multiple imputations with the statistically significant difference (463.8 U/L; 95% CI, 373.6 to 553.9U/L; *P*<0.001). The mean ALP of the two groups were 587.9 U/L *vs.* 562.3 U/L with a not statistically significant difference (25.5 U/L; 95% CI, -71.0 to 122.1 U/L; *P*=0.602).

After multiple imputations, the mean GGT of the two groups were 643.9 U/L *vs.* 183.0 U/L with the statistically significant difference (406.9 U/L; 95% CI, 371.0 to 550.8 U/L; *P*<0.001). The mean ALP of the two groups were 588.2 U/L *vs.* 564.8 U/L with a not statistically significant difference (23.4 U/L; 95% CI, -69.9 to 116.6U/L; *P*=0.621). The missing data of GGT and ALP were still in accord with the results under the assumption of missing at random after multiple imputations, proving that the analysis results under multiple imputations were reliable.

Discussion

BA is a fibrotic inflammation involving the intrahepatic and extrahepatic bile ducts, causing intrahepatic and extrahepatic biliary obstruction, leading to liver cirrhosis and end-stage liver disease about 2 years old[1, 2]. The global incidence rate of BA was ranged from 0.2/10,000 to 0.6/10,000. Occidente was from 0.5/10,000 to 0.8/10,000. Taiwan was estimated to be about 1.5/10000[7−9]. Bile drainage can be achieved by Kasai portoenterostomy, a preferred treatment for BA currently, for some infants to extend the survival time of the autologous liver. However, the best time for the operation is within 60 days after birth, and the latest time should not exceed 90 days. After surgical treatment of BA in infants over 90 days, the rate of removing jaundice is significantly descended, and direct liver transplantation is recommended[4, 5]. In this study, 19.4% of infants missed Kasai surgery treatment because their parents did not pay attention to this disease or repeated visits to several hospitals for treatment. A simple method of judging BA may help patients get diagnosis and treatment sooner.

Serum Dbil is an indicator of liver injury. Elevated Dbil indicates hepatic dysfunction or IC, with impaired bile flow[10]. The GGT in the liver is mainly in the side of the hepatocyte capillary bile duct and the whole bile duct system. Elevated GGT indicates biliary obstruction disease and liver injury[11]. Dbil gradually increases after the birth of the newborn. In western countries, early detection of BA through Dbil measurement has been advocated [12, 13]. In Japan and China Taiwan, it is advocated to use the stool color card for early BA diagnosis, which has improved the autologous liver survival rate of infants with BA[14, 15]. The Chinese mainland uses Dbil and GGT as indicators for early BA detection, for their high sensitivity and specificity in diagnosis [16].

Sanjiv Harpavatet et al.[17] performed a two-stage Dbil screening on 124,385 newborns after birth. In the first stage, newborns within 60 hours after birth were tested for Dbil. In the second stage, newborns with more than 95% Dbil were screened again in the next two weeks. It was found that patients with BA had higher Dbil than the reference range, with a sensitivity of 100%, specificity of 99.9%. The results confirmed that Dbil is a valuable indicator of the BA diagnosis. According to reports[16], for infants within 90 days with obstructive jaundice, when GGT>328 U/L, BA should be considered, with a sensitivity of 69.7% and a specificity of 83.9%. Dillman JR et al.[18] determined a sensitivity of 100.0% and a specificity of 77.8% for the diagnosis of BA in infants within three months with obstructive jaundice. In Japan, the stool color card is used for early BA screening. This method reduces the mean age of Kasai surgery for BA infants from 68.2 days to 59.7 days and increases the 12-year autologous liver survival rate from 36.6–48.5%[19]. China Taiwan has enabled more infants to receive early diagnosis and treatment using the stool color card and has reduced the mortality rate of BA infants from 26.2–15.9% [20]. These studies have confirmed the importance of stool color, Dbil, and GGT in the early diagnosis of BA.

This study combined the above factors to explore a simple and effective method for BA diagnosis. Infants with BA and IC aged less than 90 days were selected as observation subjects. The stool color card divides stool colors into 9 kinds, but there was certain subjectivity in judgment. It was difficult to popularize in practice. The stool color was divided into 3 categories, including clay color, light color, and normal color. In this study, 90.6% IC and 89.6% BA infants underwent conservative treatment (including steroid hormones, ursodeoxycholic acid, liver protection) with no significant differences between the two groups. It was observed that 58.3% BA infants had clay-colored stools. Dbil and GGT of BA infants were higher than those of IC infants, and the GGT of BA infants increased with the increase of age. In this study, infants with clay -colored stool had a 2.3 times higher rate of BA than IC, with a specificity of 82.4%, which was possibly be related to the degree of extrahepatic biliary obstruction. Infants with Dbil>75.3umol/L had high sensitivity (94.8%) but low specificity (34.1%) in the BA diagnosis because BA jaundice is more severe than IC. Infants with GGT > 252U/L had a high specificity (85.7%) in the BA diagnosis. Generally, liver injury and cirrhosis are more serious in BA, which is possibly be related to the high specificity of GGT. There are some limitations in the clinical diagnosis of diseases by a single index. The three factors combined diagnosis can improve the accuracy of BA diagnosis. In this study, the combination of clay-colored stool, Dbil > 75.3 umol/L, and GGT > 252 U/L BA diagnosis can reach an 80.0% specification and a 91.1% accuracy. This study emphasizes simplicity and effectiveness in diagnosis. Generally, Dbil and GGT are easy to obtain, which can be quickly tested in medical institutions. This approach allows more jaundiced infants to be diagnosed early and receive treatments early.

There are some limitations of this study. Because some parents did not agree with screening for genetic metabolic liver disease, the IC genetic metabolic liver disease might have had a certain impact on the study results. The early diagnosis and treatment of BA still have a long way to go because of different medical conditions and attention to the disease.

Conclusion

BA should be diagnosed and treated early. For infants within 90 days, stool color, Dbil, and GGT are simple and effective diagnostic indicators.

Abbreviations

AUC, area under the curve; BA, biliary atresia; Dbil, direct bilirubin; GGT, gamma glutamine transpeptidase; IC, intrahepatic cholestasis.; TBA, total bile acid; Tbil, total bilirubin; ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

Declarations

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Availability of data and materials

The dataset used and analyzed during this study are available from the first author upon reasonable request.

Authors’ Contributions

J.L. and Q.D. participated in research design. K.D. and J.Z. performed the research. J.L., M.J. and C.F. participated in data collect and analysis. J.L. and C.D. wrote the paper. Y.W. prepared the figure. C.D. provided critical revision of the manuscript.

Ethics approval and consent to participate

All the methods of this study were performed in accordance with relevant guidelines and hospital regulations. Written informed consent were signed from parent or guardian for participants under 16 years old.

Consent for publication

Not applicable.

Competing interests

The authors declare no conflicts of interest.

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Figures

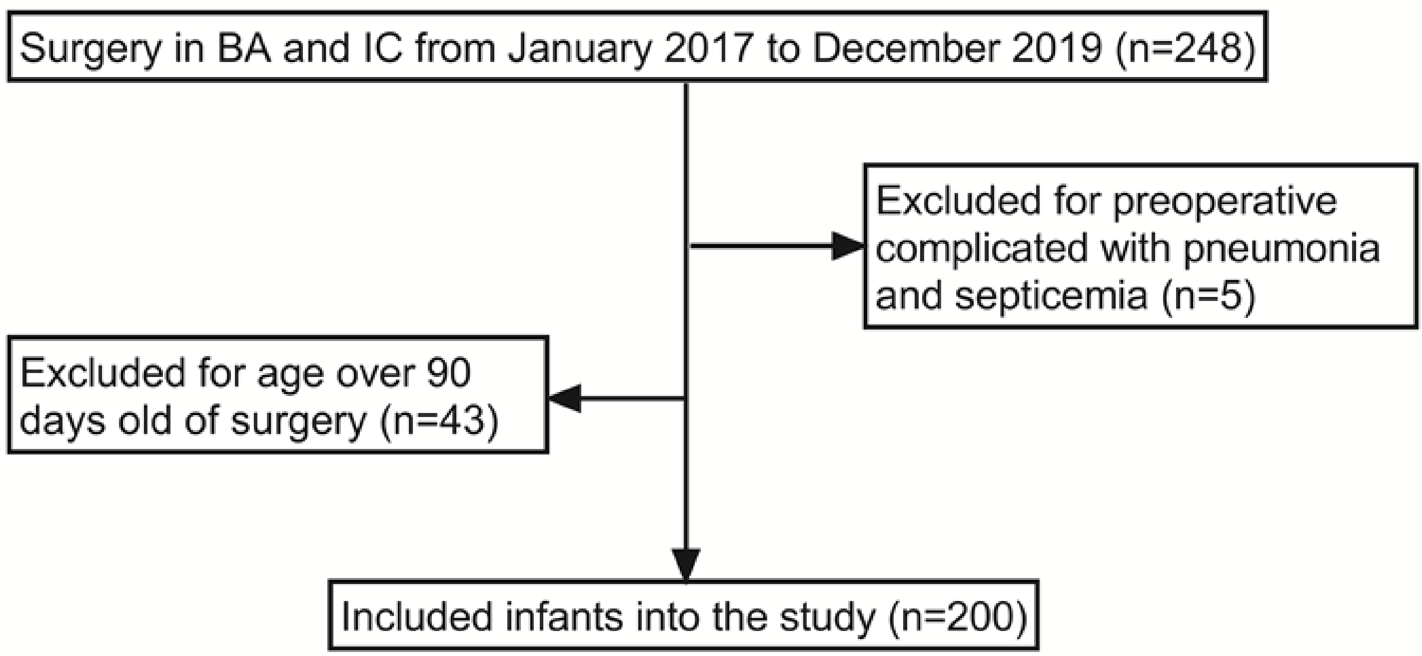

Figure 1

Flowchart of the study BA, biliary atresia; IC, intrahepatic cholestasis.

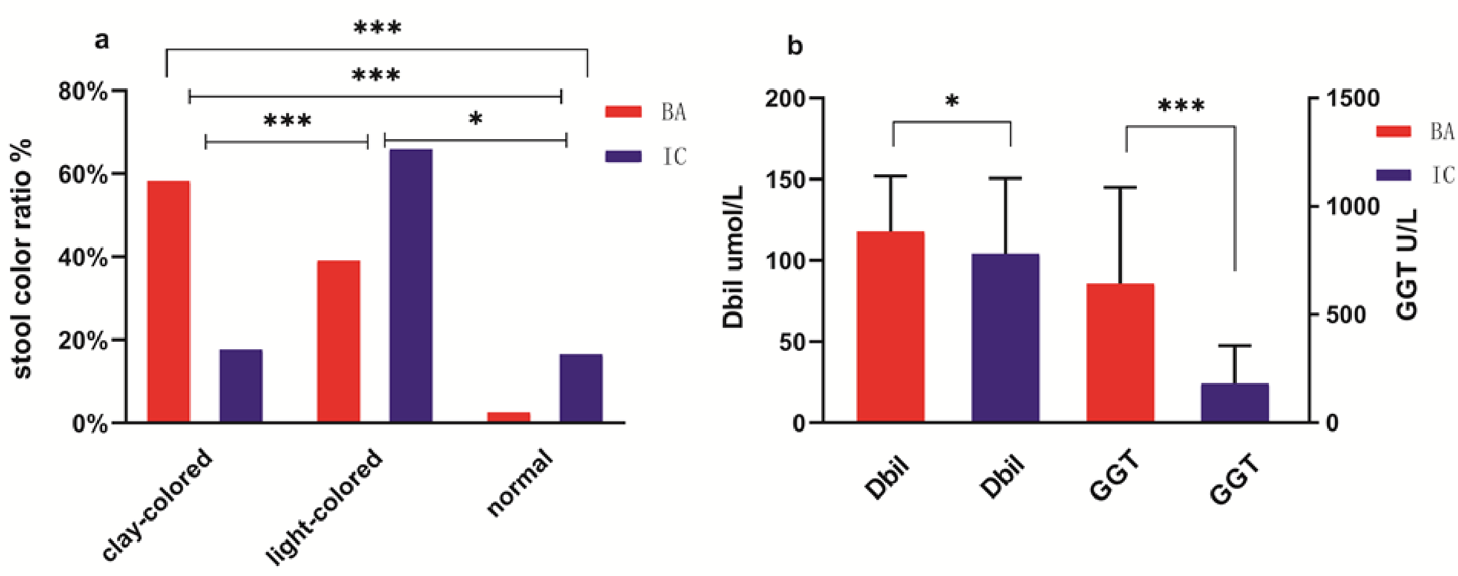

Figure 2

Comparison of stool color, Dbil and GGT between BA and IC group. a The incidence rate of clay-colored stool, light-colored stool, and normal stool in the BA group and the IC group is 58.3% vs. 17.7%, 39.1% vs. 65.9%, and 2.6% vs. 16.5%, with statistically significant differences. b Dbil of the BA group and IC group are 117.9±34.1 umol/L vs. 104.2±46.4 umol/L, and GGT of the two groups is 643.9±444.3 U/L vs. 183.0±173.7 U/L. * means P <0.05, *** means P <0.001. BA, biliary atresia; IC, intrahepatic cholestasis.

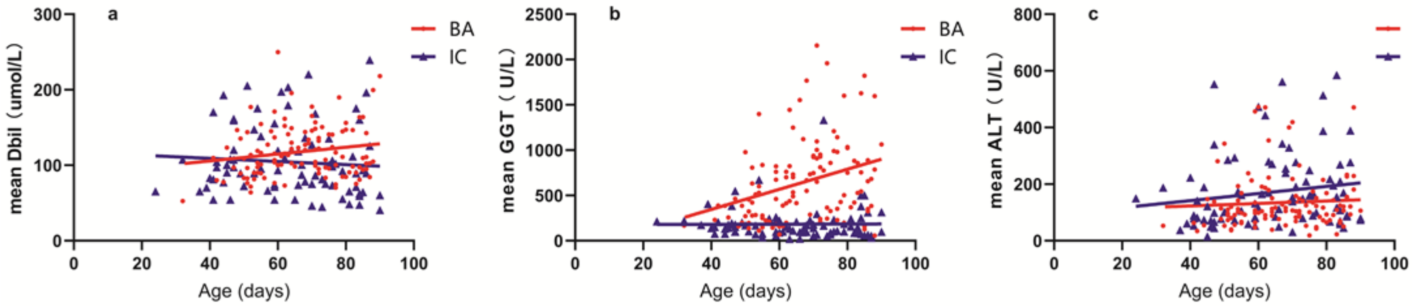

Figure 3

Regression line between Dbil, GGT, ALT, and age in BA and IC groups a Dbil of the BA group and IC group has no significant change (R2=0.030, P=0.063; R2=0.005, P=0.508) With the increase of age. b GGT increases in the BA group (R2=0.106, P<0.001), but the IC group has no significant change (R2=0.007, P=0.935) with the increase of age. c ALT of the BA group and IC group shows no significant change (R2=0.003, P=0.532; R2=0.024, P=0.153) with the increase of age. ALT, alanine aminotransferase; BA, biliary atresia; Dbil, direct bilirubin; GGT, gamma glutamine transpeptidase; IC, intrahepatic cholestasis.

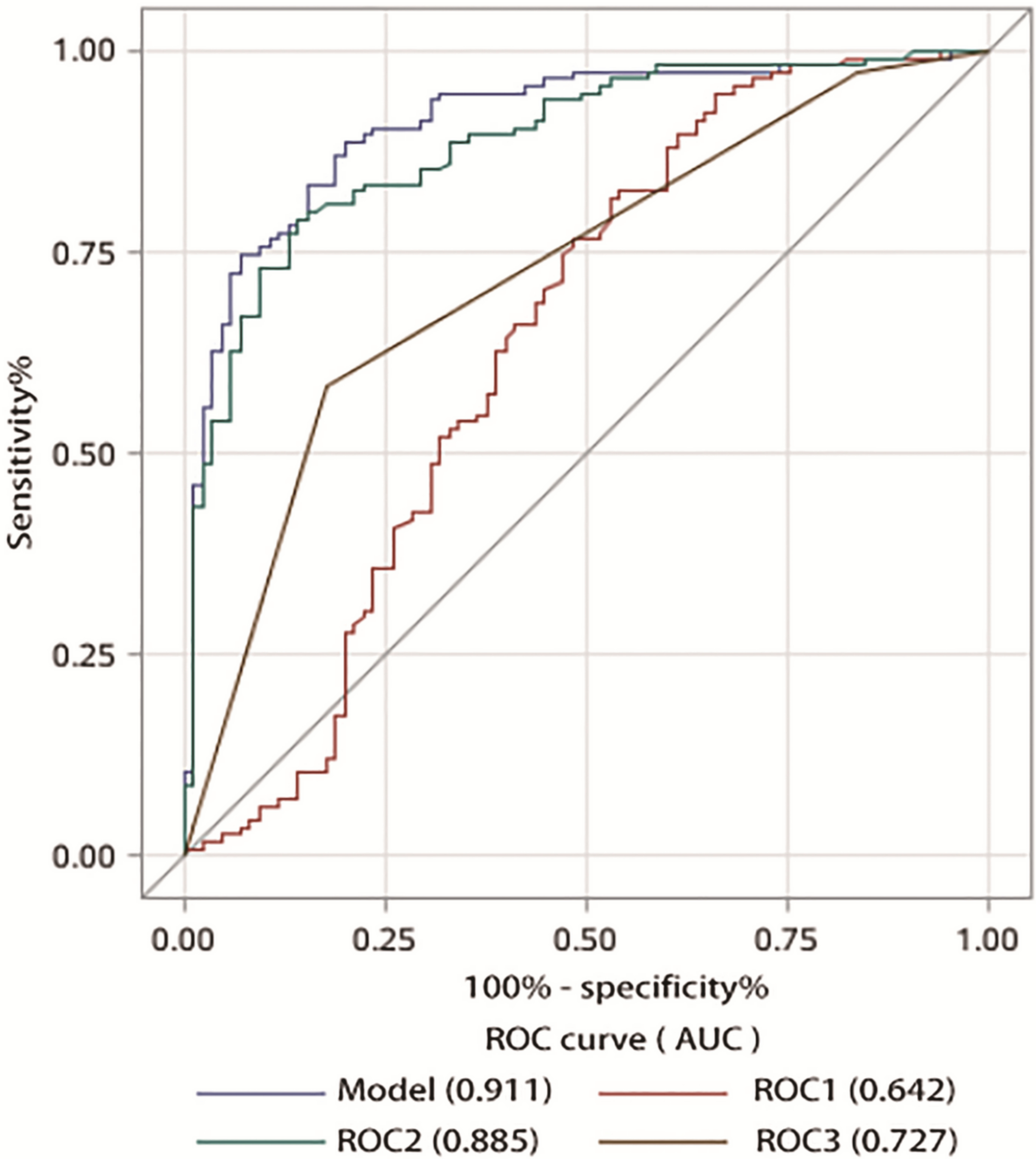

Figure 4

ROC curve of single-factor and multi-factor combination Red curve (ROC1) show diagnostic accuracy of BA basing on Dbil (AUC=0.642). Green curve (ROC2) show diagnostic accuracy of BA basing on GGT (AUC=0.885). Brown curve (ROC3) show diagnostic accuracy of BA basing on stool color (AUC=0.727). Blue curve show combining stool color, Dbil and GGT diagnosis of BA (AUCmodel=0.911; 95% CI, 0.870 to 0.952), with a sensitivity of 88.7% and specificity of 80.0%, are better than the single diagnosis by ROC curve (P <0.001). AUC, area under the curve; BA, biliary atresia; Dbil, direct bilirubin; GGT, gamma glutamine transpeptidase; IC, intrahepatic cholestasis.