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Research Paper

Development and Validation of Novel Diagnostic Models for Biliary Atresia in a Large Cohort of Chinese Patients

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ABSTRACT

Background & aims: The overlapping features of biliary atresia (BA) and the other forms of neonatal cholestasis (NC) with different causes (non-BA) has posed challenges for the diagnosis of BA. This study aimed at developing new and better diagnostic models for BA.
Methods: We retrospectively analyzed data from 1728 newborn infants with neonatal obstructive jaundice (NOJ). New prediction models, including decision tree (DT), random forest (RF), and multivariate logistic regression-based nomogram for BA were created and externally validated in an independent set of 508 infant patients.
Results: Fiver predictors, including gender, weight, direct bilirubin (DB), alkaline phosphatase (ALP), and gamma-glutamyl transpeptidase (GGT) were significantly different between the BA and non-BA groups ($P < .05$), from which DT, RF, and nomogram models were developed. The area under the receiver operating characteristic (ROC) curve (AUC) value for the nomogram was 0.898, which was greater than that of a single biomarker in the prediction of BA. Performance comparison of the three diagnostic models showed that the nomogram displayed better discriminative ability (sensitivity, 85.7%; specificity, 80.3%; PPV, 0.969) at the optimal cut-off value compared with DT and RF, which had relatively similar high sensitivity and PPV (0.941 and 0.947, respectively), but low specificity in the modeling group. In sub-analysis of the discriminative capacity between the nomogram and GGT (<300 or ≥ 300), we found that the nomogram was superior to the GGT alone in the preoperative diagnosis of BA.
Conclusions: The nomogram has demonstrated better performance for the prediction of BA, holding promise for future clinical application.

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Research in Context

Evidence Before This Study

Gamma-glutamyl transpeptidase (GGT) has been proposed as a serum marker for differentiating biliary atresia (BA) from neonatal hepatitis in the disease diagnosis. However, the reliability and reproducibility of serum GGT activity alone were limited in an accurate diagnosis of BA.Added Value of This Study

This study of a large cohort of Chinese infant patients has developed and validated a novel nomogram using GGT in combination with other BA-related factors for better diagnosis of BA.Implications of All the Available Evidence

The results demonstrate that this nomogram is superior to the GGT alone in the preoperative diagnosis of BA, and thus holds promise in the clinical application to better predict BA in newborn infants.

1. Introduction

Biliary atresia (BA) is an uncommon, but serious disorder in newborn infants, which is characterized by the obstruction of extra- or intra-hepatic bile ducts [1–4]. If left undiagnosed and untreated, BA can rapidly progress into biliary cirrhosis and hepatic failure, which will require liver transplantation, and can even lead to death within 2–3 years after birth, in a proportion of BA patients [5–8]. Although this disease rarely occurs among infants worldwide, the incidence of BA is high in the Asia-Pacific region.

Currently in Eastern Asia, BA has an overall incidence of approximately 1.51 in 10,000 live births, which is markedly greater than that in the United States [1–3]. In fact, in our hospital, which is one of the largest pediatric hospitals in China, as many as 400 infant patients per year are diagnosed with BA. A majority of these patients received the Kasai operation and postoperative conventional treatment with medications (e.g. antibiotics, hormones, ursodeoxycholic acid). In our previous study, a two-year survival rate was 53.7% in BA patients surviving with their native livers, while the remaining BA patients required subsequent liver transplantations, but the two-year survival rates of these patients were unavailable because of difficulty in patient tracking [9]. The key to restoring the flow of the bile ducts and obtaining good clinical outcomes is diagnosing and treating the disease early. However, the misdiagnosis of BA can result in inappropriate treatment and unnecessary surgery [10–15]. In our previous study, we retrospectively analyzed data obtained from 602 BA surgery cases, of which only 86% were postoperatively confirmed with BA by pathological studies [16]. Therefore, it is critical to establish reliable models for the early detection and diagnosis of BA. Unfortunately, the definitive diagnosis and confirmation of BA in suspected infants generally requires a liver biopsy and intraoperative cholangiography (IOC) during the surgical procedure, and these diagnostic methods have turned out to be invasive, time-consuming, and costly [6, 17–20]. Obviously, there is an urgent need for a reliable and better diagnostic approach to distinguish BA from other form of neonatal cholestasis (NC) with different causes.

Serum activity of gamma-glutamyl transpeptidase (GGT), as a non-invasive marker, has been extensively studied and proposed for the diagnosis of BA [21–28]. In fact, GGT >300 U/L, or a daily increase in its serum activity of 6 U/L for differentiating BA from neonatal hepatitis, had an accuracy of 85% and 88%, respectively [22]. El-Guindi and colleagues reported that the serum activity of GGT at a cutoff value (>286 U/L) had a sensitivity of 76.7% and specificity of 80% for the diagnosis of BA [29]. In our previous study, GGT activity in serum also showed good performance ability in discriminating BA from other causes in the Chinese population [21]. However, the reliability, accuracy, and reproducibility of GGT activity alone was questionable. For example, it has been demonstrated that healthy infants at birth have higher levels GGT [23], and the normal range for levels of GGT may vary dependent of age. Indeed, GGT corrected with age has shown improvement in the accuracy of predicting BA. Until now, diagnostic models using GGT in combination with other BA-related factors, which are anticipated to offer a better approach for the diagnosis of BA, have not been developed and evaluated for the diagnosis of BA.

In the present study, the demographic, clinical, and laboratory data from a large-scale of infant patients with neonatal obstructive jaundice (NOJ) were analyzed to examine the association between a number of risk factors and BA. New prediction models, including decision tree (DT), random forest (RF), and multivariate logistic regression-based nomogram were developed and validated for the diagnosis of BA. The results obtained through this study may offer a novel and better algorithm for the diagnosis of BA and hold potential for clinical application.

2. Patients and Methods

2.1. Human Subjects and Study Design

In this study, demographic, clinical, and laboratory test data of 1728 infant patients with NOJ between January 2012 and December 2017 at the Children's Hospital of Fudan University were collected, reviewed, and analyzed. Of these, 1512 patients with BA were assigned to the BA group, while 216 patients had other causes of NC, including 196 patients with neonatal hepatitis, 10 with alagille syndrome, and 8 with biliary hypoplasia, who were allocated to the non-BA group. Intraoperative cholangiography and subsequent histological examination of liver biopsies were used for diagnostic confirmation of BA and non-BA. The following inclusion criteria for BA patients were used with intent in this study: (1) Pediatric patients were diagnosed as BA by intraoperative cholangiography in combination with histological features of liver biopsies, showing ductular proliferation, canalicular and cellular bile stasis, portal or periportal inflammation, swelling and vacuolization of biliary epithelial cells, edema and monocytic inflammatory cell infiltration of portal tracts, fibrosis with the presence of bile plugs in the portal tract bile ducts, hepatocyte ballooning, and end-stage cirrhosis; (2) No other severe systematic deformity was present, such as BA splenic malformation syndrome. The inclusion criteria for pediatric patients with cholestasis were cholestasis without BA, as confirmed by intraoperative cholangiography, and no other severe malformation in other systems. Infants who had bile duct dysplasia and/or malformation of other systems were excluded from the current study.

This study was reviewed and approved by the Institutional Review Board (IRB) at the Children's Hospital of Fudan University, with a waiver of requirement for informed consent due to the nature of this retrospective study. The study was performed in compliance with the Declaration of Helsinki, and other relevant regulations.

2.2. Development and Validation of Decision Tree Model, Random Forest Model, and Logistic Regression-based Nomogram for the Diagnosis of BA

Decision tree (DT) was conducted via R package *rpart*, and a DT plot was drawn via *rattle* package. In brief, the root node asked, or the first question: Was ln(GGT) <4.8 in the patient? In generation of classification trees, “no” indicated a branch to the right, while “yes” represented a branch to the left. Terminal nodes were eventually for the prediction of BA.

Random forest (RF), a tree-based ensemble consisting of tree-structured classifiers, was built for the prediction via *RF* package with 500 regression trees. The importance of variables was shown in a figure, using mean decrease accuracy and Gini.

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