Received: 10 September 2024 | Accepted: 8 June 2025

DOI: 10.1002/jpn3.70166

JPGN

ORIGINAL ARTICLE

Hepatology

A prediction model for genetic cholestatic disease in infancy using the machine learning approach

Chi-San Tai[1] | Sung-Chu Ko[2] | Chien-Chang Lee[2,3] | Hui-Ru Yang[1] | Chia-Ray Lin[1] | Byung-Ho Choe[4] | Suporn Treepongkaruna[5] | Voranush Chongsrisawat[6] | Chau-Chung Wu[7] | Huey-Ling Chen[1,7,8]

[1]Department of Pediatrics, National Taiwan University Children's Hospital, Taipei, Taiwan

[2]Center of Intelligent Healthcare, National Taiwan University Hospital, Taipei, Taiwan

[3]Department of Emergency Medicine, National Taiwan University Hospital, Taipei, Taiwan

[4]Department of Pediatrics, Kyungpook National University Children's Hospital, South Korea

[5]Division of Gastroenterology, Department of Pediatrics, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand

[6]Division of Gastroenterology and Hepatology, Department of Pediatrics, Faculty of Medicine, Chulalongkorn University and King Chulalongkorn Memorial Hospital, Bangkok, Thailand

[7]Department and Graduate Institute of Medical Education and Bioethics, National Taiwan University College of Medicine, Taipei, Taiwan

[8]Hepatitis Research Center, National Taiwan University Hospital, Taipei, Taiwan

Correspondence

Huey-Ling Chen, Department of Pediatrics, National Taiwan University College of Medicine and Children's Hospital, 17F, No. 8, Chung-Shan South Rd, Taipei 100, Taiwan.
Email: hueyling@ntu.edu.tw

Funding information

Ministry of Science and Technology, Taiwan, Grant/Award Number: 109-2314-B-002-161-MY3

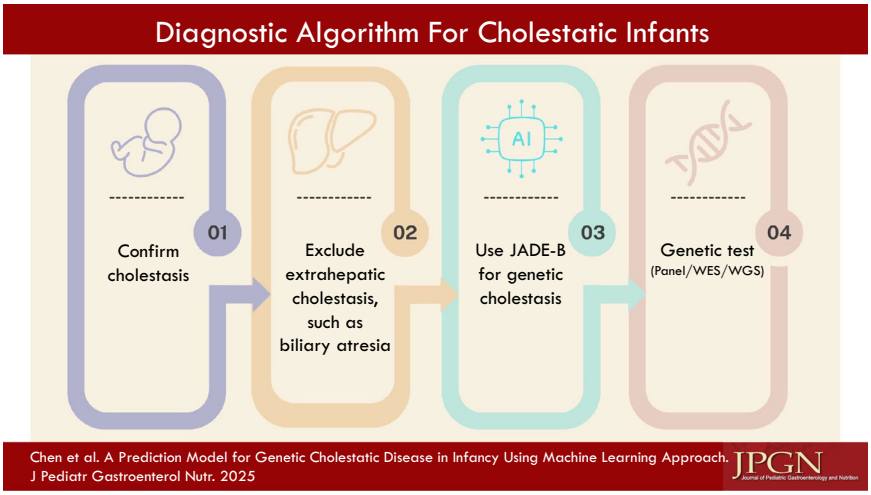
Abstract

Objectives: Cholestasis in infancy poses a complex clinical conundrum for pediatric hepatologists, warranting timely diagnosis, especially for genetic diseases. This study aims to create machine learning (ML)-based prediction models, referred to as Jaundice Diagnosis Easy for Baby (JADE-B), to identify the subjects prone to genetic causes of cholestasis.

Methods: We retrieved patient data from the Integrated Medical Database at a university-affiliated tertiary medical center from 2006 to 2018. Patients with cholestatic disease were identified using liver-disease-specific International Classification of Diseases codes. A total of 47 clinical and laboratory parameters were used for ML for predicting a positive genetic disease, defined by a disease-specific genetic diagnosis matched with phenotype. Four distinct classifiers: Logistic regression, XGBoost (XGB), LightGBM (LGBM), and Random Forests were utilized to build the models.

Results: From a patient pool of 1845, 1008 infants below 1 year of age diagnosed with cholestatic liver disease were included in the analysis. A comprehensive set of 47 pertinent clinical and laboratory features was incorporated for training the ML models. We built five sets of models (Model 1-5), yielding an area under the receiver operating characteristic curve of 0.869, 0.884, 0.855, 0.852, and 0.836, respectively. A JADE-B model was built using 20 simple and widely accessible clinical parameters at disease onset, up to 1 month, to predict patients with genetic disorders.

Conclusions: The machine learning model prioritizes cholestatic infants for the allocation of genetic diagnostic tools and patient referrals, as well as optimizes the utilization of genetic diagnostic resources.



KEYWORDS
artificial intelligence, genetic diseases, jaundice, progressive familial intrahepatic cholestasis

1 | INTRODUCTION

Neonatal or infantile cholestasis is the condition of reduced bile formation or bile flow resulting from hepatobiliary dysfunction or biliary tract obstruction. Cholestasis is one of the most encountered liver diseases worldwide, which is caused by inherited disorders or secondary insults at all ages.[1,2] More than 100 inherited and acquired etiologies can cause cholestatic liver diseases.[3] The clinical outcomes range from self-limited disease to liver failure that may be indicated for liver transplantation. Recent advances in genetic medicine and novel analytical tools such as next-generation sequencing and bioinformatics have greatly accelerated the rates of genetic diagnosis and the discovery of novel genetic disorders.[4–6] However, because of the diversity of etiologies of cholestasis and the rarity of each genetic disorder, diagnosing infant cholestasis remains one of the most challenging tasks for clinicians and pediatric hepatologists.

Most cholestatic patients present with overlapping symptoms, such as jaundice, clay stools, poor weight gain, coagulopathy, and pruritus. However, the genetic analysis tools cannot be applied to most patients at the early stages of diseases among the large cohort of jaundiced babies.[6–8] Only a few centers worldwide provide advanced genetic tests. Many patients are diagnosed at advanced stages of diseases such as cirrhosis or liver failure. The indication and algorithm of genetic analysis in clinical settings are still controversial. If we want to provide genetic analysis in the early stages of diseases, we will need to offer this test to a large number of patients. This is not practical in terms of analysis capacity and a tremendous increment in the medical cost for genetic tests.

What is Known

- Due to the diversity of etiologies of cholestasis and the rarity of each genetic disorder, diagnosing infant cholestasis remains one of the most challenging tasks for clinicians and pediatric hepatologists.
- The indications and algorithm of genetic analysis are still controversial.

What is New

- Our models empower clinicians to expedite genetic testing for high-risk cases by simplifying the diagnostic process and optimizing resource allocation.
- It utilizes 20 simple and widely accessible clinical parameters to predict patients with genetic disorders.
- This model benefits patients by making personalized treatment strategies.

Therefore, we think it is valuable and highly warranted to develop a diagnostic algorithm to determine who will be the priority patients for receiving genetic tests in cholestatic diseases at the early stage of the disease among a large number of patients. We have previously published a scoring system for the diagnosis of neonatal cholestasis caused by citrin deficiency,[8] using common clinical parameters, and also published the role of using a single marker (gamma-glutamyl transferase [GGT]) for the prediction of progressive familial intrahepatic cholestasis.[9] However, these

models are far from accurate enough to be used for the selection of patients for genetic analysis.[6]

Conventional statistical methods or models, such as logistic regression and Cox regression, have been applied to detect linear correlation and risk stratification in the long run. However, considering heterogeneous combinations of clinical information and laboratory data, a more comprehensive model is needed for risk stratification and providing individualized medical suggestions. Machine learning (ML) can easily fulfill this need by providing advanced algorithms and data analysis techniques that enable more accurate predictions and personalized solutions tailored to individual requirements. Moreover, it can be trained to analyze complex nonlinear correlations among variables.

Recently, ML has been used to investigate gastrointestinal diseases,[10] as well as to predict hospital mortality in African children with acute infections, which is helpful in the hospital setting, especially in resource-limited areas.[11] ML has also been used to develop predictive models for chronic hepatitis B or C virus infection, liver transplantation survival, and donor matching.[10,12,13] Currently, there are no reports of an ML-based diagnostic model or algorithm for cholestatic patients to aid in predicting or selecting priority candidates for advanced genetic tests.

The purpose of this study is to use data from medical records to build prediction models and to identify patterns that can inform forecasts about future outcomes. In this study, we aim to use our database of clinical data and genetic analysis results to develop models for prioritizing patients for genetic analysis.

2 | METHODS

2.1 | Ethics statement

This study was approved by the Institutional Review Board of NTUH (201912246RIND).

2.2 | Study participants and data collection

From the National Taiwan University Hospital integrated Medical Database (NTUH-iMD), we have retrieved a total of 1845 cases below 1 year of age with available liver function tests and abdominal sonography from January 2006 to December 2018 (Figure 1). Among them, 1008 cases of cholestatic liver diseases were identified by the criteria of: (1) patients who had been diagnosed with International Classification of Diseases code related to cholestatic liver disease or jaundice (Supporting Information S3: Table 1); and (2) with direct-bilirubin more than 1.0 mg/dL and/or total-bilirubin more than 1.5 mg/dL at the National Taiwan University Hospital.

The clinical medical information included gender, gestational age, prematurity status, birth body weight, age at onset of symptoms, use of total parental nutrition (PN) during infancy, and abdominal ultrasonography. Clinical parameters include serum levels of total and direct bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), GGT, and cytomegalovirus (CMV) viral load. The laboratory parameters were recorded at baseline, 1, 3, 6, and 12 months from baseline (b, p1m, p3m, p6m, p12m, eg, GGT p3m: the GGT levels at 3 months from baseline). The abnormal findings of abdominal ultrasonography included hepatomegaly, splenomegaly, abnormal hepatic echogenicity, liver cirrhosis, and ascites. The genetic diagnosis had been performed based on clinical purpose, and a positive genetic diagnosis was defined as patients with compatible clinical phenotypes associated with the specific genetic mutations detected.

2.3 | Model development

The research environment utilized Python version 3.8.10, LightGBM (LGBM) package version 3.3.2, XGBoost version 1.4.2, and the scikit-learn package (version 1.0.2) for Logistic Regression and Random Forest. The study cohort analyzed comprised 1008 cases. All personal information was de-identified before model development. A total of 47 clinical variables were selected for model development to predict whether a genetic disease was ultimately diagnosed. We used stratified random sampling to split the data set into 70% training and 30% testing sets.

Resampling, Synthesized Minority Oversampling Technique, and Edited Nearest Neighbor methods were applied due to the imbalanced data set. The candidate ML models used were Logistic Regression, Random Forest, XGBoost Classifier, and LGBM Classifier. Detailed information about the parameters used for tuning the ML algorithms is listed in Supporting Information S3: Table 2. We employed the median of gestation age and onset age to substitute missing values. For missing birth body weight data, the mean value was utilized for imputation. Additionally, missing values in time series data were replaced with the closest available data points in time.

The performance of models using datasets from different time points and analytical methods was evaluated. The model with the earliest available data and the highest AUC was selected as the Jaundice Diagnosis Easy for Baby (JADE-B) model. For external validation, retrospective data collected from the medical records of 98 patients from three centers were used, including Kyungpook National University Children's Hospital, South Korea, Ramathibodi Hospital, Thailand, and King Chulalongkorn Memorial Hospital, Thailand.

2.4 | Statistical analysis

To evaluate the differences in patients' characteristics between patients with positive or negative diagnoses for genetic diseases, we used the Mann–Whitney *U* test for comparison. We calculated the area under the receiver operating characteristic curve (AUROC), accuracy, sensitivity, specificity, precision, and F1-score to evaluate the performance of each model.

The DeLong test is applied to compare classification models, particularly in the medical field. This is mainly because medical models are often evaluated using AUC, and the DeLong test is specifically designed to assess differences in AUC between models. Additionally, since medical data often does not follow a normal distribution, the DeLong test's ability to operate without the assumption of normality makes it especially suitable for this type of data.

3 | RESULTS

3.1 | Baseline characteristics of all participants

Figure 1 demonstrates the flow of this study. Through the NTUH-iMD, we identified a total of 1008 patients admitted to the Pediatrics Department of the National Taiwan University Hospital. Among these 1008 patients, 63 had been diagnosed as positive for genetic disease during the follow-up, including neonatal intrahepatic cholestasis caused by citrin deficiency, Alagille syndrome, progressive familial intrahepatic cholestasis, and inborn errors of bile acid metabolism. The clinical characteristics and baseline laboratory data of patients with or without genetic diagnosis were shown in Supporting Information S3: Table 3. Figure 2 shows the different courses of dynamic changes in liver function tests between patients with and without genetic diseases. Those with genetic diseases had higher direct bilirubin (D-Bil) levels at 12 months (1.90 mg/dL vs. 0.87 mg/dL, $p = 0.008$), higher ALT at 6 and 12 months ($p = 0.0028$, $p < 0.0001$), higher AST at 3, 6, and 12 months ($p = 0.018$, $p < 0.0001$, and $p < 0.0001$), higher ALP at baseline ($p = 0.001$), had older age at onset of jaundice (0.38 vs. 0.25 years, $p < 0.0001$), more likely to be full term ($p = 0.002$), and had a lower proportion of using TPN (1.59% vs. 19.58%, $p < 0.001$).

3.2 | Model development

We built five prediction models using Logistic Regression, Random Forest, XGBoost Classifier, and LGBM Classifier. The workflow of model development by employing different sub-datasets was demonstrated in Figure S1. The first model (Model 1, Supporting Information S3: Table 4) used all 47 parameters with an AUC of 0.8688 (95% confidence interval [CI]: 0.76–0.95) and accuracy of 0.8515. The first laboratory value of each patient was designated as "baseline data." To increase the model accuracy without decreasing the performance of the model, we used a feature selection method. After feature selection, the number of parameters of the second model

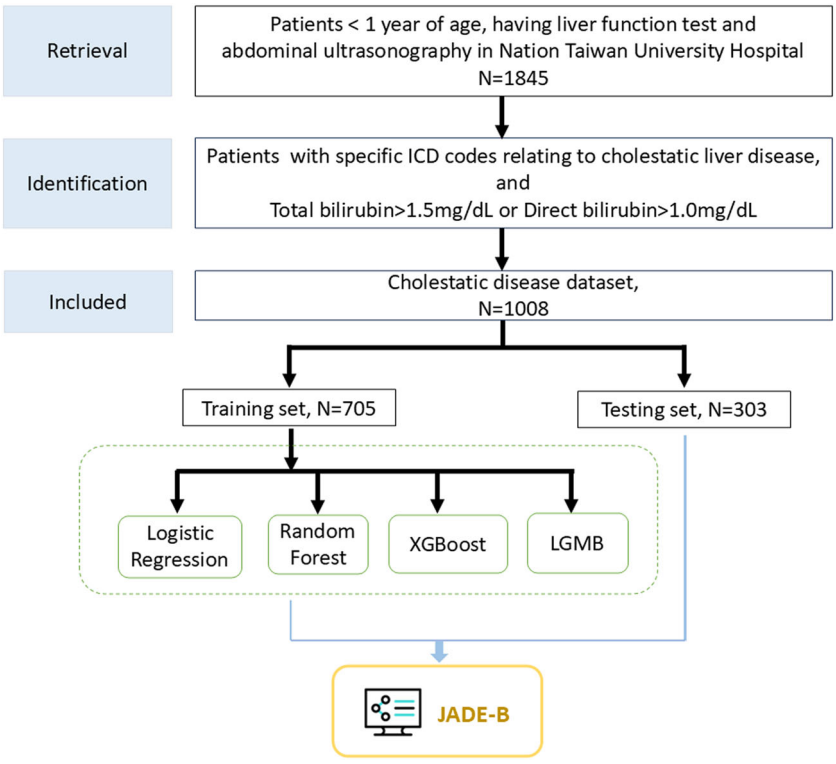


FIGURE 1 The study flow and the process of machine learning. ICD, International Classification of Diseases; JADE-B, Jaundice Diagnosis Easy for Baby; LGMB, LightGBM.

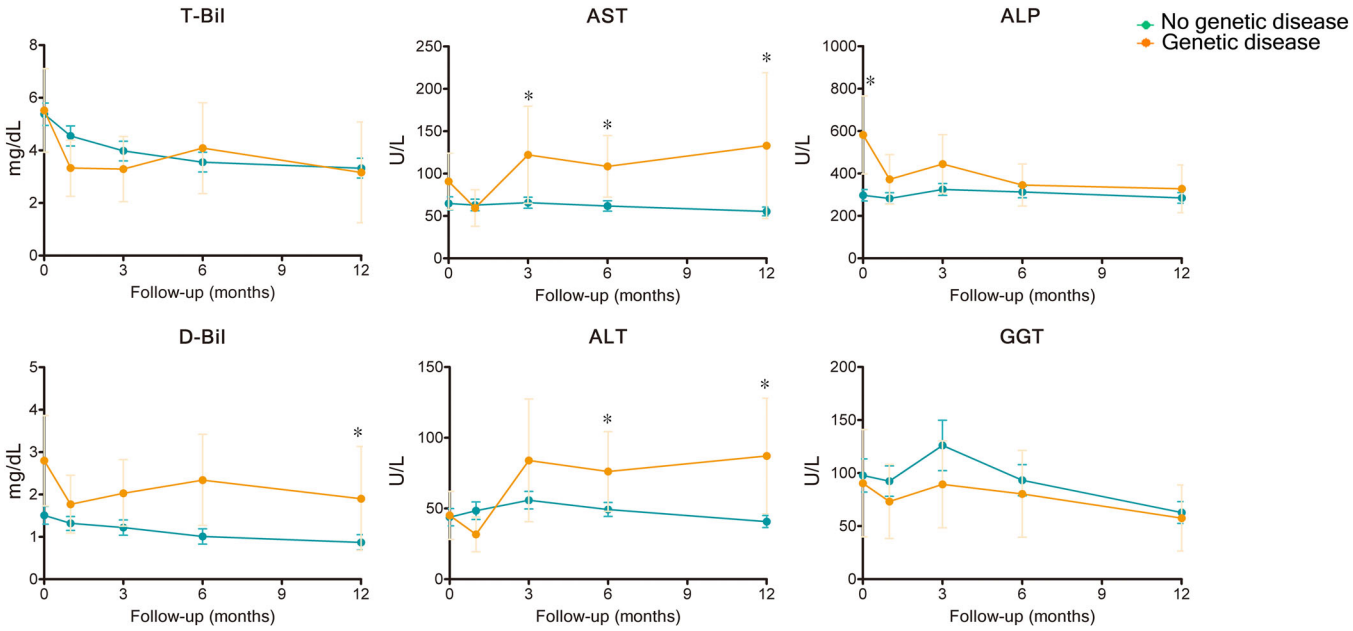


FIGURE 2 The dynamic changes of laboratory data at different time points and comparisons between patients with and without genetic diseases (* $p < 0.05$, Mann–Whitney *U* test). ALT, alanine aminotransferase; AST, aspartate aminotransferase; D-Bil, direct bilirubin; GGT, gamma-glutamyl transferase; T-Bil, total bilirubin.

(Model 2, Supporting Information S3: Table 4) decreased from 47 to 15 features. The AUC and diagnostic accuracy were 0.8838 (95% CI: 0.77–0.96) and 0.8944.

Next, we used selected parameters by using those only in the first 3 months after disease onset in the third model (Model 3, Supporting Information S3: Table 4). By doing so, we could predict the genetic disease earlier than the previous models. The AUC and diagnostic accuracy were 0.8547 (95% CI: 0.74–0.94) and 0.8548, which were comparable to the first two models. After feature selection, the fourth model (Model 4, Supporting Information S3: Table 4) was built with 20 features. The AUC and accuracy were 0.8516 (95% CI: 0.76–0.93) and 0.8152.

To develop the earliest model for prediction within 1 month after initial presentation, we used the sub-dataset including the demographic features, laboratory markers from baseline and 1 month, without ultrasonographic findings. Model 5 (Supporting Information S3: Table 4) was established by using 20 features. The AUC and accuracy were 0.8358 (95% CI: 0.71–0.93) and 0.8251.

3.3 | Performance comparison

In Model 1, using all 47 variables, the Random Forest model had a non-inferior AUC and higher sensitivity than the other three models (Figure 3, Supporting Information S3: Table 4). No significant difference was detected in the DeLong test among them.

In Model 2, after feature selection, the models of Random Forest, XGBoost Classifier, and LGBM Classifier had higher AUC performance than Logistic Regression. The LGBM classifier model had the highest sensitivity (0.9474) compared to the other three models.

Among all models for building Model 3, Random Forest had the highest AUC value (0.8547), sensitivity (0.8421), and F1-score (0.4211), although delong test showed no significant difference among them.

The model 4 used only 20 clinical features from disease onset to 3 months later and was processed with feature selection. The models of Logistic Regression, Random Forest, and XGBoost Classifier had similar performance in AUC analysis, while Random Forest models showed better performance in accuracy (0.8152), specificity (0.8134), precision (0.2319), and F1-score (0.3636).

For clinical application, it is desired to use earlier markers and widely accessible clinical laboratory parameters for predicting cases needing genetic tests. We then used data from within 1 month of presentation, without ultrasonographic findings, to develop Model 5. The model of Random Forest had the highest AUC (0.8358), accuracy (0.8251), and specificity (0.8239) than the models of Logistic Regression, XGBoost Classifier, and LGBM Classifier.

3.4 | The JADE-B model

Because a prediction model using markers at an earlier disease stage is practically preferred, we chose the Random Forest Model 5 as the suggested model for predicting genetic disease, designated as the JADE-B model, using 20 parameters, including total and direct bilirubin, AST, ALT, ALP, GGT, ALT from disease onset to

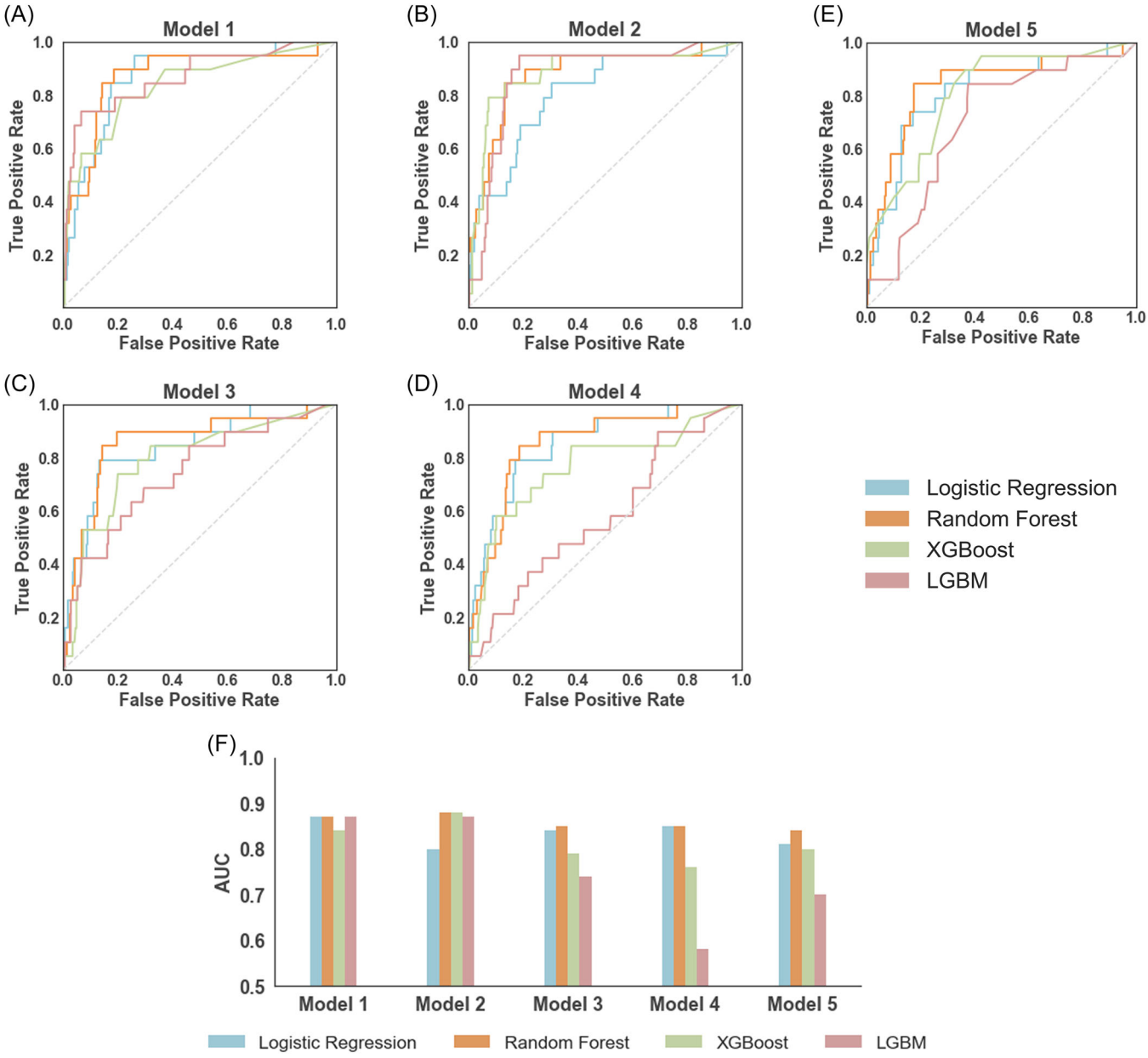


FIGURE 3 (A–F) The comparison of AUC of Models 1 to 5 by different classifiers. AUC, area under the curve; LGMB, LightGBM.

1 month and clinical features (weblink for JADE-B: https://gi-genetic-predictor.streamlit.app/). This model can be used to prioritize patients to receive genetic tests. The sensitivity, specificity, positive predictive value, and negative predictive value were 0.8421, 0.8239, 0.2424, and 0.9873, respectively.

The JADE-B model predicted that 21.8% of the NTUH validation cases were likely related to genetically cholestatic diseases. In other words, the model could help avoid 78.2% of genetic tests. This model was externally validated in 98 cases (with 36 cases with positive genetic diseases) from Thailand and Korea, achieving an AUC of 0.7115.

3.5 | Variable importance

Lundberg and Lee proposed SHapley Additive exPlanation (SHAP) as a unified approach to analyze the output of any ML models.[14] It is widely accepted for the consistent and accurate evaluation of the contribution of each variable in different models.[15] The importance of all variables demonstrated by SHAP summary plots is shown in Figure S2. Earlier onset age, prematurity, lower birth body weight, and parental nutrition were less likely to be associated with genetic disease. The higher level of direct bilirubin with prolonged duration implies a higher possibility of genetic cholestatic liver disease.

4 | DISCUSSIONS

Our study is the first to develop an ML model, JADE-B, to identify infants likely to have a genetic liver disease. We propose this model to assist clinical settings in prioritizing genetic testing for cholestatic infants, among the large populations of jaundiced or cholestatic infants. In addition, we have minimized the number of clinical parameters needed in this model, which are widely accessible in most hospitals. This feature increased the usefulness and feasibility of using the JADE-B model.

Due to the immature bile metabolic function during the first year of life, as well as many other metabolic functions under development, the causes of neonatal cholestasis are highly diverse. The first step of the usual diagnostic process is to identify or exclude extrahepatic cholestasis, mainly biliary atresia or choledochal cyst, to determine whether the infant needs intraoperative cholangiography or operation. Next, etiologies of intrahepatic cholestasis will be taken into consideration, including infection, prematurity, parenteral nutrition, hypoxic insults, monogenic diseases consisting of multiple metabolic disorders, ductal malformations, as well as endocrine and mitochondrial disorders. The diagnosis relies on detailed history taking, physical examination, numerous blood and urine tests, imaging studies, and liver biopsy for differential diagnosis. Owing to advancements in molecular diagnosis, the role of molecular diagnosis is changing since it is less time-consuming and has less expensive costs nowadays. Evaluation of neonatal cholestasis has evolved to emphasize the important role of genetic testing. New diagnostic algorithms incorporating genetic testing have been proposed for different genetic backgrounds and targeted diseases.[16,17] It may facilitate the earlier recognition of common and rare cholestatic liver diseases. Physicians can provide precision medicine regarding specific targeting therapies and inform the family of possible long-term clinical outcomes.

Despite the advantages of genetic testing in managing cholestatic disease in infancy, significant challenges remain. Because of the large population of young infants with jaundice and cholestatic liver diseases and the nonspecific clinical manifestations in the majority of patients, the demand for genetic testing is very high. The prices of whole-exome sequencing range from $500 to $7500, and those of whole-genome sequencing range from $1000 to $16,000, according to the website of the global network of laboratories (Genohub: https://genohub.com/).[18] However, the price may not be affordable globally for all parents with cholestatic infants, and most healthcare systems do not cover the expense of genetic diagnosis. Not only is the budget an issue, but also the facilities, equipment, and personnel expertise required for testing, bioinformatic analysis, and maintaining the system are not widely accessible in many parts of the world. Even in areas with available resources, the testing capacity may not provide service for all cholestatic infants. Thus, there is an urgent need to establish a predictive tool to select specific subjects with genetic cholestatic diseases.

In this study, we used several models to establish the prediction model. Model 1 employed Random Forest with 47 parameters, collecting clinical data from disease onset up to 12 months, and achieved an AUC of 0.8688 and a sensitivity of 0.8421, respectively. After feature selection, Model 2 condensed the parameters from 47 to 15. It included GGT, AST, ALT, ALP, total and direct bilirubin, and so on. Some parameters up to 12 months were used. The AUC and F1 were better than Model 1; the sensitivity decreased to 0.7895 with an elevation of specificity to 0.9014. The performance of both models is good. However, these two models can only be applied 1 year after disease onset. For some genetic liver diseases, prompt diagnosis is essential to benefit the patients and their families. Therefore, we developed Model 3 by Random Forest using features within 3 months after onset, using 33 clinical parameters. After feature selection, Model 4 used only 20 clinical variables. Model 5 (designated as JADE-B model) condensed 20 clinical parameters within 1 month after onset, excluding ultrasonographic findings. The AUC, sensitivity, and specificity were 0.8358, 0.8421, and 0.8239, respectively. Compared to Model 4, Model 5 had a similar AUC and sensitivity. Fewer variables at the early stage of disease are practically preferable by physicians for diagnosis prediction, and can save the cost of medical care. Our model provides good performance, with a positive prediction value of 0.2424, and a high negative prediction value of 0.9873, which is considered suitable for screening tool in clinical settings, comparable with previously large-scale bilirubin screening for biliary atresia with a positive predictive value of 5.9% and a negative predictive value of 100.0%.[19] By promoting simple and practically applicable prediction models for cholestatic genetic liver diseases, we can prioritize those patients for timely genetic diagnostic testing and optimize the allocation of genetic diagnostic resources.

When facing a cholestatic infant, it is crucial to prioritize diagnosing patients with biliary atresia as early as possible. Any newly developed diagnostic algorithm or prediction model cannot take the risk of delaying the diagnosis of biliary atresia, as postponing the Kasai operation will result in unfavorable outcomes and long-term complications. Thus, the causes of extrahepatic cholestasis, such as biliary atresia and choledochal cyst, should be identified first using currently established diagnostic methods. The prediction model should not overshadow established diagnostic protocols for conditions that require immediate intervention. Depending on the resource availability, the JADE-B prediction model can also be applied to all infants with cholestasis, or specifically to those with unfavorable clinical course, such as progressive cholestasis, liver cirrhosis, or failure to thrive. Early recognition of infants more likely to have genetic cholestatic diseases, along with early genetic testing and diagnosis confirmation, can assist clinicians in making prompt management decisions,

predicting long-term outcomes. We have proposed a simplified diagram illustrating the use of an ML prediction model in infantile cholestasis (Figure 4).

Clinical hepatologists or physicians usually integrate clinical information and variable laboratory data from different sources to make a diagnosis, predict long-term prognosis, and suggest treatment options. Traditionally, laboratory parameters such as GGT or clinical scores have been used to aid medical decision-making.[5,8,9] In recent years, progress in ML can extract clinically relevant information from diverse and complex datasets and help physicians make essential judgments.[20] The reported applications included liver stiffness prediction from clinical data and images,[10,12,21] diagnosis of fatty liver disease,[22–24] histologic and radiologic diagnosis of hepatocellular carcinoma,[25–27] prognosis evaluation for hepatocellular carcinoma,[27–31] recipient selection for liver transplantation.,[10,13,32,33] The application of ML in pediatric diseases is limited but is rapidly emerging. Areas of interest included microbiota analysis for inflammatory bowel disease,[34] and a mortality prediction model for cholestatic neonates.[35] The application of artificial intelligence in pediatric aspects is scant compared to the adult group. Our study introduces a new model for prioritizing genetic testing in the clinical algorithm for the vast population of cholestatic infants

The "positive cases" of genetic diseases in our cohort represented a heterogeneous group; thus, our model is not predictive of a single genetic disorder, or "hot spot" diseases, but a group of genetic disorders. This cohort reflects the real-world situation in a population with rare consanguinity. Our center has long experience with next-generation sequencing for the diagnosis of genetic liver disease, integrating conventional Sanger sequencing to a panel-based approach and exome sequencing,[17] providing services for domestic and international cases. Thus, our experience in diagnosing genetic liver diseases is well-established and representative. With the increasing demand for genetic testing worldwide, we believe our model will be of much value in future diagnostic algorithms in this situation.

Our serial data demonstrated that during the follow-up period, the levels of direct bilirubin, AST, and ALT became distinguishable, and were significantly higher in patients with genetic cholestatic liver diseases; and higher ALP levels showed differences at baseline. Interestingly, the ML model analyzing variable importance gave valuable insight into our model. In the analysis, earlier onset age, prematurity, lower birth body weight, and parental nutrition were less likely to have a genetic disease, possibly indicating that many of the cholestasis cases were related to transient neonatal cholestasis.[36–38] However, some monogenetic liver diseases can also present in early infancy, such as Alagille syndrome, Niemann-Pick type C, progressive familial intrahepatic cholestasis, and mitochondrial DNA depletion syndromes. Among the substantial number of early-onset cases without genetically related cholestasis, benign causes of transient cholestasis and cholestasis related to total parenteral nutrition likely play significant roles.[36] The levels of bilirubin, AST, ALT, and GGT are the indicators of hepatocellular, hepatobiliary cell injury, or oxidative stress, and all are conceivable to be essential parameters for liver diseases.

This study has some limitations. These prediction models were established from a single tertiary referral center. To validate the model in a larger cohort, we plan

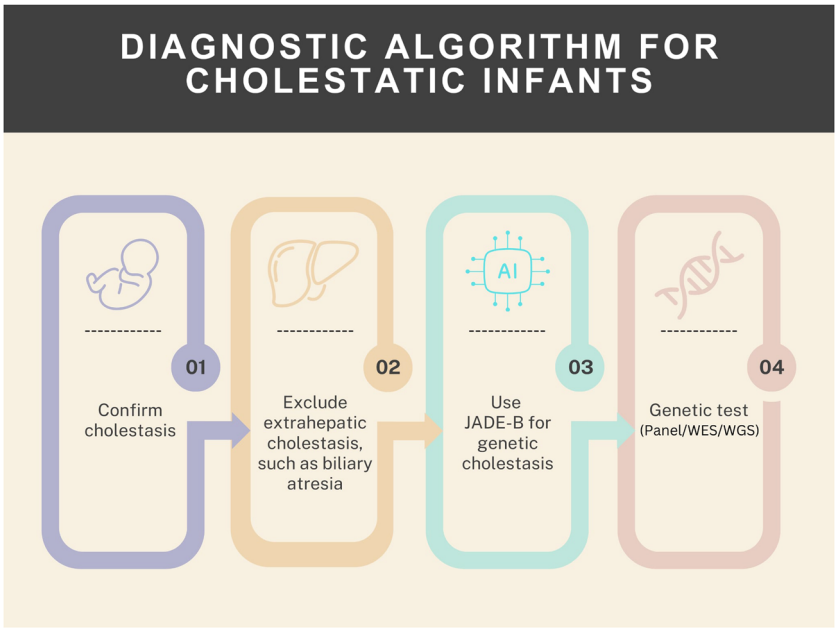


FIGURE 4 A simplified diagram illustrating the use of a machine learning prediction model in clinical settings. JADE-B, Jaundice Diagnosis Easy for Baby; WES, whole-exome sequencing; WGS, whole-genome sequencing.

to prospectively use these models for jaundiced infants in our hospital and those cared for by international physicians. In addition, we did not include consanguinity as a factor in our model development, as consanguineous marriage is prohibited by law in Taiwan and is extremely rare. Nonetheless, a family history of index cases remains an important indicator for genetic testing. In our model, we applied the most basic clinical parameters and laboratory data, aiming to serve as a quick reference prediction to aid physicians in optimizing the allocation of resources for genetic testing.

5 | CONCLUSION

We have developed a diagnostic model for applying advanced genetic tests in cholestatic patients, enabling an efficient selection of possible cases of inherited disease to receive genetic analysis, and expanding chances of finding disease-causing genes. Our long-term goal is to apply similar models to many other diseases and use this approach to develop personalized treatment plans that could benefit the patients.

ACKNOWLEDGMENTS

The authors would like to express their thanks to the staff of the Department of Medical Research for providing clinical data from the National Taiwan University Hospital-integrative Medical Database (NTUH-iMD), and the Center for Intelligent Healthcare, National Taiwan University Hospital, for their technical support. This study is supported by grants 109-2314-B-002-161-MY3 from the Ministry of Science and Technology, Taiwan. The funder played no role in the study design, data collection, or data analysis of this report.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

ORCID

Huey-Ling Chen https://orcid.org/0000-0002-4074-5838

REFERENCES

1. Bezerra JA, Balistreri WF. Cholestatic syndromes of infancy and childhood. *Semin Gastrointest Dis*. 2001;12(2):54-65.
2. Boyer J. Advancing the bile-ology of cholestatic liver disease. *Hepatology*. 2001;33(3):758-759.
3. Karlsen TH, Lammert F, Thompson RJ. Genetics of liver disease: from pathophysiology to clinical practice. *J Hepatol*. 2015;62(1 Suppl):S6-S14.
4. Chen HL, Wu SH, Hsu SH, Liou BY, Chen HL, Chang MH. Jaundice revisited: recent advances in the diagnosis and treatment of inherited cholestatic liver diseases. *J Biomed Sci*. 2018;25(1):75.
5. Fawaz R, Baumann U, Ekong U, et al. Guideline for the evaluation of cholestatic jaundice in infants: joint recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition. *J Pediatr Gastroenterol Nutr*. 2017;64(1):154-168.
6. Chen HL, Li HY, Wu JF, et al. Panel-based next-generation sequencing for the diagnosis of cholestatic genetic liver diseases: clinical utility and challenges. *J Pediatr*. 2019;205:153-159.e6.
7. Wu SH, Hsu JS, Chen HL, et al. Plectin mutations in progressive familial intrahepatic cholestasis. *Hepatology*. 2019;70(6):2221-2224.
8. Chen ST, Su YN, Ni YH, et al. Diagnosis of neonatal intrahepatic cholestasis caused by citrin deficiency using high-resolution melting analysis and a clinical scoring system. *J Pediatr*. 2012;161(4):626-631.e2.
9. Lu FT, Wu JF, Hsu HY, et al. γ-Glutamyl transpeptidase level as a screening marker among diverse etiologies of infantile intrahepatic cholestasis. *J Pediatr Gastroenterol Nutr*. 2014;59(6):695-701.
10. Spann A, Yasodhara A, Kang J, et al. Applying machine learning in liver disease and transplantation: a comprehensive review. *Hepatology*. 2020;71(3):1093-1105.
11. Kwizera A, Kissoon N, Musa N, et al. A machine learning-based triage tool for children with acute infection in a low resource setting. *Pediatr Crit Care Med*. 2019;20(12):e524-e530.
12. Wei R, Wang J, Wang X, et al. Clinical prediction of HBV and HCV related hepatic fibrosis using machine learning. *EBioMedicine*. 2018;35:124-132.
13. Briceño J, Cruz-Ramírez M, Prieto M, et al. Use of artificial intelligence as an innovative donor-recipient matching model for liver transplantation: results from a multicenter Spanish study. *J Hepatol*. 2014;61(5):1020-1028.
14. Lundberg S, Lee SI. A Unified Approach to Interpreting Model Predictions ArXiv./abs/1705.07874, 2017.
15. Lundberg S, Erion GG, Lee SI. Consistent Individualized Feature Attribution for Tree Ensembles ArXiv./abs/1802.03888, 2018.
16. Feldman AG, Sokol RJ. Neonatal cholestasis: emerging molecular diagnostics and potential novel therapeutics. *Nat Rev Gastroenterol Hepatol*. 2019;16(6):346-360.
17. Chen CB, Hsu JS, Chen PL, et al. Combining panel-based next-generation sequencing and exome sequencing for genetic liver diseases. *J Pediatr*. 2023;258:113408.
18. Payne K, Gavan SP, Wright SJ, Thompson AJ. Cost-effectiveness analyses of genetic and genomic diagnostic tests. *Nat Rev Genet*. 2018;19(4):235-246.
19. Harpavat S, Garcia-Prats JA, Anaya C, et al. Diagnostic yield of newborn screening for biliary atresia using direct or conjugated bilirubin measurements. *JAMA*. 2020;323(12):1141-1150.
20. Nam D, Chapiro J, Paradis V, Seraphin TP, Kather JN. Artificial intelligence in liver diseases: improving diagnostics, prognostics and response prediction. *JHEP Reports*. 2022;4(4):100443.
21. Gatos I, Tsantis S, Spiliopoulos S, et al. A machine-learning algorithm toward color analysis for chronic liver disease classification, employing ultrasound shear wave elastography. *Ultrasound Med Biol*. 2017;43(9):1797-1810.
22. Qu H, Minacapelli CD, Tait C, et al. Training of computational algorithms to predict NAFLD activity score and fibrosis stage from liver histopathology slides. *Comput Methods Programs Biomed*. 2021;207:106153.
23. Forlano R, Mullish BH, Giannakeas N, et al. High-throughput, machine learning-based quantification of steatosis, inflammation, ballooning, and fibrosis in biopsies from patients with nonalcoholic fatty liver disease. *Clin Gastroenterol Hepatol*. 2020;18(9):2081-2090.e9.
24. Taylor-Weiner A, Pokkalla H, Han L, et al. A machine learning approach enables quantitative measurement of liver histology and disease monitoring in NASH. *Hepatology*. 2021;74(1):133-147.
25. Aatresh AA, Alabhya K, Lal S, Kini J, Saxena P. LiverNet: efficient and robust deep learning model for automatic diagnosis

of sub-types of liver hepatocellular carcinoma cancer from H&E stained liver histopathology images. *Int J Comput Assist Radiol Surg*. 2021;16(9):1549-1563.
26. Sun C, Xu A, Liu D, Xiong Z, Zhao F, Ding W. Deep learning-based classification of liver cancer histopathology images using only global labels. *IEEE J Biomed Health Inform*. 2020;24(6):1643-1651.
27. Liao H, Xiong T, Peng J, et al. Classification and prognosis prediction from histopathological images of hepatocellular carcinoma by a fully automated pipeline based on machine learning. *Ann Surg Oncol*. 2020;27(7):2359-2369.
28. Saito A, Toyoda H, Kobayashi M, et al. Prediction of early recurrence of hepatocellular carcinoma after resection using digital pathology images assessed by machine learning. *Mod Pathol*. 2021;34(2):417-425.
29. Saillard C, Schmauch B, Laifa O, et al. Predicting survival after hepatocellular carcinoma resection using deep learning on histological slides. *Hepatology*. 2020;72(6):2000-2013.
30. Shi JY, Wang X, Ding GY, et al. Exploring prognostic indicators in the pathological images of hepatocellular carcinoma based on deep learning. *Gut*. 2021;70(5):951-961.
31. Yamashita R, Long J, Saleem A, Rubin DL, Shen J. Deep learning predicts postsurgical recurrence of hepatocellular carcinoma from digital histopathologic images. *Sci Rep*. 2021;11(1):2047.
32. Cruz-Ramírez M, Hervás-Martínez C, Fernández JC, Briceño J, de la Mata M. Predicting patient survival after liver transplantation using evolutionary multi-objective artificial neural networks. *Artif Intell Med*. 2013;58(1):37-49.
33. Lau L, Kankanige Y, Rubinstein B, et al. Machine-learning algorithms predict graft failure after liver transplantation. *Transplantation*. 2017;101(4):e125-e132.
34. Jones CMA, Connors J, Dunn KA, et al. Bacterial taxa and functions are predictive of sustained remission following exclusive enteral nutrition in pediatric crohn's disease. *Inflamm Bowel Dis*. 2020;26(7):1026-1037.
35. Choi HJ, Kim I, Lee HJ, et al. Clinical characteristics of neonatal cholestasis in a tertiary hospital and the development of a novel prediction model for mortality. *EBioMedicine*. 2022;77:103890.
36. Jacquemin E, Lykavieris P, Chaoui N, Hadchouel M, Bernard O. Transient neonatal cholestasis: origin and outcome. *J Pediatr*. 1998;133(4):563-567.
37. Champion V, Carbajal R, Lozar J, Girard I, Mitanchez D. Risk factors for developing transient neonatal cholestasis. *J Pediatr Gastroenterol Nutr*. 2012;55(5):592-598.
38. Santos Silva E, Almeida A, Frutuoso S, et al. Neonatal cholestasis over time: changes in epidemiology and outcome in a cohort of 154 patients from a Portuguese tertiary center. *Front Pediatr*. 2020;8:351.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Tai C-S, Ko S-C, Lee C-C, et al. A prediction model for genetic cholestatic disease in infancy using the machine learning approach. *J Pediatr Gastroenterol Nutr*. 2025;1-10. doi:10.1002/jpn3.70166