OPEN

The Role of a NICU Hepatology Consult Service in Assessing Liver Dysfunction in the Premature Infant

Carol Potter, MD

Abstract: Liver dysfunction is common in the neonatal intensive care unit (NICU). Literature exists on the presentation of primary liver disease in the NICU but little has been published on general liver dysfunction in the NICU. This is a retrospective observational study of hepatology consultations and outcomes in a large referral NICU. 157 babies were evaluated by a single hepatologist and followed to resolution of disease, death, or lost to follow-up as outpatients. Infectious etiologies were the most common cause for liver dysfunction in the NICU, followed by shock, genetic abnormalities, cardiac disease, large heme loads, and hypothyroidism. Primary liver disease was rare. Liver dysfunction in the sick preterm infant was often multifactorial, and the distribution of diagnoses differs from that seen in the term baby. The liver dysfunction may last well beyond discharge from the NICU and may result in death.

Key Words: premature liver, cholestasis, neonatal intensive care unit

What is Known

- Liver dysfunction is common in the premature infant.
- There are no guidelines specific to the evaluation of liver disease in the premature infant or sick newborn.
- The causes of liver disease in the otherwise healthy infant are uncommon causes of liver disease in the NICU.

What is New

- Infection, genetic disease, cardiac dysfunction, large heme loads, and hypothyroidism are common causes of liver dysfunction in the NICU.
- Evaluation must consider premature physiology, other organ disease, and the limits of blood volume.
- Expertise in hepatic care allows collaboration and improves care of infants with multisystem disease.

The premature infant is exposed to many stresses at a time when they are poorly equipped to deal with them and liver dysfunction is common in the sick premature infant. This dysfunction is usually multifactorial, often a combination of liver immaturity, comorbidities, and primary liver disease.[1] The liver of the preterm infant is characterized by a paucity of bile ducts, low levels of many hepatic enzymes and transporters, and a small bile acid pool.[2–5] The neonatal period is also the setting where many genetic abnormalities have not yet become clear and may play a role in the physiology of liver disease.

There are no guidelines for the evaluation of liver dysfunction in the NICU. This paper presents a large series of consecutive babies seen by the NICU Hepatology service in a large referral NICU with the results of their clinical evaluations and suggests a potential evaluation strategy.

METHODS

This is a retrospective observational study of liver disease in the NICU conducted at Nationwide Children's Hospital (NCH) between June 2014 and February 2020. The study was approved by the institutional review board of NCH.

Patients were evaluated by 1 hepatologist (CP) at a 114 bed referral NICU at the request of the NICU attending. Babies with short bowel syndrome were followed by a separate service and not included unless the intestinal rehabilitation team felt their liver disease was not consistent with intestinal failure associated liver disease (IFALD). Babies were followed until their liver disease resolved, death, or they were lost to follow-up.

Evaluation for liver disease was done as clinically indicated. The state newborn screen was reviewed. Results of the evaluation were obtained from the medical record. Data recorded included gestation age and weight at birth; age of first abnormal liver imaging or laboratory testing; peak direct bilirubin (DB); peak glutamyl transpeptidase (GGT); Alkaline phosphatase (AP); thyroid function tests; infectious studies including cytomegalovirus (CMV) PCR; urine and blood cultures; viral testing as clinically indicated; head ultrasound (US); sources of heme load; necrotizing enterocolitis (NEC) evaluations; liver US results; cholangiogram and liver biopsy results; genetic studies; parenteral nutrition (PN) exposure, cardiac evaluation; and gastrointestinal surgery.

RESULTS

A total of 157 babies were evaluated from June 2014 to February 2020. Gestational age at birth ranged from 23 to 40 (median 34) weeks post menstrual (PMA).

Presentation

Consultation was usually for elevated DB. At the time of consultation 97% had elevated DB, 74% elevated aminotransferases, 26% prolonged coagulation studies, and 50% had abnormal imaging. Liver abnormalities were noted during routine clinical care by the

Received September 15, 2020; accepted October 23, 2020.
From the Nationwide Children's Hospital, The Ohio State University, Columbus, OH.
Disclosure: The author declares no funding and conflict of interest.
Supplemental digital content is available for this article. Direct URL citations appear in the printed text, and links to the digital files are provided in the HTML text of this article on the journal's Web site (www.jpgn.org).
Correspondence: Carol Potter, MD, Nationwide Children's Hospital, The Ohio State University, 700 Childrens Drive, Columbus, OH 43205. E-mail: carol.potter@nationwidechildrens.org

JPGN Reports (2020) 2:1(e031)
ISSN: 2691-171X
DOI: 10.1097/PG9.0000000000000031

neonatology service in the first week of life in 66%, while 16% had abnormalities noted in the second-third week of life. Since NCH is a referral center, all babies were transported to this center and results from the birth hospital were not always available.

Risk Factors for Liver Dysfunction

Contributors to liver dysfunction were determined by the attending hepatologist (see Figure 1a). Multiple risk factors were common. Eight babies had 6 risk factors, 17 had 5 risk factors, 25 had 4 risk factors, 37 had 3 risk factors, 35 had 2 risk factors, and 25 had 1 risk factor identified for their liver dysfunction.

(1) Infections

Infections were defined as risk factors when therapy resulted in improvement of liver dysfunction. Sepsis (viral or bacterial) was defined as a positive culture or peritonitis from perforation.

(2) PN Exposure

PN exposure was common. In some who were transferred later in their course, the records of PN exposure were not available. The majority of infants did not have prolonged exposure to PN since babies with short bowel syndrome were rarely included and lipid sparing protocols, and Smoflipid are common practice in this NICU. As noted above, 82% of this cohort had liver dysfunction in the first 3 weeks of life, before significant PN exposure. PN longer than 60 days was present in 13 infants. Twelve had additional infectious, medical, or surgical risk factors for cholestasis in addition to PN. The other patient's only identifiable liver disease was a hemangioma in the liver.

(3) Heart Disease

Twenty-nine infants had cardiac disease contributing to liver dysfunction. All had evidence of congestion on liver Doppler or lesions leading to ischemia documented on cardiac catheter or echo.

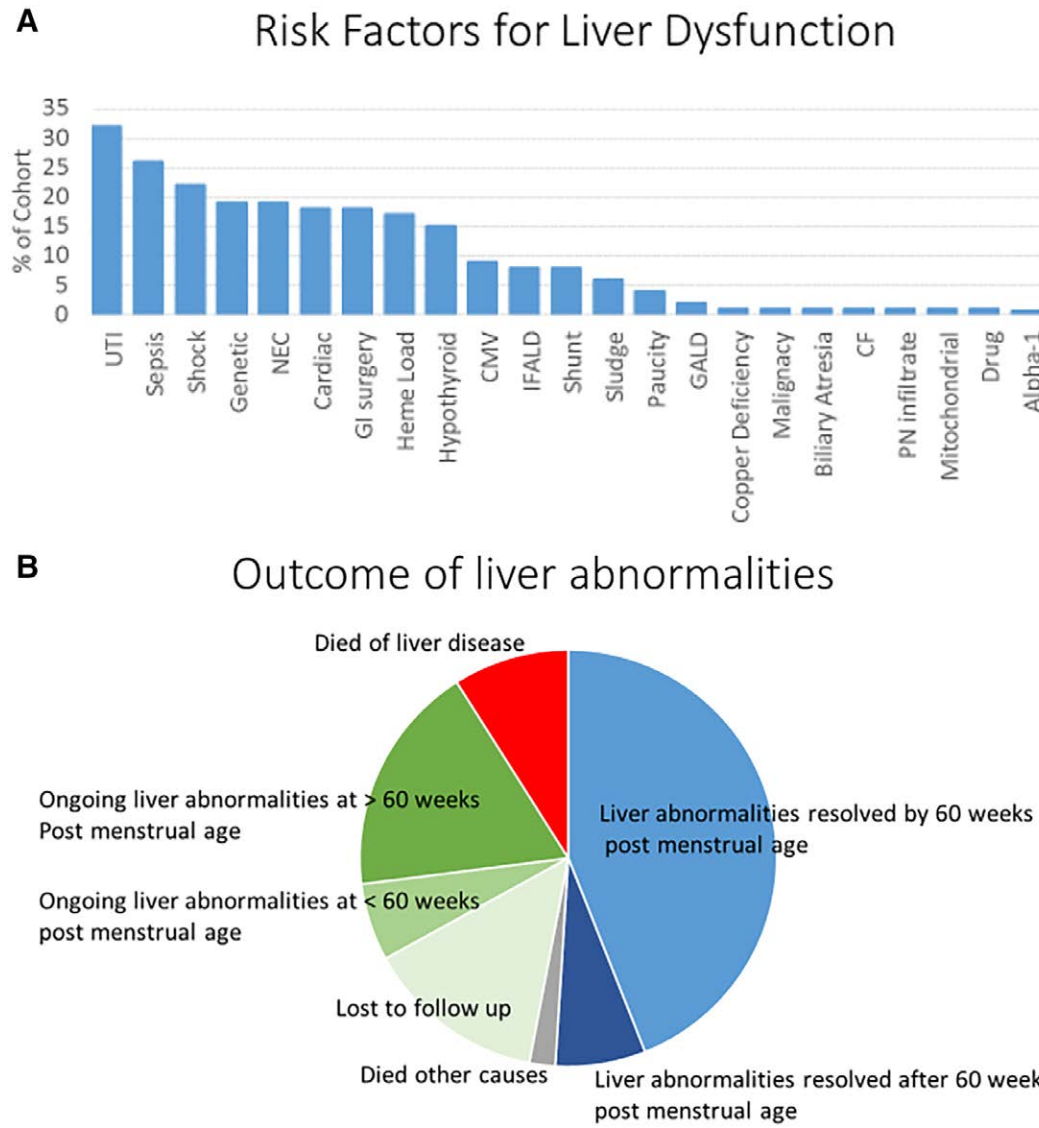

FIGURE 1. Risk factors for liver dysfunction and longterm outcomes. A, Percent of babies in the cohort with a diagnosis that clinically correlated with their liver dysfunction. More than one diagnosis was common. B, Babies with liver dysfunction were followed until laboratory evaluation and physical exam normalized. The pie chart demonstrates the time frame for resolution and those babies with ongoing disease at the end of the study. Some infants were lost to follow up. The babies who died of liver disease and from other cause with ongoing liver disease are depicted.

(4) Genetics

Trisomy 21 was the most common genetic diagnosis (see Table, Supplemental Digital Content 1, http://links.lww.com/PG9/A6)

Genetic cholestasis panels were sent on 64 babies. Five had testing for mutations in 5 genes, and 59 had testing with a large panel of >60 genes. Twenty-one had at least 1 pathogenic mutation identified for an autosomal recessive disease and often multiple heterozygous mutations were detected for recessive disorders. Genetic diagnoses made this way included alpha-1 antitrypsin deficiency, Senior-Loken syndrome, and cystic fibrosis. Our cohort included ethnic backgrounds from northern Africa that are poorly represented in the existing databases.

(5) Thyroid

Abnormalities of thyroid hormone metabolism occur more often in the premature infant than the term baby.[6] Small for gestational age babies have an even higher risk.[7] Twenty-four babies in our cohort required therapy with levothyroxine with cholestasis often being the indication for thyroid evaluation.

(6) Imaging Abnormalities

Abnormalities were seen in 63% of US evaluations including abnormal liver texture and size, abnormal doppler, splenomegaly, duct abnormalities, masses, and infarct. Abnormalities with Doppler evaluation included shunts, varices, clots, pulsatile portal vein flow, increase in arterial resistance, and hemangiomas.

Portosystemic liver shunts were found in 12 infants. Six had patent ductus venosus, and 6 had type 2 Abernathy shunts. One Abernathy shunt required surgical closure due to encephalopathy and progressive cholestasis. Two babies with shunts had secondary hypoglycemia that was able to be managed with enteral feeds. One baby required prolonged intravenous glucose but also had deletion of the growth hormone receptor, congenital hypothyroidism, complex congenital heart disease, and many congenital malformations. The rest of the shunts were well tolerated.

Biopsy Findings

Liver biopsy was obtained in 40 babies with 1 complication in a very small baby with severe heart disease and massive hepatomegaly who had intraperitoneal bleeding. The baby was transfused and recovered without sequella. Cholangiogram was obtain in 17 with 7 being abnormal (see Tables 2 and 3, Supplemental Digital Content, http://links.lww.com/PG9/A6).

Resolution of Disease

Babies were followed in the NICU by 1 hepatologist until their liver disease resolved. Outpatient follow up was every 2–4 weeks until stability or improvement was established and then extended to every 3–6 months. Fourteen percent were lost to follow after discharge from the NICU because of distance or parent choice.

Slightly more than half of the babies had resolution of liver test abnormalities with no evidence of clinical liver disease by the end of the first year of life. Continued liver dysfunction was seen in 6% followed to 60 weeks PMA or less and 18% followed to >60 weeks PMA (range 64–208 median 92) weeks. Death from liver failure or with liver disease being a significant cofactor occurred in 9% (see Figure 1b). Three patients died of causes not related to their liver (see Table 1a and 1b).

TABLE 1. (a) Factors in Patients With Continued Liver Disease and (b) Diagnosis of Infants Dying With Severe Liver Disease or Failure

a

- 25 week gestation, CFTR hetero zygote, 2 other VOUS, cirrhosis, sepsis
- 25 week gestation, multiple episodes of sepsis, pulmonary artery hypoplasia, resolved hypothyroidism
- 26 week gestation with multiple comorbidities
- 27 week gestation, sepsis with multiorgan failure
- 27 week gestation, sepsis, intestinal perforation, large PDA
- Abernathy type 2 shunt
- Abernathy type 2 shunt with double outlet right ventricle
- Alpha-1 antitrypsin deficiency
- Biliary atresia
- Biliary atresia
- CMV
- CMV
- CMV, post PDA coil, hypothyroidism
- DORV, prolonged sepsis, cirrhosis, multiple malformations
- Fanconi anemia
- GALD
- GALD with liver transplant
- Hemolytic disease
- Hypothyroidism, aldolase B deficiency, sepsis
- Large PN infiltrate, prolonged sepsis, bowel perforation, large PDA
- Large PN infiltrate, prolonged sepsis, large PDA
- Multiple malformations, sepsis, mother with uncontrolled diabetes mellitus
- Prolonged hypoglycemia
- Prolonged sepsis, cirrhosis
- Prolonged sepsis, months of fungal meningitis, cirrhosis
- 3 CFTR mutations and negative sweat chloride
- Severe HIE
- Severe HIE
- Severe HIE with ductus venosus and liver infarct
- Severe IUGR and hypoglycemia
- Severe IUGR, 1 TJP2 VOUS
- Trisomy 21 after leukemia therapy
- Trisomy 21 with coiled PDA
- Trisomy 21 with forked bile duct and history of cholangitis
- Trisomy 21, alpha-1 MS, patent ductus venosus

b

- DORV, ECMO for 7 weeks, multiorgan failure
- Multiorgan failure, sepsis, liver failure
- PFIC 2 with hepatorenal syndrome during sepsis
- Liver malignancy with hepatorenal syndrome
- Multiorgan failure, pan hypopituitarism from CNS bleed
- NOMID, liver drug toxicity, respiratory failure, CFTR mutation
- Mitochondrial disease
- Severe HIE with pan hypopituitarism, sickle cell, cholestasis
- Probable GALD, cirrhosis, hepatorenal syndrome
- DORV, ischemic gut, congested and ischemic liver, heart failure
- Trisomy 18 with heart and liver failure
- Trisomy 13 with liver and heart failure
- 23 week gestation with intraabdominal sepsis
- Stoma variceal bleeding from compressed portal vein
- Enterovirus sepsis

CFTR, cystic fibrosis transmembrane receptor; VOUS, variant of unknown significance; HIE, hypoxic ischemic encephalopathy; IUGR, intrauterine growth retardation; DORV, double outlet right ventricle; CMV, cytomegalovirus; CNS, central nervous system; GALD, gestational alloimmune liver disease; NOMID, neonatal onset multisystem inflammatory disease; PDA, patent ductus arteriosus; PFIC, progressive familial intrahepatic cholestasis; PN, parenteral nutrition.

DISCUSSION

Described here are 157 consecutive NICU babies evaluated and followed by a single hepatologist. The data underscores the importance of understanding and considering the effect of

comorbidities in the evaluation of these complex and fragile babies. Primary liver disease was rare and should not be the only focus of evaluation. Systemic or urinary tract infection was the most common risk for liver dysfunction identified. Liver disease due to multiple causes was frequent. Shock, genetic disease, NEC, and other comorbidities were also common. Congenital heart disease and large patent ductus arteriosus with increased right-sided heart pressure were common cofactors in babies that died from liver disease or had unresolved liver dysfunction. Expertise in physiologic response of the preterm liver to secondary insults is critical in accurate interpretation of imaging and laboratory findings in these infants.[1] Liver disease was significant cause of morbidity and mortality with 9% of the cohort dying of liver disease and 25% continuing to have liver dysfunction at 60 weeks PMA. Lessons learned over the course of the study period established a strategy for evaluation of such infants.

Evaluation should be done in a tiered approach. Newborn screen should be reviewed, but it should be noted that a normal newborn screen does not completely exclude thyroid dysfunction or in one patient cystic fibrosis. In the well and stable premature with elevated DB; aminotransferases, AP, GGT, glucose, T4, TSH, UC, urine CMV PCR, and US with Doppler evaluation should be obtained.[8] Elevated heme load from bleeding or hemolysis should be considered. Coagulation studies in well babies with other evidence of good synthetic function are not necessary. If the evaluation is negative, a trial of ursodeoxycholic acid may be started with weekly reevaluation.[9] Babies with sudden increase in DB and ALT should be evaluated for sepsis and CMV.[8,10,11] All babies should be evaluated for nutritional implications of liver disease and supported with MCT and vitamin supplementation.

US with Doppler evaluation is the preferred imaging study in the NICU. Structural abnormalities and changes in liver blood flow are not uncommon. Significant portosystemic shunts were found that were not suspected.[12] Doppler is most helpful for focal flow abnormalities such as shunts, vascular compression, abnormal transmission of cardiac pressure, elevated arterial resistance, hemangioma, and areas of ischemia. Changes in liver flow can be helpful in cardiac disease management decisions, such as timing of surgery. Personal collaboration with the radiologist with detailed clinical information aided interpretation.

Genetic panels are indicated in babies with no obvious risk factors after the first tier of studies. Large panel screening because of the amount of information obtained with 1 blood sample and because of limited blood volume.[13–18] In critically ill babies with multisystem disease, critical whole exome sequencing (WES) is faster and provides broader results.

Babies with coagulopathy and marked elevation of aminotransferases who have multiorgan failure in the first few days of life need to be evaluated for perinatal complications, severe metabolic disease, and gestational alloimmune liver disease (GALD). In this period, ischemic shock or infectious disease is much more common than primary liver disease, but the presentations can overlap.

Liver biopsy should be pursued in babies whose cholestasis is not improving and the diagnosis is unclear. Liver biopsy can be combined with a percutaneous cholangiogram to prove bile duct patency when biliary atresia is a concern. Additionally the cholangiogram has proven therapeutic in instances where sludge was occluding the duct. The degree of liver fibrosis and nature of the liver disease is important to the cardiologists as they consider the risk of interventions, particularly those involving bypass and single ventricle physiology. Liver biopsy at the time of planned abdominal surgery can provide information on fibrosis to help inform ongoing risk and monitoring.

Babies receiving long-term PN who meet the definition of intestinal failure associated liver disease (IFALD) may have additional modifiable risk factors and should have the same systematic evaluation as other premature babies with cholestasis. Particular attention should be paid to liver blood flow because of previous abdominal surgery. They may have advanced fibrosis. All the babies with IFALD in this cohort had other risk factors for liver disease, except one whose liver disease resolved before she was off PN.

As the collaboration with the NICU matured over the course of the study period, the role of the NICU hepatologist expanded to identifying co-morbidities that could be improved, monitoring the effects of heart disease on the liver, advising on fluid and nutrition management with severe liver disease and portal hypertension, and interpreting subtle changes in liver flow and laboratory data to optimize care. The hormonal and hemodynamic changes of portal hypertension, ascites, and hepatorenal syndrome are rare in neonates but do occur, as evidenced by the 9% of babies who died with liver disease being a major component. The hepatologist can help prevent and manage these complications. As a result of this approach, the number of consults requested increased each year from 16 for babies born in 2015 to 40 for babies born in 2019.

Premature babies may have liver dysfunction for a prolonged period of time. The commitment to follow the baby until resolution of the liver disease also allowed for detection of subtle changes and timely adjustments in supportive care and nutrition.

The major strength of this study is that all babies were followed by one senior hepatologist from the time of consult until resolution of disease. In very complicated babies who often had multiple causes of liver dysfunction, this continuity made the contribution of different components more clear. This service was started with the goal of improving consistency in the NICU Hepatology consults; the unintended consequences was having a clearer idea of causes liver dysfunction in the NICU.

The weakness of the study is missing data. Consultation of the hepatology service was at the discretion of the neonatologist. Babies were not evaluated by protocol. Some studies that were recommended were not obtained due to attending choice or inability to obtain. As noted, the nature of the consults changed over time.

In summary, the baby in the NICU presents a unique challenge. They are physiologically different than the healthy term infant and frequently have more liver insults that are poorly tolerated. Because preterm infants are in the hospital for a prolonged period, have very limited blood volume, and are unable to tolerate some evaluation, they benefit from continuity of care by a thoughtful NICU hepatologist. Close collaboration with the neonatologist, radiologist, and other consultants is key to the complex care of these infants.

REFERENCES

1. Potter CJ. Cholestasis in the Premature Infant. *Clin Perinatol.* 2020;47:341–354.
2. Heubi JE. Bile Acid Metabolism. In: *Pediatrics and Perinatology.* Second ed. London: Arnold; 1996:663–668.
3. Chen HL, Chen HL, Liu YJ, et al. Developmental expression of canalicular transporter genes in human liver. *J Hepatol.* 2005;43:472–477.
4. Watkins JB, Szczepanik P, Gould JB, et al. Bile salt metabolism in the human premature infant. Preliminary observations of pool size and synthesis rate following prenatal administration of dexamethasone and phenobarbital. *Gastroenterology.* 1975;69:706–713.
5. Tomer G, Ananthanarayanan M, Weymann A, et al. Differential developmental regulation of rat liver canalicular membrane transporters Bsep and Mrp2. *Pediatr Res.* 2003;53:288–294.
6. Schmaltz C. Thyroid hormones in the neonate: an overview of physiology and clinical correlation. *Adv Neonatal Care.* 2012;12:217–222.
7. Uchiyama A, Watanabe H, Nakanishi H, Totsu S. Small for gestational age is a risk factor for the development of delayed thyrotropin elevation in infants weighing less than 2000 g. *Clin Endocrinol (Oxf)*. 2018;89:431–436.
8. Ruangkit C, Satpute A, Vogt BA, et al. Incidence and risk factors of urinary tract infection in very low birth weight infants. *J Neonatal Perinatal Med.* 2016;9:83–90.

9. Lewis T, Kuye S, Sherman A. Ursodeoxycholic acid versus phenobarbital for cholestasis in the Neonatal Intensive Care Unit. *BMC Pediatr.* 2018;18:197.
10. Whiting JF, Green RM, Rosenbluth AB, et al. Tumor necrosis factor-alpha decreases hepatocyte bile salt uptake and mediates endotoxin-induced cholestasis. *Hepatology.* 1995;22(4 Pt 1):1273–1278.
11. Lanzieri TM, Dollard SC, Josephson CD, et al. Breast milk-acquired cytomegalovirus infection and disease in VLBW and premature infants. *Pediatrics.* 2013;131:e1937–e1945.
12. Bernard O, Franchi-Abella S, Branchereau S, et al. Congenital portosystemic shunts in children: recognition, evaluation, and management. *Semin Liver Dis.* 2012;32:273–287.
13. Goldschmidt ML, Mourya R, Connor J, et al. Increased frequency of double and triple heterozygous gene variants in children with intrahepatic cholestasis. *Hepatol Res.* 2016;46:306–311.
14. Dröge C, Bonus M, Baumann U, et al. Sequencing of FIC1, BSEP and MDR3 in a large cohort of patients with cholestasis revealed a high number of different genetic variants. *J Hepatol.* 2017;67:1253–1264.
15. 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.
16. Henkel SA, Squires JH, Ayers M, et al. Expanding etiology of progressive familial intrahepatic cholestasis. *World J Hepatol.* 2019;11:450–463.
17. Gomez-Ospina N, Potter CJ, Xiao R, et al. Mutations in the nuclear bile acid receptor FXR cause progressive familial intrahepatic cholestasis. *Nat Commun.* 2016;7:10713.
18. Maddirevula S, Alhebbi H, Alqahtani A, et al. Identification of novel loci for pediatric cholestatic liver disease defined by KIF12, PPM1F, USP53, LSR, and WDR83OS pathogenic variants. *Genet Med.* 2019;21:1164–1172.