Long-term Outcomes and Health Perceptions in Pediatric-onset Portal Hypertension Complicated by Varices

Luoto, Topi T.

John Wiley and Sons Inc.
2020-05

Luoto, T T, Koivusalo, A & Pakarinen, M P 2020, 'Long-term Outcomes and Health Perceptions in Pediatric-onset Portal Hypertension Complicated by Varices', Journal of Pediatric Gastroenterology and Nutrition, vol. 70, no. 5, pp. 628-634. https://doi.org/10.1097/MPG.0000000000002643

http://hdl.handle.net/10138/328546
10.1097/MPG.0000000000002643

acceptedVersion

Journal of Pediatric Gastroenterology and Nutrition, Publish Ahead of Print

DOI : 10.1097/MPG.0000000000002643

LONG-TERM OUTCOMES AND HEALTH PERCEPTIONS IN PEDIATRIC-ONSET PORTAL HYPERTENSION COMPLICATED BY VARICES

Topi **Luoto**, MD, Antti **Koivusalo**, MD, Mikko **Pakarinen**, MD

Section of Pediatric Surgery, Pediatric Liver and Gut Research Group, Pediatric Research Center, Children's Hospital, University of Helsinki and Helsinki University Hospital, Helsinki, Finland

Correspondence and reprints:

Topi Luoto, Section of Pediatric Surgery, Children's Hospital, Stenbäckinkatu 11, PL 281, 00029-HUS, Helsinki, FINLAND, tel: +358 9471 73774, fax: +358 9471 75314, Email: topi.luoto@fimnet.fi

The study was supported by the Finnish Pediatric Research Foundation, the Sigrid Juselius Foundation, and the Helsinki University Central Hospital Fund.

ABSTRACT

Objectives: Outcomes of pediatric-onset portal hypertension are poorly defined. We aimed assess population-based long-term outcomes of pediatric-onset portal hypertension complicated by varices.

Methods: All children with esophageal varices (n=126) were identified from 14144 single nationwide referral center endoscopy reports during 1987-2013, and followed up through national health care and death registers. A questionnaire was sent to survivors (n=94) of whom 65 (69%) responded.

Results: Nineteen underlying disorders included biliary atresia (35%), extrahepatic portal vein obstruction (35%), autosomal recessive polycystic kidney disease (7%), and other disorders (23%). During median follow-up of 15.2 (range 0.5-43.1) years patients underwent median 9 (1-74) upper gastrointestinal endoscopies. Esophageal varices were first observed at median age 4.0 (0.3-18.2) years, 112 (89%) patients underwent median 6 (1-56) sclerotherapy/banding sessions, and 61 (48%) experienced median 2 (range 1-20) variceal bleeding episodes. Forty-eight surgical shunt procedures were performed to 41 (36%) patients and 38% underwent liver transplantation. Portal hypertensive biliopathy was diagnosed in 4 patients. Hepatopulmonary syndrome necessitated liver transplantation in 2 patients, hepatic encephalopathy in 2 and hepatorenal syndrome in 1. No patient died of variceal bleeding. Patient reported perception of health on a scale of 1-10 was 9 (range 4-10), and 86% reported no current symptoms attributable to esophageal varices.

Conclusions: Pediatric-onset portal hypertension is a heterogeneous disease with significant long-term morbidity, requiring multimodal approach with

considerable resources and continuation of follow-up in adulthood. Although mortality to variceal bleeding was avoided, bleeding episodes recurred also in adulthood, while patient reported health of long-term survivors was encouraging.

Key words: Children; Hypersplenism; Long-term; Portal Hypertension; Shunt surgery; Varices

What is Known

- The management of pediatric onset portal hypertension has significantly evolved during the last decades.
- Management depends on the underlying liver disease.
- Outcomes of pediatric-onset portal hypertension are poorly defined.

What is New

- Pediatric-onset portal hypertension is a heterogeneous disease with significant long-term morbidity.
- With multimodal approach mortality to variceal bleeding was avoided.
- Mortality was related to other complications of advanced liver disease and its treatment rather than variceal bleeding.
- Bleeding episodes recurred also in adulthood, although patient reported health of long-term survivors was good.

Abbreviations: ARPKD, Autosomal Recessive Polycystic Kidney Disease; BA, Biliary Atresia; EHPVO, Extrahepatic Portal Vein Obstruction; LT, Liver Transplantation; PH, Portal Hypertension

INTRODUCTION

In portal hypertension (PH) the pressure gradient between portal and venous systems increases over the physiological threshold (10 mmHg), resulting in abnormal portosystemic venous communications to decompress the portal venous system. The increase in the portal venous pressure results from increased blood flow resistance or obstruction either at a prehepatic, intrahepatic (parenchymal) or posthepatic level, or as their combination. In addition to gastroesophageal varices, other common complications of PH include splenomegaly and hypersplenism (1,2). Less common, but well-defined complications associated with PH, include portal hypertensive biliopathy, hepato-pulmonary syndrome, portopulmonary hypertension, hepatorenal syndrome and hepatic encephalopathy (3-9). Management and outcomes of pediatric PH depend on the underlying liver disease, and may include repeated surveillance endoscopies with primary prophylaxis as well as different surgical shunt procedures, which may have a significant effect on health outcomes (1,2,10-13).

Extrahepatic portal vein obstruction (EHPVO) is the most common prehepatic cause for PH in children (9). Numerous diseases of the liver parenchyma and bile ducts may lead to cirrhosis and PH (13). In biliary atresia (BA), despite successful Kasai portoenterostomy, liver fibrosis progresses rapidly leading to complicated PH in most (14,15). Other typical intrahepatic conditions in children include congenital hepatic fibrosis with or without autosomal recessive polycystic kidney disease (ARPKD), autoimmune liver diseases, and other conditions leading to cirrhosis. Posthepatic causes of PH, such Budd-Chiari syndrome, are rare in children (12,16).

The management of pediatric PH has significantly evolved during the last decades (1). Mesoportal bypass or Rex shunt was introduced in 1992 by de Ville de Goyet et al and is now considered the surgical treatment of choice for EHPVO. The

procedure restores physiologic portal venous blood flow and may be considered even pre-emptively when anatomical limitations are not encountered (17-22). Results of Kasai portoenterostomy for BA and liver transplantations (LT) have also improved as management protocols have evolved (14,23,24). The role of endoscopic variceal surveillance with primary prophylaxis using sclerotherapy or band ligation remains debatable and is variably performed in different centers (10-12,22,25-29).

Only few reports are available on long-term outcomes of pediatric-onset PH and these studies typically focus on one specific disease with relatively short follow-up times (15,20,30-32). Comparative long-term data extending to adulthood on management and outcomes are few. In the present single center registry-based national follow-up study, we analyzed long-term outcomes and patient reported health perceptions of pediatric onset PH complicated by varices.

METHODS

Study population and design

In total, 14 144 consecutive upper gastrointestinal endoscopy reports from 1987-2013 were reviewed to identify all consecutive patients treated for PH complicated by gastroesophageal varices in the Helsinki University Children's Hospital (See Supplemental Figure 1, Supplemental Digital Content 1, http://links.lww.com/MPG/B773, which demonstrates the study population and design). The hospital patient records were reviewed for demographics, underlying diagnoses, medications, laboratory test and liver biopsy results, imaging results, endoscopic and surgical procedures, complications, variceal bleeding episodes, and survival. All patients were followed up through the Finnish National Care Register for Health Care (National Institute for Health and

Welfare, Finland, http://www.thl.fi/en_US/web/en/statistics/information/register_descriptions/careregister_healthcare#data) from 1972 to 2013 to assure complete data capture. The register maintains nationwide data of diagnosis and treatments in Finnish hospitals. A systematic search was performed by linking personal identity codes to the International Classification of Diseases codes (ICD-8, ICD-9 and ICD-10) and the Nordic Classification of Surgical Procedures (NCSP) or the Finnish Classification of Surgical Procedures (before introduction of NCSP in 1997). Causes of death were verified from the nationwide Archive of Death Certificates of Statistics Finland (http://www.stat.fi/tup/kuolintodistusarkisto/index_en.html). A structured questionnaire was sent to all survivors to gather data on current follow-up, treatment, symptoms and health perceptions (See Supplemental Digital Content 2, http://links.lww.com/MPG/B774, which includes the structured questionnaire).

We defined hypersplenism as blood platelet count consistently less than 150 E9/L, and splenomegaly as spleen length measured in abdominal ultrasound examination above 1 SD of age-specific reference value (33).

Management of portal hypertension and esophageal varices

The Helsinki University Children's Hospital is the nationwide tertiary referral center for pediatric liver diseases in Finland and established national pediatric LT program in 1987. Since then Finnish BA patients and other children with significant liver diseases have been followed-up in Helsinki, where they undergo yearly endoscopic variceal surveillance combined with abdominal ultrasound examination and blood tests (34,35). In BA, the endoscopic surveillance was

started at 12 months, or earlier, if clinical signs of advanced PH or bleeding occurred. In other patients, endoscopies were commenced once the diagnosis was established.

Upper gastrointestinal endoscopies were performed under general anesthesia by an experienced endoscopist. Number and grade of esophageal varices were recorded according to Cales classification (36). Other location of varices and the presence of portal hypertensive gastropathy was also recorded. When encountered, grade 2 and 3 esophageal varices were treated with prophylactic injection sclerotherapy using sodium tetradecyl sulfate (Fibrovein, Std Pharmaceutical Product Ltd, Hereford, UK, or Sotradecol, AngioDynamics, New York). Sclerotherapies were repeated at 2- to 4-week intervals until varices were considered eradicated. Surveillance endoscopies were usually repeated at yearly intervals. Instead of injection sclerotherapy, band ligations were increasingly performed beyond infancy towards the end of inclusion period. If acute variceal bleeding was not successfully controlled endoscopically, Sengstaken-Blakemore tube was introduced with or without octreotide therapy. Propranolol was used as a secondary prophylaxis in selected high-risk patients or in those with recurrent variceal bleeding episodes despite endoscopic sclerotherapy.

Surgical treatment of biliary atresia was nationally centralized to Helsinki in 2005 (16). Pediatric portosystemic shunt surgery is also centralized to Helsinki, where mesoportal bypass operations were started in 2002 (19). Mesoportal bypass (Rex shunt) is offered to all EHPVO patients with favorable anatomy, while other shunts are performed individually based on symptoms, liver function and underlying liver disease.

Ethics

The study conforms to the principles of the 1975 Declaration of Helsinki and was approved by the hospital ethical committee and the National Institute for Health and Welfare. All patients participated in the study on a voluntary basis. An informed written consent was received from all participating patients and/or their parents.

Statistical analyses

Data are presented as median and range. Continuous independent variables were compared with Mann Whitney U test. Comparisons between categorical variables were performed with the chi-square test. Correlations were analyzed with Spearman rank correlation test. Cumulative risks were assessed with the Kaplan-Meier method. SPSS version 25.0 (IBM SPSS Statistics, Armonk, NY) was used for statistical analyses. For analytic purposes, patients were divided into three groups (BA, EHPVO and others) based on the underlying etiology. Level of statistical significance was set at 0.05.

RESULTS

Patient characteristics

In total, 126 patients with median follow-up of 15.2 (0.5-43) years were included. Patient characteristics are summarized in Table 1. The level of PH was classified as intrahepatic in 63%, prehepatic in 36% and posthepatic in only one case (0.8%). As expected, of the 19 different underlying conditions, BA (35%) and EHPVO (35%) were the most common ones. Fifty-seven (45%) patients had associated disorders, including respiratory diseases (n=9), neurologic conditions (n=8), congenital cardiac

defects (n=7), extra-hepatic malignancies (n=4), inflammatory bowel disease (n=4), Down syndrome (n=2), Sotos syndrome (n=1), and an unidentified metabolic syndrome (n=1). Four patients (9% of BA patients) had splenic malformations related to BA, including polysplenia (n=3), and asplenia (n=1). Forty-two (95%) BA patients had undergone Kasai portoenterostomy procedure to relieve cholestasis.

Gastroesophageal varices and endoscopic management

Patients underwent median 9 (1-74) upper gastrointestinal endoscopies during the follow-up. The first endoscopy was performed at age of 4.8 (0.2-17.0) years. Endoscopic findings are summarized in Table 2. Gastric varices were encountered in 19 (15%) patients, always in conjunction with esophageal varices in the fundus (n=11), antrum (n=3), corpus (n=2), duodenum (n=1) or multiple locations (n=3). Hypertensive gastropathy was observed in 69 (55%) patients with comparable frequency in different groups, although earlier in BA patients. Esophageal varices were observed and they bled earlier in BA patients than in others (Table 2 and Fig. 1). Overall, median of 6 (1-56) sclerotherapies or band ligations (6 patients in 11 sessions) were performed to 112 (89%) patients.

Surgical procedures to alleviate portal hypertension

Including LT, 88 (70%) individual patients underwent surgery to alleviate PH. Forty-eight (38%) patients underwent LT at median age 5.5 (0.4-29.2) years. Forty-eight surgical shunt procedures were performed to 41 (36%) patients, including mesoportal bypass (n=27), mesocaval shunt (n=7), side-to-side splenorenal shunt (n=6), distal (Warren) splenorenal shunt n=4, proximal splenorenal shunt (n=2) and other shunts (n=2). Median age at first shunt

procedure was 8.0 (0.4-13.7) years. Of the patients who underwent shunt surgery, 88% (n=36) had EHPVO, while none of EHPVO patients were transplanted. Two BA patients with a mesocaval shunt and one ARPKD patient with a side-to-side splenorenal shunt required subsequently LT due to liver failure or hepatic encephalopathy. Cumulative patency rates for surgical shunts are shown in Figure 1. Patency rates for different shunt types were as follows: mesoportal bypass 74% (20/27), side-to-side splenorenal shunt 83% (5/6), Warren shunt 100% (4/4), proximal splenorenal shunt 50% (1/2), mesocaval shunt 29% (2/7), and other shunt 50% (1/2). Overall, 84% (32/38) of surviving patients had a functioning shunt at the end of follow-up.

Variceal bleeding

Overall, 61 (48%) patients experienced median of 2 (range 1-20) variceal bleeding episodes. Thirty-seven (61%) patients bled also after commencing endoscopic sclerotherapy and 8 patients after shunt surgery (See Supplemental Figure 2, Supplemental Digital Content 1, http://links.lww.com/MPG/B773, which demonstrates the cumulative survival without variceal bleeding after first surgical shunt procedure and first endoscopic sclerotherapy session). Nine patients experienced variceal bleeding at some point after the first LT (n=4; 8.5%) or shunt surgery (n=5; 12%). Median number of bleeding episodes/patient was comparable in different groups. Ectopic varices bled in 6 (30% of patients with ectopic varices) patients. Variceal bleeding necessitated balloon tamponade in 8 (13% of patients with variceal bleeding) cases, and an emergency shunt procedure (mesocaval shunt) in one BA patient due massive bleeding after band ligation of cardiac varices. Betablockers were used in 24 (19%) patients to

prevent recurrent variceal bleeding. Overall, cumulative survival without variceal bleeding at age of 5, 10, 15, and 20 years, was 78%, 61%, 47%, and 39%, respectively. As shown in Fig. 2, cumulative risk of variceal bleeding was comparable among the three groups (p=0.116).

Splenomegaly, hypersplenism and splenic complications

Splenomegaly and hypersplenism occurred in 93% and 81% of patients, respectively. Maximal spleen length varied from 7 cm to 25 cm. Splenomegaly was equally common but developed earlier in BA patients than in others (Table 2). Hypersplenism was less common in BA patients, although it was detected earlier when compared to others. Thirty-six (29%) patients experienced severe thrombocytopenia (<50E9/L). Three patients suffered from additional splenic complications. One un-operated EHPVO patient experienced a spontaneous splenic rupture at 19 years of age requiring splenectomy. Two patients with BA and familial cirrhosis bled from a splenic artery aneurysm requiring endovascular coiling and splenectomy. No symptomatic splenic infarcts were reported. Overall, 12 (10%) patients underwent a splenectomy at a median age of 10.2 (range 2.0-26.5) years. Following LT, mesoportal bypass or other shunt surgery complete reversal of splenomegaly (<1 SD) was achieved in 65%, 75%, and 50%, and blood platelet count normalized in 47%, 60%, and 46% of patients, respectively. The increase in blood platelet count correlated with follow-up time (r=0.322, p=0.005).

Other complications of portal hypertension

Symptomatic portal hypertensive biliopathy was observed in 4 patients with EHPVO at median age of 22.9 (13.6-24.8) years. Magnetic resonance cholangiopancreatography showed abnormal biliary tract dilatation in every case. Two patients suffered cholangitis and one required endoscopic biliary dilatation and stenting due a choledochal stricture. Two BA patients developed hepatopulmonary syndrome and required LT at the age of 0.6 and 6.5 years. One BA patient listed for LT died due to hepatorenal syndrome after cholangitis at the age of 5 months. Hepatic encephalopathy was reported in two patients. The patient with BA had undergone mesocaval shunt at 5 months age and developed liver failure and progressive hepatic encephalopathy requiring LT at the age of 15 years. The patient with ARPKD had undergone a side-to-side splenorenal shunt at 10 years age and suffered repeated episodes of hyperammonemia in addition to progression of liver manifestations (fibrosis, cystic biliary dilatation) and kidney graft failure requiring combine liver kidney transplantation at the age of 13 years. No cases of portopulmonary hypertension were documented.

Mortality

Overall survival was 75% and median age at death 9.4 (0.5-29.4) years. None of the deaths were related to variceal bleeding, while all EHPVO patients survived. The causes of death were BA (n=16), cystic fibrosis (n=3), undefined liver failure (n=3), ARPKD (n=2), non-Hodgkin lymphoma (n=2), Alagille syndrome (n=2), alpha-1 antitrypsin deficiency (n=1), hepatocellular carcinoma (n=1), IFALD (n=1), and trauma (n=1). Twenty-one (66%) of succumbed patients had undergone LT. Statistically significant difference in survival between different

time periods was no seen. Survival of patients born between 1970 and 2004, and between 2005 and 2011 was 73% and 80%, respectively (p=0.483). Survival of patients born between 1970 and 1990, and between 1991 and 2000, and between 2001 and 2011 was 63%, 83%, and 78%, respectively (p=0.089).

Patient reported outcomes

Sixty-five (69%) patients answered the questionnaire at a median age of 17.0 (4.8-43.3) years. The responders (n=65) and non-responders (n=29) were comparable regarding sex (male 48% vs 41%, p=0.57), frequency of underlying liver disease (BA n=18 vs n=10; EHPVO n=34 vs n=10; other n=13 vs n=9; p=0.26), and follow-up age (17.4 (4.3-43.1) years vs 15.2 (2.9-41.4) years, p=0.45). Median body mass index of respondents was 20.6 (12.6-31.2) kg/m^2. Of them, 57% (n=37) were under active surveillance for esophageal varices, eighteen (28%) currently used of betablockers, and five (8%) had been hospitalized for variceal bleeding during the preceding year. Although 86% reported no current symptoms related to varices, 58% and 9% experienced abdominal pain occasionally or weekly. Perception of general health on numeric scale (1-10) was 9 (4-10). Of the adult respondents (>18 years of age, n=31) 48% (n=15) were under active follow-up for esophageal varices, and 6% (n=2) had been hospitalized for variceal bleeding during the preceding year.

DISCUSSION

Underlying diseases in pediatric-onset PH are numerous. As in previous studies, BA and EHPVO were the most common conditions, comprising 70% of the patients in the study population (9,12,13,37). Congenital hepatic fibrosis was

mainly associated with ARPKD (90%) (9,38), while other underlying diseases were infrequent and classified as intrahepatic. Although certain characteristics of esophageal varices, surgical management and survival were dependent on the underlying disease, the cumulative risk of variceal bleeding was comparable in different underlying disease groups. None of our patients died due to variceal bleeding, while the estimated mortality rate of variceal hemorrhage in children with chronic liver disease is 1-3% (2). In the largest series up to date by Duché and coworkers (12), high-risk varices caused life-threatening complications in 1/5 of children with cirrhosis who bled spontaneously and 2 (2%) patients with non-cirrhotic PH died due to refractory bleeding. In BA complications of PH develop in an early phase (12), and according to our experience high mortality was related to other complications of advanced liver disease and its treatment rather than variceal bleeding.

Recently, management of children with PH has evolved significantly. In Finland, BA treatment has been centralized in 2005 to Helsinki resulting in increased 5-year native liver survival (from 38% to 70%) and 5-year overall survival (from 68% to 94%) (14). Mesoportal bypass has helped to eliminate long-term consequences and morbidity of EHPVO in patients with well-preserved intrahepatic portal veins (18,20,22,39). Routine preoperative imaging with retrograde portography may enhance correct identification of these individuals and thereby improve long-term Rex shunt patency rates (40,41). As previous studies suggest, Warren shunt and a side-to-side splenorenal shunt seem to be rational options with satisfactory long-term patency and symptom relief, if mesoportal bypass is not feasible (1,9,18,42). According to our limited experience other portosystemic shunts exhibited a relatively high tendency for thrombosis in

the long-term. Following shunt surgery recurrence of variceal bleeding was exclusively related to shunt occlusion or stenosis.

Ideal evidence-based treatment algorithms regarding primary and secondary prophylaxis of variceal hemorrhage in children are lacking (2,10,22,26,28,43). Our long-term results may support endoscopic primary prophylaxis (12,25,27) in prevention of variceal bleeding related mortality. However, prophylactic endoscopic treatment was combined with surgical procedures in a significant proportion of patients, reflecting results our multimodal interdisciplinary approach. Hypersplenism is rarely a major issue in children and does not cause clinical concern in most cases (1). Severe hypersplenism was the main indication for surgery (n=4) or splenic embolization (n=1) in only 5% of patients with hypersplenism. Despite successful shunt surgery, hypersplenism persist in some patients for incompletely understood reasons. It seems that in some patients splenomegaly is irreversible and splenic sequestration of blood elements continues despite decreased portal pressure (44-47).

Limited literature is available on long-term health of patients with pediatric-onset PH. Health-related quality of life is similar between BA patients and matched general population controls (48,49). EHPVO patients seem to have reduced quality of life despite variceal eradication mainly due to massive splenomegaly and growth retardation (50). Some improvement of QOL scores is seen after surgery on a short-term follow-up (50). Despite significant long-term morbidity, health perception of our patients was good and majority reported no abdominal pain or other symptoms attributable to PH or esophageal varices. At median age of 17 years majority of the patients were under endoscopic

surveillance and 8% had recently required treatment for variceal bleeding. These results combined with the other observed complications of PH highlight the importance of continuing follow-up in adult expert service.

The study population is relatively large representing nearly all patients with complicated pediatric-onset PH in Finland since 1987. None of the patients were lost to follow-up. Overall, 69% of the survivors answered the questionnaire, which is a clear limitation of the study. However, responders and non-responders were comparable making generalization of the results more reliable. Another limitation of the present study was the significant evolvement of diagnostic and management protocols during the study period, including non-invasive detection of PH and esophageal varices. In addition, the retrospective study design unavoidably leads to some inaccuracies in data collection. Despite these limitations, these data provide useful and novel information on long-term outcomes of pediatric PH for patient counselling and planning of transition to adult service.

REFERENCES

1. de Ville de Goyet, J, D'Ambrosio G, Grimaldi C. Surgical management of portal hypertension in children. Semin Pediatr Surg 2012;21:219-32.

2. Grammatikopoulos T, McKiernan PJ, Dhawan A. Portal hypertension and its management in children. Arch Dis Child 2018;103:186-91.

3. de Mattos ÁZ, de Mattos AA, Méndez-Sánchez N. Hepatorenal syndrome: Current concepts related to diagnosis and management. Ann Hepatol 2016;15:474-81.

4. Chattopadhyay S, Govindasamy M, Singla P, et al. Portal biliopathy in patients with non-cirrhotic portal hypertension: does the type of surgery affect outcome? HPB (Oxford) 2012;14:441-7.

5. Lee WS, Wong SY, Ivy DD, et al. Hepatopulmonary Syndrome and Portopulmonary Hypertension in Children: Recent Advances in Diagnosis and Management. J Pediatr 2018;196:14-21.

6. Srivastava A, Chaturvedi S, Gupta RK, et al. Minimal hepatic encephalopathy in children with chronic liver disease: Prevalence, pathogenesis and magnetic resonance-based diagnosis. J Hepatol 2017;66:528-36.

7. Bass LM, Shneider BL, Henn L, et al. Clinically Evident Portal Hypertension: An Operational Research Definition for Future Investigations in the Pediatric Population. J Pediatr Gastroenterol Nutr 2019;68:763-7.

8. Borkar VV, Poddar U, Kapoor A, et al. Hepatopulmonary Syndrome in children: a comparative study of non-cirrhotic vs. cirrhotic portal hypertension. Liver Int 2015;35:1665-72.

9. Khanna R, Sarin SK. Non-cirrhotic portal hypertension - diagnosis and management. J Hepatol 2014;60:421-41.

10. D'Antiga L. Medical management of esophageal varices and portal hypertension in children. Semin Pediatr Surg 2012;21:211-8.

11. de Franchis R, Baveno VI Faculty. Expanding consensus in portal hypertension: Report of the Baveno VI Consensus Workshop: Stratifying risk and individualizing care for portal hypertension. J Hepatol 2015;63:743-52.

12. Duche M, Ducot B, Ackermann O, et al. Portal hypertension in children: High-risk varices, primary prophylaxis and consequences of bleeding. J Hepatol. 2017;66:320-7.

13. Pinto RB, Schneider AC, da Silveira TR. Cirrhosis in children and adolescents: An overview. World J Hepatol 2015;7:392-405.

14. Hukkinen M, Kerola A, Lohi J, et al. Treatment Policy and Liver Histopathology Predict Biliary Atresia Outcomes: Results after National Centralization and Protocol Biopsies. J Am Coll Surg 2018;226:46-57.

15. Parolini F, Boroni G, Milianti S, et al. Biliary atresia: 20-40-year follow-up with native liver in an Italian centre. J Pediatr Surg 2019;54:1440-4.

16. Nagral A, Hasija RP, Marar S, et al. Budd-Chiari syndrome in children: experience with therapeutic radiological intervention. J Pediatr Gastroenterol Nutr 2010;50:74-8.

17. de Ville de Goyet, J, Clapuyt P, Otte JB. Extrahilar mesenterico-left portal shunt to relieve extrahepatic portal hypertension after partial liver transplant. Transplantation 1992;53:231-2.

18. Lautz TB, Keys LA, Melvin JC, et al. Advantages of the meso-Rex bypass compared with portosystemic shunts in the management of extrahepatic portal vein obstruction in children. J Am Coll Surg 2013;216:83-9.

19. Luoto T, Pakarinen M, Mattila I, et al. Mesoportal bypass using a constructed saphenous vein graft for extrahepatic portal vein obstruction--technique, feasibility, and outcomes. J Pediatr Surg 2012;47:688-93.

20. Sharif K, McKiernan P, de Ville de Goyet, J. Mesoportal bypass for extrahepatic portal vein obstruction in children: close to a cure for most! J Pediatr Surg 2010;45:272-6.

21. Superina R, Bambini DA, Lokar J, et al. Correction of extrahepatic portal vein thrombosis by the mesenteric to left portal vein bypass. Ann Surg 2006;243:515-21.

22. Shneider BL, de Ville de Goyet, J, et al. Primary prophylaxis of variceal bleeding in children and the role of MesoRex Bypass: Summary of the Baveno VI Pediatric Satellite Symposium. Hepatology 2016;63:1368-80.

23. Cuenca AG, Kim HB, Vakili K. Pediatric liver transplantation. Semin Pediatr Surg 2017;26:217-23.

24. Kasahara M, Umeshita K, Sakamoto S, et al. Liver transplantation for biliary atresia: a systematic review. Pediatr Surg Int 2017;33:1289-95.

25. Angelico R, Pietrobattista A, Candusso M, et al. Primary Prophylaxis for Gastrointestinal Bleeding in Children With Biliary Atresia and Portal Hypertension Candidates for Liver Transplantation: A Single-Center Experience. Transplant Proc 2019;51:171-8.

26. Bozic MA, Puri K, Molleston JP. Screening and Prophylaxis for Varices in Children with Liver Disease. Curr Gastroenterol Rep 2015;17:27-4.

27. Goncalves ME, Cardoso SR, Maksoud JG. Prophylactic sclerotherapy in children with esophageal varices: long-term results of a controlled prospective randomized trial. J Pediatr Surg 2000;35:401-5.

28. Jeanniard-Malet O, Duche M, Fabre A. Survey on Clinical Practice of Primary Prophylaxis in Portal Hypertension in Children. J Pediatr Gastroenterol Nutr 2017;64:524-7.

29. Zargar SA, Javid G, Khan BA, et al. Endoscopic ligation compared with sclerotherapy for bleeding esophageal varices in children with extrahepatic portal venous obstruction. Hepatology 2002;36:666-72.

30. Fonck C, Chauveau D, Gagnadoux MF, et al. Autosomal recessive polycystic kidney disease in adulthood. Nephrol Dial Transplant 2001;16:1648-52.

31. Maksoud-Filho JG, Goncalves ME, Cardoso SR, et al. Long-term follow-up of children with extrahepatic portal vein obstruction: impact of an endoscopic sclerotherapy program on bleeding episodes, hepatic function, hypersplenism, and mortality. J Pediatr Surg 2009;44:1877-83.

32. Sasaki H, Tanaka H, Nio M. Current management of long-term survivors of biliary atresia: over 40 years of experience in a single center and review of the literature. Pediatr Surg Int 2017;33:1327-33.

33. Megremis SD, Vlachonikolis IG, Tsilimigaki AM. Spleen length in childhood with US: normal values based on age, sex, and somatometric parameters. Radiology 2004;231:129-34.

34. Lampela H, Kosola S, Koivusalo A, et al. Endoscopic surveillance and primary prophylaxis sclerotherapy of esophageal varices in biliary atresia. J Pediatr Gastroenterol Nutr 2012;55:574-9.

35. Luoto TT, Pakarinen MP, Jahnukainen T, et al. Liver disease in autosomal recessive polycystic kidney disease: clinical characteristics and management in relation to renal failure. J Pediatr Gastroenterol Nutr 2014;59:190-6.

36. Abby Philips C, Sahney A. Oesophageal and gastric varices: historical aspects, classification and grading: everything in one place. Gastroenterol Rep (Oxf) 2016;4:186-95.

37. Poddar U, Thapa BR, Rao KLN, et al. Etiological spectrum of esophageal varices due to portal hypertension in Indian children: is it different from the West? J Gastroenterol Hepatol 2008;23:1354-7.

38. Shorbagi A, Bayraktar Y. Experience of a single center with congenital hepatic fibrosis: a review of the literature. World J Gastroenterol 2010;16:683-90.

39. Di Giorgio A, De Angelis P, Cheli M, et al. Etiology, presenting features and outcome of children with non-cirrhotic portal vein thrombosis: A multicentre national study. Dig Liver Dis 2019;51:1179-84.

40. Carollo V, Marrone G, Cortis K, et al. Multimodality imaging of the Meso-Rex bypass. Abdom Radiol (NY) 2019;44:1379-94.

41. Bertocchini A, Falappa P, Grimaldi C, et al. Intrahepatic portal venous systems in children with noncirrhotic prehepatic portal hypertension: anatomy and clinical relevance. J Pediatr Surg 2014;49:1268-75.

42. Triana Junco P, Alvarez A, Dore M, et al. Long-Term Results after Diversion Surgery in Extrahepatic Portal Vein Obstruction. Eur J Pediatr Surg 2019;29:23-7.

43. Ling SC, Walters T, McKiernan PJ, et al. Primary prophylaxis of variceal hemorrhage in children with portal hypertension: a framework for future research. J Pediatr Gastroenterol Nutr 2011;52:254-61.

44. Tutar NU, Isiklar I, Ulu EMK, et al. Spleen size changes in pediatric liver transplant recipients with functioning grafts. Transplant Proc 2007;39:3199-201.

45. Boyer TD, Habib S. Big spleens and hypersplenism: fix it or forget it? Liver Int 2015;35:1492-8.

46. Mitchell O, Feldman DM, Diakow M, et al. The pathophysiology of thrombocytopenia in chronic liver disease. Hepat Med 2016;8:39-50.

47. Peck-Radosavljevic M. Thrombocytopenia in chronic liver disease. Liver Int 2017;37:778-93.

48. Lampela H, Pakarinen MP, Jahnukainen T, et al. Quality of Life and Parental Worrying in a National Cohort of Biliary Atresia Children Living With Their Native Livers. J Pediatr Gastroenterol Nutr 2017;64:883-7.

49. Kelay A, Davenport M. Long-term outlook in biliary atresia. Semin Pediatr Surg 2017;26:295-300.

50. Menon P, Rao KLN, Bhattacharya A, et al. Extrahepatic portal hypertension: quality of life and somatic growth after surgery. Eur J Pediatr Surg 2005;15:82-7.

FIGURE LEGENDS

Figure 1. Cumulative shunt patency (Kaplan-Meier curve) for different shunt types. *Uniform line* presents mesoportal bypasses (n=27). *Dotted line* presents all types (Warren, side-to-side, proximal) of splenorenal shunts (n=12). *Dash line* presents mesocaval shunts (n=7). Patients with patent shunt at LT or death were censored for survival analysis.

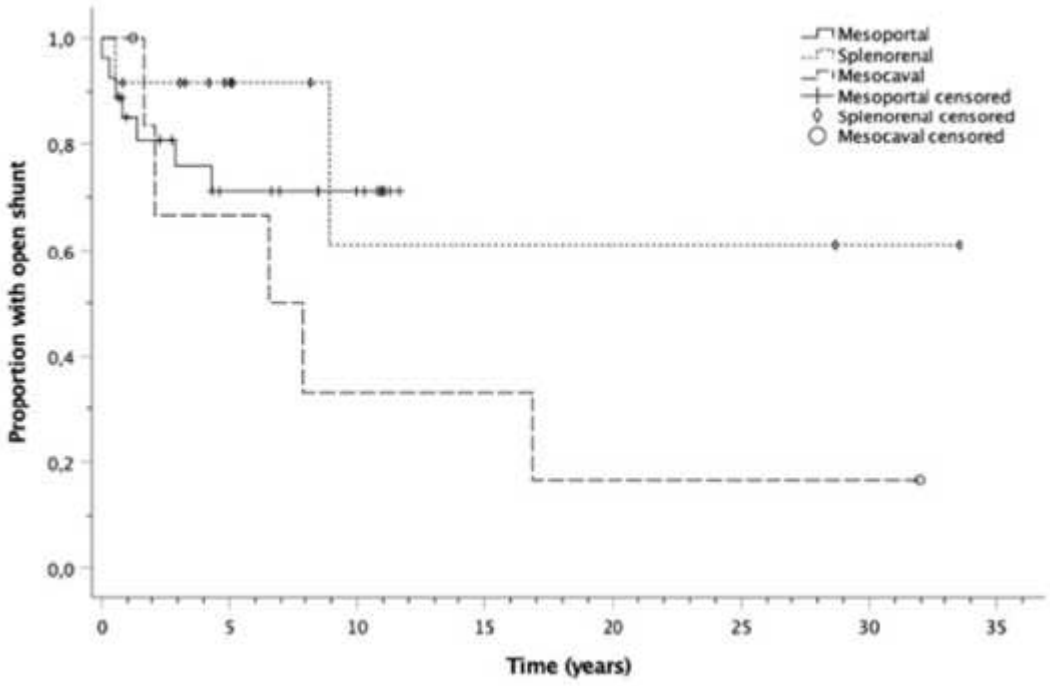

Figure 2. Cumulative survival (Kaplan-Meier curve) without variceal bleeding in three groups based on underlying etiology of portal hypertension. *Uniform line* presents patients with biliary atresia (BA, n=44). *Dotted line* presents patients with extrahepatic portal vein obstruction (EHPVO, n=44). *Dash line* presents patients with other underlying condition (n=38).

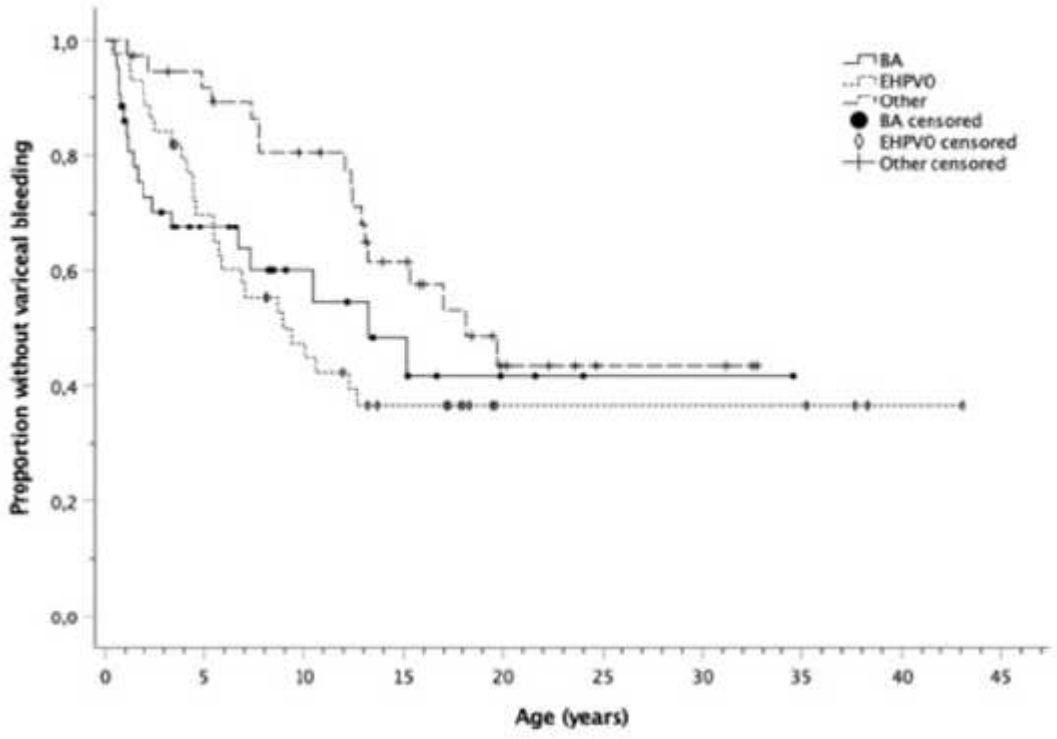

Table 1. Patient characteristics (n=126)

Characteristic	***n (%)***
Male	57 (45)
Underlying liver disease	
BA	44 (35)
EHPVO	44 (35)
ARPKD	9 (7)
Autoimmune hepatitis	3 (2.4)
Cystic fibrosis	3 (2.4)
Alagille syndrome	2 (1.6)
Alpha-1 antitrypsin deficiency	2 (1.6)
Familial cirrhosis	2 (1.6)
Tyrosinemia	2 (1.6)
IFALD	2 (1.6)
Primary sclerosing cholangitis	2 (1.6)
Wilson's disease	2 (1.6)
AV malformation	1 (0.8)
Budd-Chiari syndrome	1 (0.8)
Hepatoblastoma	1 (0.8)
Hepatocellular carsinoma	1 (0.8)
Biliary hypoplasia	1 (0.8)
Isolated CHF	1 (0.8)
Hepatopatia (unknown)	3 (2.4)
Sclerotherapy	112 (89)
Variceal bleeding	61 (48)
Splenomegaly	117 (93)
Hypersplenism	102 (81)
Surgery for portal hypertension	
Liver transplantation	48 (38)
Mesoportal bypass	27 (21)
Splenorenal shunt	12 (10)
Mesocaval shunt	7 (6)
Splenectomy	12 (10)
Deaths	32 (25)

BA=biliary atresia; EHPVO=extrahepatic portal vein obstruction; IFALD=intestinal failure-associated liver disease; CHF=congenital hepatic fibrosis

Table 2. Characteristics and comparison of different underlying disease groups

Characteristic	All (n=126)	BA (n=44)	EHPVO (n=44)	Other (n=38)	p-value
Age at follow-up, y *	15.2 (0.5-43.1)	7.9 (0.5-34.6)	18.4 (3.4-43.1)	19.8 (1.4-33.3)	0.001
Male, n	57 (45%)	15 (34%)	25 (57%)	17 (45%)	0.101
Age at diagnosis, y *	0.7 (0-17.3)	0.2 (0.1-1.0)	5.0 (0-13.2)	0.8 (0-17.3)	0.001
Esophageal varices diagnosed, y *	4.0 (0.3-18.2)	1.1 (0.3-8.7)	5.5 (0.3-13.2)	9.2 (0.8-18.2)	0.001
Gastric varices, n	20 (16%)	4 (9%)	7 (16%)	9 (24%)	0.161
Age at diagnosis, y *	10.1 (1.1-17.5)	7.0 (1.1-11.6)	9.3 (5.2-12.4)	12.4 (3.6-17.5)	0.144
Hypertensive gastropathy, n	69 (55%)	26 (59%)	24 (54%)	19 (32%)	0.734
Age at diagnosis, y *	8.1 (0.4-28.0)	1.9 (0.4-13.0)	9.2 (1.2-16.9)	11.5 (1.2-28.0)	0.001
Variceal bleeding, n	61 (48%)	18 (41%)	26 (59%)	17 (45%)	0.229
Age at first bleed, y *	5.5 (0.4-19.7)	1.5 (0.5-15.2)	5.0 (0.4-12.7)	12.4 (1.1-19.7)	0.001
Sclerotherapy/ligation, n	112 (89%)	40 (91%)	40 (91%)	32 (84%)	0.607
Number of sessions, n	6 (1-56)	4 (1-56)	7 (2-29)	7 (1-42)	0.060
Age at first session, y *	4.6 (0.3-18.2)	1.2 (0.4-8.7)	6.3 (0.3-11.2)	9.5 (1.2-18.2)	0.001
Splenomegaly, n	117 (93%)	38 (86%)	42 (95%)	37 (97%)	0.630
Age at diagnosis, y *	2.5 (0.01-17.1)	0.5 (0.01-4.1)	4.2 (0.3-13.2)	5.3 (0.1-17.1)	0.001
Hypersplenism, n	102 (81%)	29 (66%)	39 (88%)	34 (89%)	0.011
Age at diagnosis, y *	3.8 (0.01-17.1)	1.4 (0.01-8.0)	4.5 (1.2-13.2)	9.5 (0.2-17.1)	0.001
Died, n	32 (25%)	16 (36%)	0	16 (42%)	0.001

* Median (range)