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Poor performance of noninvasive predictors of esophageal varices during primary prophylaxis surveillance in biliary atresia☆,☆☆

Hanna Lampela [a,*], Maria Hukkinen [b], Silja Kosola [c], Timo Jahnukainen [d], Mikko P Pakarinen [b]

[a] Gastrointestinal surgery, University of Helsinki and Helsinki University Hospital, Espoo, Finland
[b] Department of Pediatric Surgery, Pediatric Liver and Gut Research Group, Pediatric Research Center Children's Hospital, University of Helsinki and Helsinki University Central Hospital, Helsinki, Finland
[c] Pediatric Research Center, Children's Hospital, University of Helsinki and Helsinki University Hospital, Helsinki, Finland
[d] Department of Pediatric Nephrology and Transplantation, Children's Hospital, University of Helsinki and Helsinki University Hospital, Helsinki, Finland

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ABSTRACT

Objective: Our objective was to analyze performance of noninvasive markers for significant esophageal varices in relation to outcomes of endoscopic surveillance and primary prophylaxis in biliary atresia (BA).
Methods: This was a prospective follow-up study of a national cohort of BA patients born between 1989 and 2017, including 72 consecutive patients who underwent variceal surveillance endoscopies. The risk for developing significant varices (grade ≥ 2) and variceal bleeding was compared between successful (postoperative total bilirubin ≤34 μmol/L) and failed portoenterostomy (PE) patients. AUROC analyses and Wilcoxon signed ranks test were used to assess accuracy of noninvasive measures to predict the presence of significant varices after successful PE.
Results: In total, 72 patients underwent 471 endoscopies during 427 follow-up years. Among 45 successful PE patients (63%), varices appeared later [at median age 1.6 (0.7–14) vs. 0.8 (0.4–1.9) years] and bled less often [7% vs. 41%, $p < 0.001$ for both] than after failed PE. Liver biochemistry, stiffness, and predictive scores showed poor accuracy for the presence of significant varices. After failed PE, lowered plasma albumin concentration predicted varices with an AUROC of 0.69 (95% CI 0.52–0.85, $p = 0.030$). After successful PE the varices prediction rule with AUROC 0.72 (95% CI 0.64–0.79) was the most accurate predictor. Individual predictors showed no meaningful changes between the two consecutive endoscopies leading to discovery of varices.
Conclusion: Accurate targeting of endoscopies based on noninvasive predictors remains difficult during primary variceal prophylaxis protocol in BA. The differing prognoses after successful and failed PE should be considered in variceal surveillance and future studies.
Type of study: Diagnostic/prognosis study.
Level of evidence: Level II.

Biliary atresia (BA) is a destructive cholangiopathy of infancy, which leads to death unless treated. Portoenterostomy (PE) is the primary surgical treatment, followed by liver transplantation (LT), which may be indicated if bile flow is not restored by PE or later in life owing to advanced liver disease and its complications, including portal hypertension, esophageal varices and associated gastrointestinal (GI) bleeding. Currently, no evidence-based guidelines exist on the indications for primary endoscopic prophylaxis of esophageal or gastric varices in children with diagnoses other than extrahepatic portal vein obstruction [1]. In adults, six-week mortality of variceal bleeding is 10%–20% [2]. In children, mortality after the first variceal bleeding may be as low as 1% [1]. Duche et al. performed endoscopies on 641 BA patients with signs of portal hypertension and found high-risk varices in 173 (29%) patients at a median age of 1.2 years [3]. GI bleeding occurred in 16% of all patients and in 60% of those with high-risk varices. Of them, 17% (3% of all patients) experienced a life threatening consequence of the bleeding. The authors suggested endoscopic primary prophylaxis of high-risk varices. On the other hand, Shneider et al. recently reported a 7% incidence of variceal bleeding by the age of two years in a program with no routine endoscopic screening [4]. Identification of patients with high-risk varices using clinical, laboratory, and ultrasound

Abbreviations: APRI, aspartate to platelet ratio index; AUROC, area under receiving operator curve; BA, biliary atresia; CI, confidence interval; CPR, clinical prediction rule; EIS, endoscopic injection sclerotherapy; GI, gastrointestinal; HR, hazard ratio; K-VaPS, King's variceal prediction rule; LT, liver transplantation; NPV, negative predictive value; PE, portoenterostomy; VPR, varices prediction rule.

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* Corresponding author at: Jorvi Hospital, Turuntie 150, 00029, HUS, Finland. Tel.: +358504286224.
E-mail address: hanna.lampela@hus.fi (H. Lampela).

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findings has been the goal of some previous studies [5–8] but these studies have pooled BA patients with successful and failed PE.

Avoiding unnecessary endoscopies is important as increasing evidence implies that repeated general anesthesias in early childhood may predispose to neurodevelopmental impairment [9–11]. Furthermore, frequent hospital visits are the most important factor that lowers BA patients' health related quality of life [12,13].

Our nationwide hepatobiliary unit follows all BA patients in Finland and screening endoscopies are included in the follow-up protocol. We aimed to evaluate the current results of our endoscopic surveillance and primary prophylaxis protocol and assess the accuracy of various noninvasive markers for significant varices.

1. Methods

Between 1989 and 2017, 89 patients were diagnosed with BA in Finland. Seventy-two (81%) patients, who underwent one or more upper GI endoscopies were prospectively followed, and included in this study (Fig. 1). Follow-up continued until LT, death, or end of the study period on December 11, 2018. Seventeen infants were excluded: six with multiple untreatable anomalies leading to early death, 10 who died or underwent LT before commencing endoscopic surveillance, and one one-year-old with successful PE who had not yet attended endoscopy. Forty-two patients were included in our previous study with a follow-up until 2008 [14].

1.1. Patient management

Since 2005, BA treatment in Finland has been centralized to Helsinki University Hospital, which has also run the nationwide pediatric LT program since 1987. Patients are followed at three-month intervals in Helsinki or local hospitals but all return to Helsinki for annual follow-up visits, which include a clinical examination, laboratory assessment, abdominal ultrasound, liver elastography, and a screening upper GI endoscopy for varices. For patients with normal bilirubin levels and no varices, the interval between the screening endoscopies may be extended to up to two years.

After failed PE, the first screening endoscopy is approximately at six months after PE and after successful PE, at one year of age. Pediatric surgeons with substantial experience in endoscopic procedures perform or supervise all endoscopies. Any grade 2 or 3 esophageal varices are treated with endoscopic injection sclerotherapy (EIS) using sodium tetradecyl sulfate. After EIS for varices, the next endoscopy is planned within two to four weeks until eradication of varices. Endoscopies are also performed when clinically indicated to diagnose GI bleeding or other symptoms.

1.2. Data collection

Data collection included age at PE, all endoscopy findings, treatment of varices, complications, laboratory results (alanine transferase, ALT; aspartate transferase, AST; γ-glutamyl transferase, GGT; albumin; prealbumin; total and direct bilirubin; platelets) at three and six months after PE and at the time of each endoscopy, ultrasound measured spleen length and liver stiffness results before each endoscopy, and the timing of GI bleeding episodes. Liver stiffness was measured with a transient elastography device (FibroScan; Echosens, Paris, France) as described in detail previously [7]. Patients were grouped according to the success of PE (successful PE: ≤34 μmol/L any time after PE; failed PE: >34 μmol/L) owing to differing prognoses. Significant varices were defined as grade 2 or 3 esophageal varices, or gastric varices.

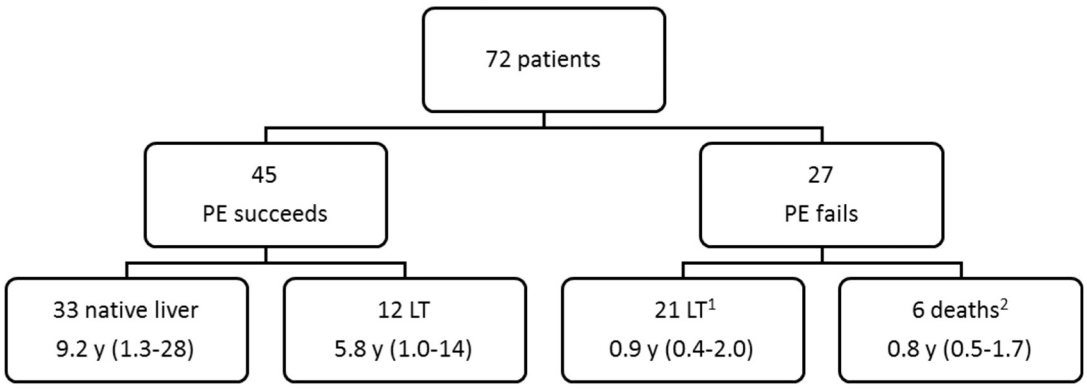
The following previously published scores were calculated for successful primary treatment patients before each screening and scheduled control endoscopy: AST to Platelet Ratio Index (APRI): [(observed AST/AST upper limit of normal)/platelet count]*100 [15]; spleen size Z score (SAZ): (observed spleen length − expected spleen length)/SD of the age and gender-based spleen length [16]; Varices Prediction Rule (VPR): albumin*platelet count/1000 [17]; Clinical Prediction Rule (CPR): (0.75*platelet count)/(SAZ + 5) + 2.5*albumin [18]; and King's Variceal Prediction Rule (K-VaPS): 3*albumin − 2*equivalent adult spleen size [5].

2. Ethics

The Ethics committee of the Helsinki and Uusimaa Hospital district approved this study. Since patients were not contacted for the purpose of this study, no consent was needed.

3. Statistics

We used SPSS 22 statistics software (IBM, Somers, NY). Data are presented as frequencies, percentages, and medians with ranges. Longitudinal changes in different variceal markers between two consecutive endoscopies leading to discovery of varices were assessed with Wilcoxon signed ranks test. The associations between variceal markers and the presence of significant varices were visualized as scatterplots and evaluated using area under the receiver operating characteristic (AUROC) analyses. We chose cutoff values using the highest sum of



[1] Includes one with late referral and primary LT at 0.8 years.

[2] Comprises patients who died without LT, including one fatality of esophageal perforation and sepsis as a complication of endoscopic injection sclerotherapy.

Fig. 1. Patient flowchart. Median age (range) is given as years at study endpoints. Successful portoenterostomy (PE) was defined as decrease in plasma total bilirubin concentration ≤ 34 μmol/L at any point after PE. LT, liver transplantation.

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Table 1
Frequency of varices, endoscopic injection sclerotherapy (EIS) treatments, gastrointestinal (GI) bleeds, and variceal bleeds in all, successful portoenterostomy (PE), and failed PE patients.

	All patients	Successful PE	Failed PE	p
Patients	72	45	27	
Esophageal varices of any grade, or gastric varices	46 (64%)	27 (60%)	19 (70%)	0.452
EIS treatments	37 (51%)	21[a] (47%)	16 (59%)	0.338
GI bleeding	21 (29%)	8 (18%)	13 (48%)	**0.008**
Bleeding from varices	14 (19%)	3 (7%)	11 (41%)	**0.001**
GI bleeding before the first endoscopy	7 (10%)	1[b] (2%)	5 (19%)	**0.025**
Bleeding from varices after commencing EIS	6 (8%)	2 (4%)	4 (15%)	0.189

[a] One patient was once treated with endoscopic variceal ligation, included in EIS treatments.
[b] The patient had a vitamin K deficiency associated bleeding as the first sign of BA at age two days, but after PE has had no further GI bleeding.

sensitivity and specificity from AUROC curve analyses. All analyses were performed separately for patients, whose PE succeeded or failed. We used STROBE checklist as a guideline in reporting.

4. Results

4.1. Patients

The study comprised 72 patients, 427 follow-up years, and 471 endoscopies (average 1.1 endoscopies per follow-up year). Gastric or esophageal varices of any grade were encountered in two thirds of the patients in 228 (48%) of the endoscopies, and 51% of the patients received EIS in 191 sessions (Table 1). In total, 21 (29%) patients experienced GI bleeding, while only 14 (19%) of them had varices verified in endoscopy at the time of bleeding, and 6 (8%) patients experienced variceal bleeding after commencing EIS. No patient died of variceal bleeding. PE succeeded in 45 patients (63%). Patients with successful PE developed varices later and experienced fewer variceal bleeding episodes than did patients whose PE failed (Table 1, Fig. 2).

4.2. Varices and bleeding after successful PE

Successful PE patients underwent 382 endoscopies [1.0 per follow-up year, median 6 (1–40) per patient] and 136 EIS treatments (0.3 per follow-up year), and their follow-up ended at a median age of 8.6 years (1.0–28). Most endoscopies ($n = 353$, 92%) were screenings or scheduled controls after EIS, in 28 (7%) the indication was GI bleeding, and in one instance GI symptoms. Half of the patients ($n = 21$, 47%) underwent EIS, with a median of five [1–22] treatments per patient. The first EIS was performed at median age 1.6 years (0.7–14). In ten patients, varices were eradicated but reappeared later, and EIS was resumed (Fig. 3). Eight patients experienced GI bleeding, the first bleeding episode occurring at median age of 2.2 (0–12) years. In three, bleeding originated from varices (grade 2 in one, grade 3 in two; associated with gastric varices in one) and in five from other sources (one ulcerative colitis, one Dieulafoy lesion, one vitamin K deficiency, and two undefined sources of bleeding despite extensive workup including colonoscopy, capsule endoscopy, and enteroscopy). Five of the eight patients with GI bleeding had received primary prophylactic EIS before the first bleeding episode. As shown in Table 1, only two (4%) patients bled from varices after commencing EIS. EIS treatments caused no significant complications.

4.3. Varices and bleeding after failed PE

Failed PE patients underwent 89 endoscopies [3.1 per follow-up year, median 2 (1–13) per patient] and 55 EIS treatments (1.9 per follow-up year), and their follow-up ended at median 0.9 year (0.4–2.0). Three quarters of endoscopies ($n = 68$, 76%) were screenings or scheduled controls after EIS. In 20 (23%) patients the indication was

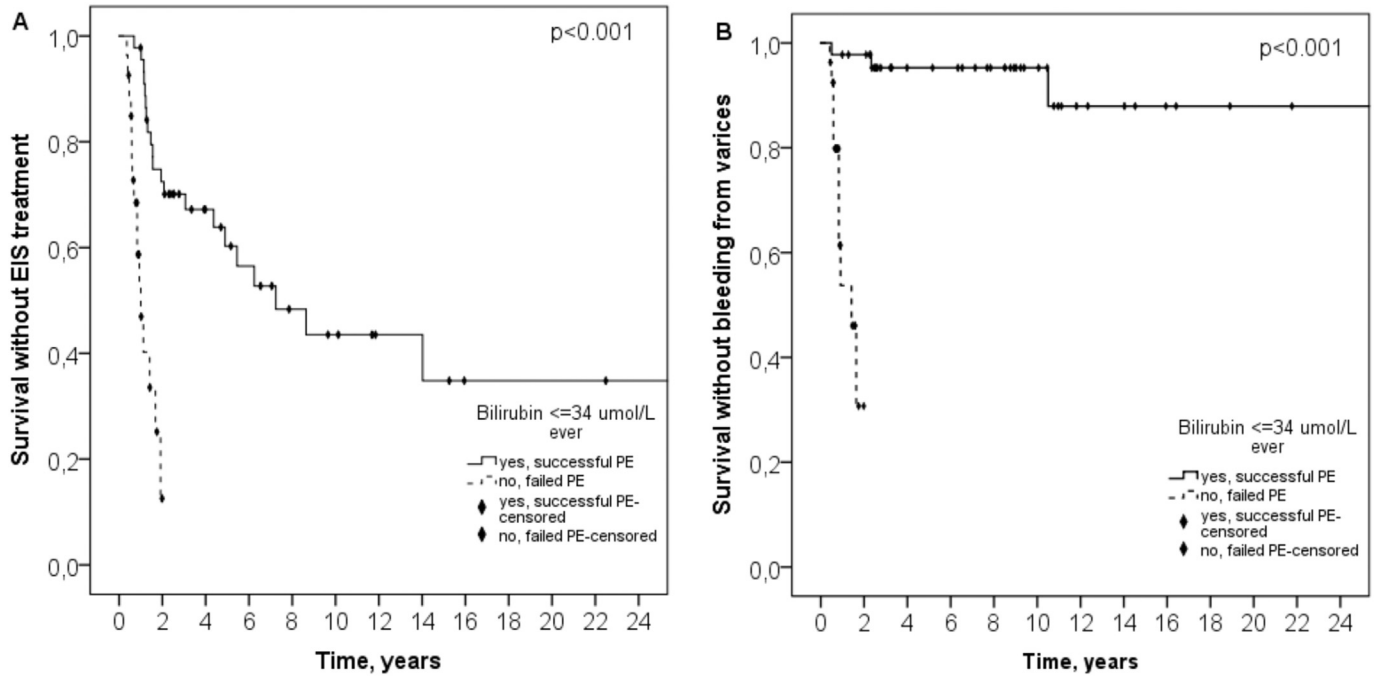

Fig. 2. (A–B) Survival without significant varices and endoscopic injection sclerotherapy EIS (A) and without variceal bleeding (B) for successful and failed portoenterostomy (PE) patients. Group comparisons with log rank test.

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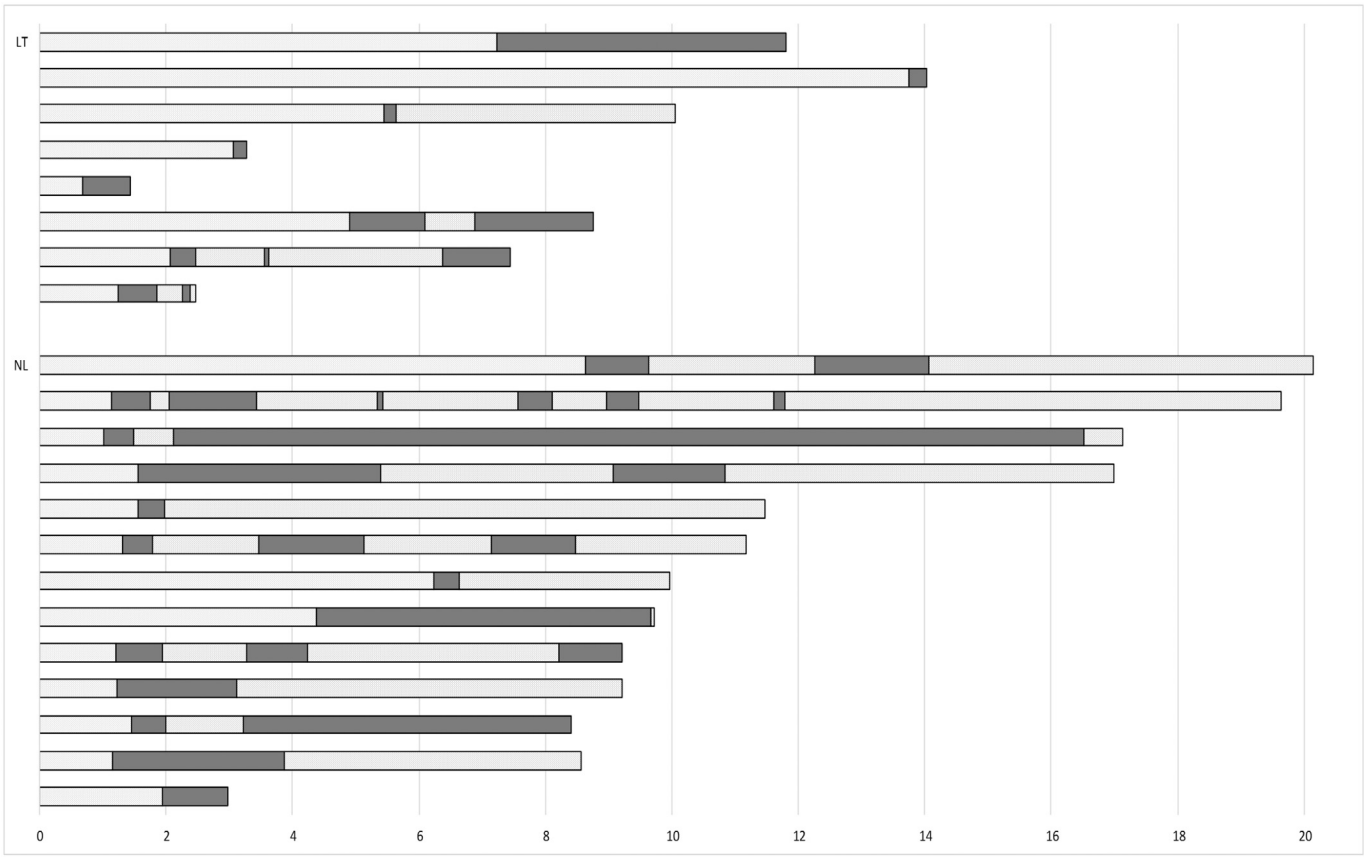

Fig. 3. Follow-up findings in 21 representative successful portoenterostomy patients who were treated with endoscopic injection sclerotherapy for significant varices. Each bar represents one patient's follow-up with spotted bar parts representing periods without significant varices and gray parts periods when significant varices were treated. In the upper part of the figure, the follow-up ended at liver transplantation (LT), and in the lower part, follow-up continues with native liver (NL). Follow-up time is in years.

GI bleeding, and in one instance GI symptoms. Sixteen patients (59%) received EIS, median 2 (1–11) treatments per patient. The first EIS occurred at median age 0.8 years (0.4–1.9). EIS treatment induced variceal bleeding requiring red blood cell transfusion and esophageal ulceration in three occasions each. One patient with terminal liver failure and repeated variceal bleeding died of esophageal perforation and mediastinitis as a complication of EIS. As shown in Table 1, 13 (48%) patients experienced GI bleeding, which originated from varices in 11 (41%) [median grade 2 (1–3) associated with gastric varices in four]. In total, five (19%) patients experienced GI bleeding before the first endoscopy, while four (15%) had variceal bleeding after commencing EIS. The first bleeding episode occurred at median age 0.7 (0.4–1.6) years. In 9 out of 11 patients with variceal bleeding, EIS treatments continued until LT or death. Age at PE was comparable between patients with and without GI bleeding [0.18 (0.04–0.70) versus 0.21 (0.11–0.25) year, p = 0.791, respectively].

4.4. Noninvasive identification of significant varices

Following successful PE, liver biochemistry, liver stiffness, and different predictive scores obtained at the time of endoscopy identified the presence of significant varices with poor accuracy (AUROC 0.61–0.72, Table 2 and Fig. 4). Individual liver biochemistry tests and scores showed no meaningful changes between the two consecutive endoscopies leading to discovery of varices (Table 3). Among failed PE patients, lowered plasma albumin concentration (optimal cutoff 25 g/L, sensitivity 0.71, specificity 0.67) indicated the presence of significant varices with an AUROC of 0.69 (95% CI 0.52–0.85, p = 0.030). In the

Table 2
Prediction of significant varices at time of endoscopy among successful portoenterostomy (PE) patients (bilirubin <34 μmol/L at any point after PE, 45 patients, total 353 surveillance endoscopies).

	N	AUROC (95% CI)	Cutoff	Sensitivity	Specificity	PPV	NPV	p
Total bilirubin, μmol/L	329	0.61 (0.54–0.67)	18	0.41	0.79	0.52	0.70	0.001
GGT, U/L	304	0.61 (0.55–0.68)	144	0.48	0.68	0.43	0.71	0.017
APRI	287	0.64 (0.57–0.70)	1.01	0.92	0.49	0.43	0.90	<0.001
Varices prediction rule[a]	212	0.72 (0.64–0.79)	2.76	0.74	0.57	0.49	0.80	<0.001
Clinical prediction rule[b]	126	0.69 (0.60–0.79)	105	0.51	0.85	0.09	0.60	<0.001
Kings variceal prediction rule[c]	126	0.67 (0.58–0.77)	68	0.67	0.68	0.16	0.58	0.002
Liver stiffness, kPa	97	0.67 (0.56–0.79)	14.1	0.88	0.49	0.37	0.92	0.010

The cutoff was set at the highest sum of sensitivity and specificity. AUROC, area under receiver operating characteristic; CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value; APRI, AST to platelets ratio index.
[a] Albumin * platelets / 1000.
[b] 0.75*platelet count)/(spleen size z-score + 5) + 2.5*albumin.
[c] 3*albumin − 2*equivalent adult spleen size.

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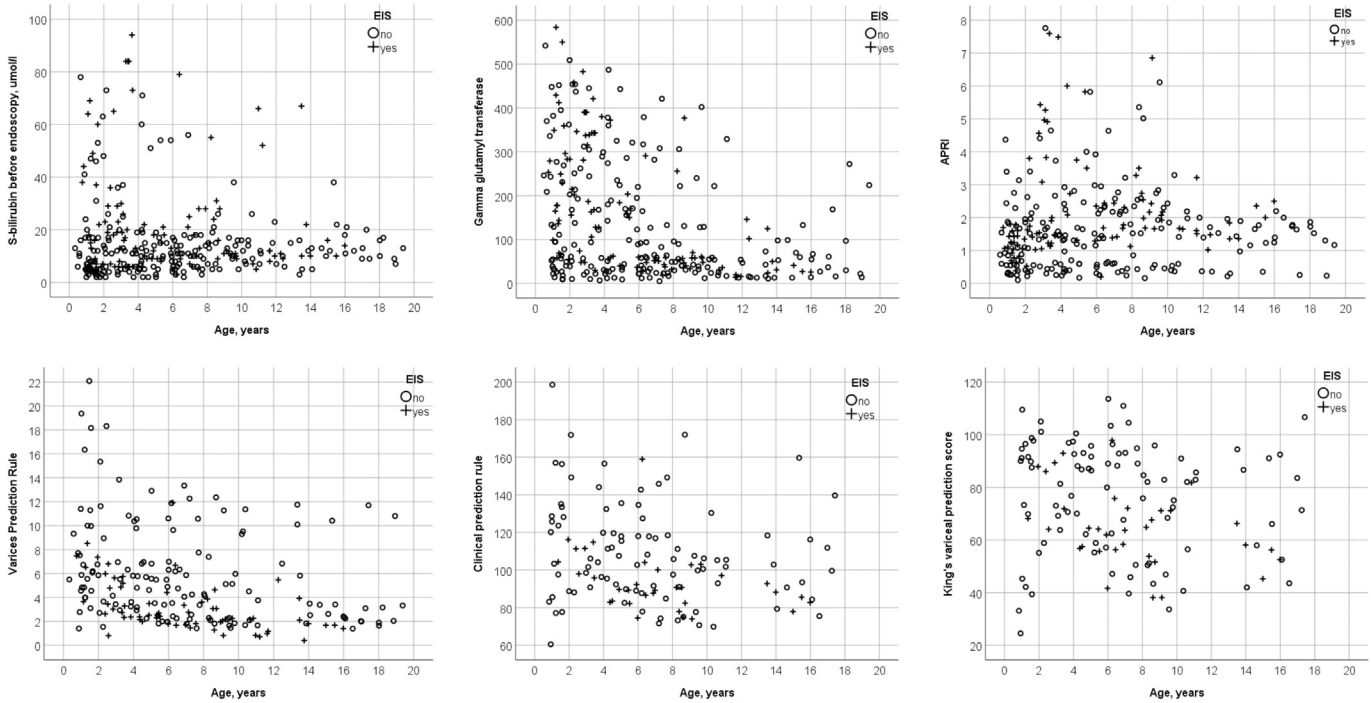

Fig. 4. Scatterplots for individual markers aimed to predict the presence of significant varices at time of endoscopy among successful portoenterostomy (PE) patients (bilirubin ≤34 μmol/L at any point after PE, 45 patients, total 353 surveillance endoscopies). APRI, AST to platelets ratio index.

entire patient cohort, PE success was the strongest predictor of variceal bleeding (Table 1).

5. Discussion

The future looks very different for BA patients whose PE succeeds or fails. Shneider et al. showed that total bilirubin greater than or less than 34 μmol/L three months after PE is a strong predictor of short-term outcome [4]. Our data support this finding, confirming that esophageal varices appear earlier and bleed more often among patients whose post-PE bilirubin remains elevated. In most previous studies addressing varices and variceal bleeding in BA [5,17,19,20], all patients were analyzed as one group although their pretest probability of liver disease complications differs markedly. The fact that the postoperative course of the liver disease depends essentially on PE success should be considered in future studies.

Our findings indicate that following successful PE, esophageal varices may appear and reappear at any time during long-term follow-up (Fig. 3). Although current studies are still limited in duration, the lifelong incidence of varices and GI bleeding increases with longer follow-up. Within our primary prophylaxis program, varices that developed after successful PE were controlled efficiently as only two (4%) patients experienced variceal bleeding after commencing EIS. We can only speculate what the incidence and severity of GI bleeding in this group might have been without the screening and primary prophylaxis program. In a systematic review of 14 studies with BA patients with 20-year native liver survival, 35 out of 162 (22%) patients had experienced GI bleeds [21].

In the present study, the accuracy of the noninvasive predictors for varices was disappointing. During longitudinal endoscopic variceal surveillance, we found poor predictive values both before any endoscopic interventions and after commencing EIS. However, VPR, CPR and K-VaPS are originally derived from treatment-naïve children, which could explain their poor accuracy after EIS. Although VPR was the most accurate predictor of varices, its AUROC remained less than 0.8 indicating only modest accuracy. VPR components, albumin and platelets, are easily available, but no online calculator seems to exist. CPR and K-VaPS are less suitable for clinical work since they require calculations with spleen size reference charts, which are based on a study with only six to 36 children in each age and sex group [16]. Targeting screening endoscopies to those with APRI >1.01 would have reduced endoscopies by 29%, and we would have missed significant varices in 10% of patients excluded from endoscopy. AST and platelets as well as APRI calculators are easily available.

Our patients underwent a large number of screening endoscopies under general anesthesia necessitating a considerable amount of resources. Repeated and especially prolonged general anesthesias may predispose children to neurodevelopmental harm [9–11]. However, general anesthesias for surveillance endoscopies are typically short, which have not been associated with later neurodevelopmental issues [22]. EIS is also associated with severe complications and the procedure related mortality may be as high as 0.3% [1]. The risk of death as a consequence of variceal bleeding appears to be 1%–3% in BA [1,3], but may be lower if liver disease is otherwise compensated [1]. In two surveys of doctors treating BA patients in Europe and Canada, 77%–85% would perform a screening gastroscopy if they clinically suspected varices in a BA patient and 58%–100% would start primary prophylaxis measures for varices [23,24]. Canadian families were less willing to accept endoscopy related risks than Canadian doctors [24]. In previous studies, BA patients

Table 3
Wilcoxon signed ranks test to explore individual changes in liver biochemistry and scores when varices first appeared during follow-up before sclerotherapy.

	Number of pairs	Negative ranks	Positive ranks	Ties	p
Total bilirubin	32	12	16	4	0.45
GGT	31	21	8	2	0.02
APRI	29	20	9	0	0.09
Varices prediction rule.[a]	15	8	7	0	0.98

Data pairs (total 38) were measured before two consecutive endoscopies: with no significant varices and with significant varices.
For liver stiffness, Clinical prediction rule, and King's variceal prediction rule <10 data pairs were available.
[a] Albumin*platelets / 1000.

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reported frequent hospital visits as the most important factor lowering their quality of life [12,13]. For these reasons, we are actively looking for the optimal and safest ways to reduce the number of endoscopies.

The Baveno VI consensus workshop pediatric symposium concludes that EVL is preferable to EIS whenever possible and that EIS is only indicated in secondary prophylaxis [1]. Our material includes two major complications, both associated with secondary prophylactic treatment of varices, one with EIS and one with EVL. The currently available EVL devices are too large for infants, including most of the failed primary treatment patients in this study. Following successful PE, it might be wise to wait and perform the first screening endoscopy only when the child is large enough to undergo EVL for primary prophylaxis. Our center now uses EVL instead of EIS for all patients who weigh more than 10 kg.

The descriptive nature, uncontrolled intervention, and lengthy inclusion period are the main limitations of our study. The strengths include comprehensive, prospective standardized endoscopic follow-up of a national cohort of BA patients and a relatively long follow-up time in the successful PE group. Carefully collected long-term follow-up data on endoscopic primary prophylaxis surveillance of esophageal varices are scarce and our findings are a significant addition to international evidence.

Despite primary prophylactic EIS in the failed PE group, 19% of patients had GI bleeds before the first endoscopy and 15% had variceal bleeding episodes after commencing EIS. The bleeds occurred early and permanent eradication of varices rarely succeeded before LT. In these patients, the treatment focused on securing survival and thriving until they received LT. Since variceal bleeding occurred often before the first endoscopy and permanent eradication of varices was inconceivable, earlier start of surveillance endoscopies seems indicated after failed PE.

6. Conclusions

BA patients may benefit from endoscopic surveillance and primary prophylaxis of varices after successful PE. Targeting of endoscopies based on liver biochemistry, stiffness, and different prediction scores remains unreliable during primary variceal prophylaxis protocol in BA. Differing prognoses of successful and failed PE patients should be considered in future studies addressing esophageal varices and associated bleeding in BA.

Acknowledgments

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References

[1] Shneider BL, de Ville de Goyet J, Leung DH, 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(4):1368–80.
[2] 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(3):743–52.
[3] 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(2):320–7.
[4] Shneider BL, Magee JC, Karpen SJ, et al. Total serum bilirubin within 3 months of hepatoportoenterostomy predicts short-term outcomes in biliary atresia. J Pediatr. 2016;170(211):7.e1 2.
[5] Witters P, Hughes D, Karthikeyan P, et al. King's variceal prediction score: a novel noninvasive marker of portal hypertension in pediatric chronic liver disease. J Pediatr Gastroenterol Nutr. 2017;64(4):518–23.
[6] Chongsrisawat V, Vejapipat P, Siripon N, et al. Transient elastography for predicting esophageal/gastric varices in children with biliary atresia. BMC Gastroenterology. 2011;18(11):41.
[7] Voutilainen S, Kivisaari R, Lohi J, et al. A prospective comparison of noninvasive methods in the assessment of liver fibrosis and esophageal varices in pediatric chronic liver diseases. J Clin Gastroenterol. 2016;50(8):658–63.
[8] Adami MR, Ferreira CT, Kieling CO, et al. Noninvasive methods for prediction of esophageal varices in pediatric patients with portal hypertension. World J Gastroenterol. 2013;19(13):2053–9.
[9] Wang X, Xu Z, Miao C. Current clinical evidence on the effect of general anesthesia on neurodevelopment in children: an updated systematic review with meta-regression. PLoS ONE [Electronic Resource]. 2014;9(1):e85760.
[10] Andropoulos DB, Greene MF. Anesthesia and developing brains — implications of the FDA warning. N Engl J Med. 2017;376(10):905–7.
[11] FDA drug safety communication. FDA review results in new warnings about using general anesthetics and sedation drugs in young children and pregnant women [internet]. USA: U.S. Food & Drug Administration; 2017 [updated 27.04.2017; cited 01.10.2017]. Available from: https://www.fda.gov/Drugs/DrugSafety/ucm532356.htm.
[12] Sundaram SS, Alonso EM, Haber B, et al. Health related quality of life in patients with biliary atresia surviving with their native liver. J Pediatr. 2013;163(4):1052,7.e2.
[13] 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(6):883–7.
[14] 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(5):574–9.
[15] Wai CT, Greenson JK, Fontana RJ, et al. A simple noninvasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C. Hepatology. 2003;38(2):518–26.
[16] Megremis SD, Vlachonikolis IG, Tsilimigaki AM. Spleen length in childhood with US: normal values based on age, sex, and somatometric parameters. Radiology. 2004;231(1):129–34.
[17] Isted A, Grammatikopoulos T, Davenport M. Prediction of esophageal varices in biliary atresia: derivation of the "varices prediction rule", a novel noninvasive predictor. J Pediatr Surg. 2015;50(10):1734–8.
[18] Gana JC, Turner D, Roberts EA, et al. Derivation of a clinical prediction rule for the noninvasive diagnosis of varices in children. J Pediatr Gastroenterol Nutr. 2010 Feb;50(2):188–93.
[19] Gana JC, Turner D, Mieli-Vergani G, et al. A clinical prediction rule and platelet count predict esophageal varices in children. Gastroenterology. 2011;141(6):2009–16.
[20] Duche M, Ducot B, Ackermann O, et al. Experience with endoscopic management of high-risk gastroesophageal varices, with and without bleeding, in children with biliary atresia. Gastroenterology. 2013;145(4):801–7.
[21] Bijl EJ, Bharwani KD, Houwen RHJ, et al. The long-term outcome of the Kasai operation in patients with biliary atresia: a systematic review. Neth J Med. 2013;71(4):170–3.
[22] Davidson AJ, Disma N, de Graaff JC, et al. Neurodevelopmental outcome at 2 years of age after general anaesthesia and awake-regional anaesthesia in infancy (GAS): an international multicentre, randomised controlled trial. Lancet. 2016;387(10015):239–50.
[23] Jeanniard-Malet O, Duche M, Fabre A. Survey on clinical practice of primary prophylaxis in portal hypertension in children. JPediatr Gastroenterol Nutr. 2017;64(4):524–7.
[24] Gana JC, Valentino PL, Morinville V, et al. Variation in care for children with esophageal varices: a study of physicians', patients', and families' approaches and attitudes. J Pediatr Gastroenterol Nutr. 2011;52(6):751–5.

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