A Model for Early Endoscopic Detection of High-Risk Gastroesophageal Varices in Children With Biliary Atresia

*Oanez Ackermann, †Paul de Boissieu, ‡Olivier Bernard, *Emmanuel Gonzales, *Emmanuel Jacquemin, and §Mathieu Duché

ABSTRACT

Objective: In children with biliary atresia and portal hypertension, progression to gastroesophageal varices carrying a risk of bleeding depends on age, total serum bilirubin concentration and initial endoscopic features. We report an attempt to use these factors for early detection of high-risk varices (HRVs).

Methods: Based on different combinations of these factors, a model was set to estimate the probabilities of emergence of HRVs at various time intervals. A 10% probability was chosen to set the date of the next endoscopy in children who did not display HRVs initially. A total of 113 children without HRVs who underwent their first endoscopy before age 8 in 2013–2020 were included. A comparison was made with children seen during the period 1990–2012 when this model was not used.

Results: In all, 65 of the 113 children underwent one to five additional endoscopies at dates set according to the model. The emergence of HRVs was recorded in 22 children after a mean interval of 14 months and was managed by endoscopic primary prophylaxis in all but one who underwent liver transplantation. Three other children bled before the next planned endoscopy. Compared with 175 children of the same age ranges without HRVs in the period 1990–2012, the use of the model was associated with a faster detection of HRVs with a lower number of endoscopic procedures ($P = 0.0022$ and $P = 0.023$, respectively).

Conclusion: The results suggest that the model reported may be a useful tool for the early detection of HRVs to allow primary prophylaxis of bleeding.

Key Words: gastrointestinal bleeding, infants, primary prophylaxis of bleeding, upper gastrointestinal endoscopy

(*JPGN* 2022;74: 643–650)

Received October 5, 2021; accepted November 25, 2021.

From the *Hepatologie et Transplantation Hépatique Pédiatriques, Centre de reference de l'atrésie des voies biliaires et des cholestases génétiques, FSMR FILFOIE, ERN RARE LIVER, Hôpital Bicêtre, AP-HP, Université Paris-Saclay, Hepatinov, Inserm U 1193, Le Kremlin-Bicêtre, the †Service d'epidemiologie et de sante publique, Hopital Bicetre AP-HP, the ‡Hépatologie et Transplantation Hépatique Pédiatriques, Centre de reference de l'atrésie des voies biliaires et des cholestases génétiques, FSMR FILFOIE, ERN RARE LIVER, Hôpital Bicêtre, AP-HP, Le Kremlin-Bicêtre, and the §Hépatologie et Transplantation Hépatique Pédiatriques, Centre de reference de l'atrésie des voies biliaires et des cholestases génétiques, FSMR FILFOIE, ERN RARE LIVER, and Radiologie pédiatrique, Hôpital Bicêtre, AP-HP, Université Paris-Saclay, Hépatinov, Inserm U 1193, and Radiologie pédiatrique, Hôpital Bicêtre, AP-HP, Le Kremlin-Bicêtre, France.

Address correspondence and reprint requests to Oanez Ackermann, MD, Hépatologie et Transplantation Hépatique Pédiatriques, CHU Bicêtre, 78 rue du Général Leclerc, 94275 Le Kremlin, Bicêtre, cedex (e-mail: oanez.ackermann@aphp.fr).

The authors report no conflicts of interest.

Funding Source: None.

DOI: 10.1097/MPG.0000000000003375

What Is Known

- Gastrointestinal bleeding occurs in 20% of children with biliary atresia at a median age of 17 months.
- Characteristic variceal patterns on gastroesophageal endoscopy carry a high risk of bleeding.
- Speed of emergence of high-risk varices in children who do not display these signs initially depends on age, serum bilirubin and initial endoscopic features.

What Is New

- A model based on combinations of these factors estimates the probability of emergence of high-risk varices at various time intervals.
- The use of this model, based on a 10% probability, allows early identification of high-risk varices allowing primary prophylaxis of bleeding.

Portal hypertension develops early in children with biliary atresia. In one report, gastroesophageal varices were found on upper gastrointestinal endoscopy in 63% of children at a median age of 13 months, and 31% of the latter presented with gastrointestinal bleeding at a median age of 17 months (1). Although it is still debated among pediatric gastroenterologists, primary prophylaxis of bleeding for children with biliary atresia and portal hypertension by endoscopic band ligation of gastroesophageal varices, or sclerotherapy in younger infants, is increasingly reported (2–16). Gastroesophageal varices carrying a high risk of bleeding (high-risk varices, HRVs) and warranting primary prophylaxis of bleeding were found in 266 of 734 (36%) children with biliary atresia and portal hypertension who underwent upper gastrointestinal endoscopy, at a median age of 14 months (9). In some children with biliary atresia, HRVs are found at the first endoscopic examination; in other children who do not display HRVs at the first endoscopic examination, the question arises as to when the next endoscopic examination should be scheduled in order to detect HRVs and carry out primary prophylaxis before spontaneous bleeding occurs. We have previously reported that four factors are related to the emergence of HRVs in children in whom a previous endoscopy didnot disclose HRVs: age, number and grade of esophageal varices, and total serum bilirubin concentration at the time of the endoscopic examination (17). Here, we report an attempt to put into practice these predicting factors for the endoscopic surveillance of children with biliary atresia and portal hypertension.

PATIENTS AND METHODS

From January 1990 to June 2020, 864 children with biliary atresia who presented with palpable splenomegaly and/or ultrasonographic signs of portal hypertension underwent ≥1 upper gastrointestinal endoscopic examination(s), and the following items were recorded at each examination (9): grade of esophageal varices (18), red wale markings on esophageal mucosa (19), gastric varices along the cardia (20) and portal hypertensive gastropathy. Based on previous experiences both in adults and children (1,9,21–24), HRVs were defined as grade 3 esophageal varices, grade 2 esophageal varices with red markings and/or gastric varices along the cardia, or gastric varices along the cardia with or without esophageal varices. To assess the severity of the endoscopic pattern, we devised the HRV score, a composite score calculated as follows: one point for grade 1 esophageal varices, two points for grade 2 esophageal varices, three points for grade 3 esophageal varices, and one point each for the presence of red markings or gastric varices along the cardia. When esophageal varices of different grades were present, the highest grade was used for the calculation of the score.

Each endoscopic procedure was performed or supervised by the same endoscopist (M.D.), and the criteria for recording the endoscopic signs remained unchanged throughout the study period. Between 1990 and 2012, no systematic rule was applied concerning the frequency of repeat endoscopies in children who had already undergone a first examination showing absence of HRVs. Starting from January 2013, a program of endoscopic surveillance was established to detect the emergence of HRVs in children with low-risk varices at the first examination, according to a model based on the four factors previously reported to be linked to the emergence of HRVs: age, total serum bilirubin concentration and number and grade of esophageal varices at the time of the first endoscopic examination. The data used to develop this model had been obtained in children with biliary atresia who displayed low-risk varices at the first endoscopic examination and who had undergone at least one additional examination (17). Using data from the Cox model analysis reported in this previous article (17), different patterns according to each combination of the four factors were established and probabilities of emergence of HRVs after 6, 12, 24, and 36 months were estimated for each of the patterns. Children with biliary atresia who did not display HRVs at the first examination performed before the age of 8 years were scheduled to undergo a second endoscopic examination after the time period defined by the model, based, as a rule, on a 10% probability of emergence of HRVs according to their age, number and grade of esophageal varices, and total serum bilirubin concentration at the time of the initial endoscopy. This 10% probability was chosen because it had been reported in a similar study performed in adult patients (25). The date of the next endoscopy could be brought forward if the total serum bilirubin concentration increased in the meantime; in younger infants the time to the next endoscopy could be halved in the event of a rapid increase in the serum bilirubin concentration. In children for whom the model predicted a >10% probability of emergence of HRVs after 6 months, primarily young infants with early failure of the Kasai operation, very high serum bilirubin concentration and poor clinical condition, the next endoscopy was scheduled within a few weeks or months after the first one, depending on the severity of the clinical condition and of the endoscopic pattern. In children for whom the model predicted a <10% probability of emergence of HRVs after 36 months, primarily older children after a successful restoration of bile flow after the Kasai operation, the next endoscopy was scheduled 36 months after the previous one. The results of this endoscopic surveillance form the basis of this report and were compared with the period 1990–2012 with respect to the speed of detection of HRVs. Because the study period was limited to 8 years, only children who underwent their first endoscopy before the age of 8 years between 1990 and 2012 and underwent an additional endoscopy within 8 years of the first were included in this comparison.

Parents were informed of the endoscopic findings, of the risk of bleeding in case of progression to HRVs and of the potential preventive treatment if HRVs were found on a subsequent examination. Informed consent from each child's parents was obtained in writing before each session. According to French legislation, ethics committee agreement is not required for the retrospective collection of data corresponding to current practice. The data collection was carried out according to the recommendations of the French Data Protection Authority (''Commission nationale de l'informatique et des libertéis'') and in accordance with the General Data Protection Regulation.

Descriptive statistics were performed using frequency (percentage) for qualitative variables and median (range) for quantitative variables. Comparisons between children with their first upper GI endoscopy 1990–2012 and 2013–2020 were performed using the t-test for quantitative variables or Fisher test for qualitative variables.

RESULTS

Description of the Model

Table 1 shows the various probabilities (in %) of emergence of HRVs depending on three age ranges (<12, 12–18, and >18 months), on two serum bilirubin concentrations (≤100 and >100 μM) and on seven possible low-risk endoscopic patterns (from no esophageal varices to three grade 2 esophageal varices) recorded at the time of the first examination. For each combination of age, bilirubin concentration and endoscopic pattern, the figures estimate the probabilities of emergence of HRVs 6, 12, 24, and 36 months later. The probability of emergence of high-risk gastroesophageal varices is estimated to be highest and the emergence of these high-risk signs fastest in children below 12 months of age, with a serum bilirubin concentration > 100 μM and displaying three grade 2 varices; conversely, the probability of emergence of HRVs is estimated to be lowest and the emergence of these HRVs slowest in children >18months, with a serum bilirubin concentration ≤100 μM and displaying no varices.

Results of the Scheduled Endoscopic Surveillance

From January 2013 to June 2020, 154 children with biliary atresia and portal hypertension underwent a first endoscopic examination before the age of 8 years, at a median age of 11 months (range, 3 months—7 years) (Table 2 and Fig. 1). Forty-one children (27%) displayed HRVs at this first examination. One hundred and thirteen children (73%) did not display HRVs at the first examination and were included in the endoscopic monitoring according to the model. Forty-eight of these 113 children did not undergo the second endoscopic examination at the date set by the model, either because they bled spontaneously or because they underwent liver transplantation before the date set for the second endoscopic examination (2 and 17 children, respectively), or because they had not yet reached the date set for the next examination at the time of writing, a median of 20 months after the first examination (29 children). Thus, 65 of the 113 children underwent ≥1 additional endoscopic examination(s) at dates set according to the model; these 65 children underwent a total of two to six endoscopies (median, 2), with the last one at a median interval of 12 months (range, 26 days–6 years) after the first one. The interval between the

TABLE 1. Probability (in %) of emergence of high-risk gastroesophageal varices at a given endoscopic examination as estimated by the Cox model, according to age, characteristics of esophageal varices and total serum bilirubin concentration at the previous endoscopic examination

Age	>18 mo		12–18 mo		<12 mo	
bilirubin (μM)	≤100	>100	≤100	>100	≤100	>100
Endoscopy						
No EV						
6 mo	0.2	1	1	1	2	4
12 mo	1	2	3	6	7	15
24 mo	2	5	6	13	14	31
36 mo	4	9	10	23	25	50
One EV grade 1						
6 mo	0.4	**1**	1	2	3	6
12 mo	2	**4**	4	9	11	23
24 mo	3	**8**	9	19	22	44
36 mo	6	**14**	16	33	37	67
Two EV grade 1						
6mo	1	1	2	4	4	10
12 mo	2	6	6	14	16	34
24mo	5	12	13	29	32	60
36 mo	10	21	24	48	52	83
Three EV grade 1						
6mo	1	2	2	6	7	15
12 mo	4	9	10	22	25	49
24mo	8	18	20	42	46	77
36 mo	15	32	35	64	69	94
One EV grade 2						
6 mo	1	3	4	9	10	23
12 mo	6	14	15	33	36	66
24 mo	13	27	31	58	63	90
36 mo	23	45	50	81	85	99
Two EV grade 2						
6 mo	2	5	6	14	16	33
12 mo	9	21	23	47	51	82
24 mo	19	40	44	75	79	98
36 mo	33	62	67	93	95	99
Three EV grade 2						
6mo	4	8	10	21	24	48
12 mo	14	31	34	63	68	93
24 mo	29	56	60	89	92	99
36 mo	48	79	83	98	99	100

Data are extracted from the study of children with biliary atresia displaying low-risk varices at the first endoscopic examination and who underwent at least one additional examination, previously reported in Duche *et al.* (17). For example (figures in bold), for an >18-month-old child with one grade 1 esophageal varix and a serum bilirubin concentration >100 μM, the probability of emergence of high-risk gastroesophageal varices is estimated to be 1% after 6 months, 4% after 12 months, 8% after 24 months, and 14% after 36 months. EV = esophageal varices; mo: months.

first and the second endoscopic examinations was <6 months (median, 3 months; range, 26 days–5 months) in 16 infants (ages: 3–10months, and total serum bilirubin concentrations: 101–395 μM at the first endoscopy). Emergence of HRVs was recorded at the second endoscopy in 8 of these 16 children. In total, HRVs were detected in 22 of the 65 children (34%) 40 days to 5 years (median, 7 months) after the first endoscopy. Twenty-one of these 22 children underwent endoscopic primary prophylaxis of bleeding and one underwent liver transplantation. One of the 43 other children who did not display HRVs at the second endoscopy bled before the date set for the third endoscopic examination. In all, in this population of 113 children, three children bled because of progression to HRVs that were not present on the initial or second endoscopy and were missed. In one child, aged $4^{1}/_{2}$ months with a total serum bilirubin concentration of360 μM, the initial endoscopy displayed three grade 2 varices with no red markings and no gastric varices along the cardia. The second endoscopy was scheduled 4 weeks later but delayed for a few days because of an intercurrent respiratory infection. Bleeding occurred 27 days after the initial endoscopy and endoscopy at the time of bleeding showed the emergence of red markings and gastric varices; liver transplantation was necessary one month after the bleeding episode because of hepatic decompensation in spite of eradication of the varices by endoscopic secondary prophylaxis. Another child missed the scheduled appointment for the second endoscopy and escaped medical supervision for 32 months until bleeding occurred after progression to HRVs. In the third child, already mentioned, the grade of varices at the second endoscopy may have been underestimated, resulting in advising a 36-month interval until the next endoscopy while progression of varices and bleeding occurred 17 months later. None of these two children died or required emergency liver transplantation as a consequence of bleeding. Therefore, during the 8 years of this study, 25 children without HRVs at the initial endoscopy displayed HRVs on the occasion of an additional endoscopy planned according to the model (22 children) or on the occasion of an episode of gastrointestinal bleeding (three children) (Fig. 1).

To determine whether the proposed model would improve the detection of HRVs before bleeding, we compared the intervals between the date of the first endoscopy that did not show HRVs and the date of the endoscopy showing HRVs, in the period 2013–2020 of the present study and in the period 1990–2012 when this model was not used. The number of endoscopic examinations between these dates was also compared. For that purpose, 67 children who underwent ≥ 2 endoscopies during the 8 years of the present study, the second or third endoscopy being performed either at dates planned by the model or because of spontaneous variceal bleeding, were compared with 175 children who underwent a first endoscopy before age 8 between 1990 and 2012 and ≥1 additional endoscopy within the following 8 years. The results shown in Table 3 suggest that, in these age ranges, the current model is associated with a faster detection of HRVs with a smaller number of endoscopic examinations.

DISCUSSION

These results suggest that the model reported may provide a useful tool for the early detection of HRVs before spontaneous bleeding and allow primary prophylaxis to lower the risk of spontaneous bleeding in children with biliary atresia and portal hypertension.

In children with biliary atresia, spontaneous bleeding from gastroesophageal varices carries a risk of death, sometimes requires emergency liver transplantation or results in severe morbidity (9,13,16,26–33). Detection of HRVs before spontaneous bleeding has become a key element in the management of this population. Bleeding can occur in children at an age ≤6 months (1,10,11,13,16,34). In one report, gastroesophageal varices were found on upper gastrointestinal endoscopy at the time of the Kasai operation in over half of the children (35). There is clearly a population of children exposed to early development of HRVs and spontaneous bleeding. This raises the issue of the date of the first endoscopy to provide the best possibility of early detection of HRVs. A portal pressure > 15 cm saline measured during the Kasai operation is associated with a 20% risk of bleeding or of emergence of grade ≥2 esophageal varices and/or gastric varices before the age

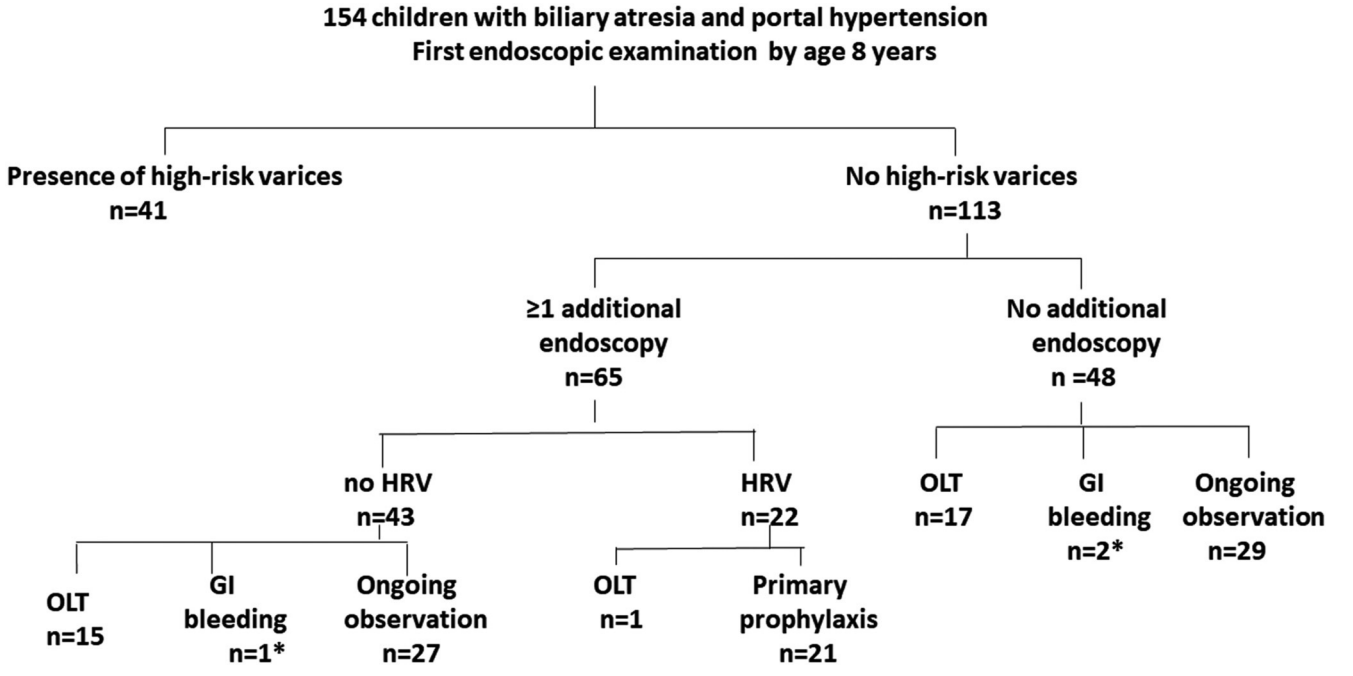

FIGURE 1. Flowchart of 154 children with biliary atresia who underwent a first upper gastrointestinal endoscopic examination before the age of 8 years between 2013 and 2020. *Three children bled because of progression to high-risk varices prior to the date of emergence of HRV predicted by the model or for not attending the planned date of the next examination.

of 10months (36). It has also been reported that early bleeding is primarily seen in children in whom the Kasai operation is unsuccessful (10,11); total serum bilirubin is indeed an independent factor combined with a risk of emergence of grade 2 or 3 esophageal varices or gastric varices (1,35,36); however, children whose serum bilirubin normalizes are also exposed to early significant signs of portal hypertension if portal pressure is raised at the time of the Kasai operation (36). Therefore, we suggest that the measurement of portal pressure be part of the surgical procedure (37) and that upper gastrointestinal endoscopy be carried out early in children whose portal pressure measurement is >15 cm saline. The date of this first endoscopy cannot be ascertained, but the lowest age of spontaneous bleeding reported in the literature was 4months (1,11,38). We suggest endoscopy be performed at 4 months of age to allow time for primary prophylaxis if deemed necessary and, in children who do not display HRVs at this first endoscopy, to apply endoscopic surveillance according to the model reported here, especially since, in the first year of life, progression to HRVs can be extremely rapid. Since the median age of spontaneous gastrointestinal bleeding was reported to be 17 months in children with biliary atresia (1), a first endoscopy performed at an earlier age, as reported in the present study, may contribute to an earlier detection of HRVs. In children whose portal pressure is not available, the presence of palpable splenomegaly and/or ultrasonographic signs of portal hypertension could be used to decide on early upper gastrointestinal (GI) endoscopy (39). This is especially important in children for whom the Kasai operation is unsuccessful (10,11). The use of other surrogate markers of portal hypertension can be disappointing in this population of children (11).

The use of the model presented here appears to be associated with a decrease in the occurrence of spontaneous bleeding. Among the children in whom HRVs emerged during the study period, three episodes of spontaneous variceal gastrointestinal bleeding were recorded and 22 HRVs were detected without spontaneous bleed-

TABLE 2. Distribution, according to the age at the first endoscopic examination, of 154 children with biliary atresia and portal hypertension investigated between 2013 and 2020

Age at first endoscopy (y)	154 children who underwent ≥1 endoscopic examination(s)	113 children with no HRV at first endoscopy	65 children with no HRV who underwent ≥ 2 endoscopic examinations
0–1	86	58	38
1–2	33	27	14
2–3	15	11	4
3–4	8	7	6
4–5	1	1	1
5–6	3	2	0
6–7	7	6	2
7–8	1	1	0

TABLE 3. Main featuresand detection of high-risk gastroesophageal varices in 242 children with biliary atresia who did not display high-risk varices on their first upper gastrointestinal endoscopic examination performed before age 8 and who underwent ≥1 additional upper endoscopic examination(s) during the next 8 y

	Date of first upper GI endoscopy		
	1990–2012 n = 175	2013–2020 n = 67	*P* value[†]
Age at Kasai operation (days)			
Range	15–210	20–159	0.025
Mean	64	54	
Not done (n)	8	4	
At first endoscopic examination			
Age			
Mean	22 mo	16 mo	0.029
Range	4 mo–7 y	3mo–6 y	
Median	13 mo	10 mo	
Total serum bilirubin (μM)			
Mean	122	137	0.41
Range	3–688	4–395	
<17 μM, n	51	24	0,35
Prothrombin ratio <70%, n	18	12	0.12
Serum albumin (G/L)			
Mean	36	36	0.76
Range	23–45	24–44	
Number of esophageal varices			
Mean	1.13	1.22	0.49
Range	0–4	0–3	
Grade of esophageal varices			
No varices, n	48	16	
Grade 1, n	91	30	
Grade 2, n	36	21	
Grade 3, n	0	0	
Mean grade	0.93	1.07	0.15
Red markings[*],n	6	0	
Gastric varices along the cardia, n	0	0	
High-risk varices, n	0	0	
Portal hypertensive gastropathy, n	38	21	0.13
At last endoscopic examination			
Time from first endoscopy			
Mean	31 mo	21 mo	0.011
Range	20 days–7 y	26 days–6y	
Total serum bilirubin (μM)			
Mean	151	145	0.84
Range	3–1180	4–523	
≤ 17 μM, n	49	22	0.52
Prothrombin ratio <70%, n	35	19	0.16
Serum albumin (G/L)			
Mean	34	36	0.075
Range	21–44	24–43	
Number of endoscopies			
Mean	2.7	2.6	0.41
Range	2–8	2–6	

TABLE 3. (continued)

	Date of first upper GI endoscopy		
	1990–2012 n = 175	2013–2020 n = 67	*P* value[†]
Number of esophageal varices			
Mean	1.63	1.51	0.40
Range	0–4	0–3	
Grade of esophageal varices			
No varices, n	31	11	
Grade 1, n	55	14	
Grade 2, n	58	32	
Grade 3, n	31	10	
Mean grade	1.51	1.61	0.45
Red markings, n	55	22	0.87
Gastric varices along the cardia, n	59	13	0.04
Portal hypertensive gastropathy, n	74	33	0.38
High-risk varices, n	77	25	0.38
HRV score[**], mean	3.66	3.80	0.48
Number of endoscopies to detect HRV			
Mean	3.19	2.44	0.023
Range	2–8	2–6	
Time from first endoscopy to detection of HRV			
Mean	31 mo	14 mo	0.0022
Range	20 days–7 y	27 days–5y	
Median	25 mo	7 mo	
Spontaneous GI bleeding with HRV, n	26 (14.8%)	3 (4.4%)	0.02

Children are sorted into two periods of time depending on the date of the first endoscopic examination: 1990–2012 when no systematic rule was applied concerning the frequency of repeat endoscopies and 2013 -2020 when a set program of surveillance was established based on age, total serum bilirubin concentration and endoscopic pattern at the time of the first examination. [*]On grade 1 esophageal varices. [**]In children with high-risk varices, a composite score was calculated as follows: one point for grade 1 esophageal varices, two points for grade 2 esophageal varices, three points for grade 3 esophageal varices and one point each for the presence of red markings or gastric varices along the cardia. Sixty-four children who underwent ≥1 additional endoscopic examination(s) at dates set by the model and did not bleed spontaneously from gastroesophageal varices and three children whose progression to high-risk varices and bleeding occurred during the period of study but was missed (see text). [†]t-test or Fisher exact test where appropriate. On grade 2 or 3 esophageal varices. GI = gastrointestinal; HRV = high-risk varices.

ing, allowing primary prophylaxis of bleeding. This amounts to a 12% rate of spontaneous variceal bleeding among children with HRVs, which is lower than the expected rate of spontaneous bleeding in children with biliary atresia and HRVs who do not undergo primary prophylaxis (≥60% in (1,9,17)).

In addition to the need for the parents and their child to comply with the recommendations concerning the dates of the endoscopies and to the occasional error in the interpretation of the endoscopic pattern, which explain two of the three missed developments of HRVs reported here, data presented in this report suggest that there are two points that should be improved in the use of the model. First, in younger infants < 18 months of age in whom the Kasai operation is unsuccessful and who carry the highest risk of bleeding (10,11), isolated grade 2 esophageal varices without red markings and gastric varices along the cardia should probably warrant primary prophylaxis of bleeding because, as seen in one patient in this report and in another previously mentioned (9), progression to a more serious endoscopic pattern and bleeding can be extremely rapid, in a matter of a few weeks. In addition, effective sclerotherapy is likely to be more easily carried out at this age on isolated grade 2 esophageal varices than on grade 2–3 varices with red markings and/or gastric varices. Moreover, as early bleeding can occur in children with a functioning Kasai operation and normal or near-normal total serum bilirubin concentration, this recommendation should also apply to them. Variceal bleeding without jaundice was reported at ages ranging from 9 to 18 months (30,40) and we have encountered, in the period 1990–2012, two infants who bled at the age of 7 months and who displayed total serum bilirubin concentrations of 32 and 35 μM, respectively. Second, in older children after a successful Kasai operation, the main drawback of the model reported here is the number of repeat upper gastrointestinal endoscopic examinations performed at dates recommended by the model but which did not display HRVs. This number was not, on average, higher than the numbers recorded during the preceding period when no defined protocol was used and the use of yearly endoscopies has been reported by others (3,41). Nevertheless, it would be useful to be able to reduce the frequencies of endoscopies without missing the emergence of HRVs. On the one

hand, there is the risk of performing excessive numbers of endoscopies with their psychological and possibly neurocognitive consequences. These children are generally over 3 years of age, have a total serum bilirubin concentration $\leq 50\ \mu M$ (42,43) after a successful Kasai operation and should be left to lead as normal a life as possible. On the other hand, severe bleeding can occur at any age and require emergency liver transplantation or a TIPS procedure (29,30,44). Choosing a higher probability of emergence of HRVs in Table 1, resulting in a later date for the next endoscopic examination, could be attempted. Simple, reliable and consistent noninvasive methods predicting HRVs based on the study of large numbers of children with biliary atresia would be welcome to complement the model we present (24,45–47).

Acknowledgments: We are deeply indebted to Beatrice Ducot, MD, now retired, who performed the statistical analysis leading to Table 1.
We thank AMFE (Association Maladie Foie Enfants, Malakoff, France), MLD (Monaco Liver disorder, Monaco), Association ''Pour Louis 1000 Foie Merci'' (Fournet-Luisans, France), Association ''Il était un foie'' (Plouescat, France) and Fondation Rumsey-Cartier (Geneve, Switzerland) for their support.

REFERENCES

1. Duche M, Ducot B, Tournay E, et al. Prognostic value of endoscopy in children with biliary atresia at risk for early development of varices and bleeding. *Gastroenterology* 2010;139:1952–60.
2. Stringer MD, Howard ER, Mowat AP. Endoscopic sclerotherapy in the management of esophageal varices in 61 children with biliary atresia. *J Pediatr Surg* 1989;24:438–42.
3. Sasaki T, Hasegawa T, Nakajima K, et al. Endoscopic variceal ligation in the management of gastroesophageal varices in postoperative biliary atresia. *J Pediatr Surg* 1998;33:1628–32.
4. Gonçalves 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.
5. Celińska-Cedro D, Teisseyre M, Woynarowski M, et al. Endoscopic ligation of esophageal varices for prophylaxis of first bleeding in children and adolescents with portal hypertension: preliminary results of a prospective study. *J Pediatr Surg* 2003;38:1008–11.
6. Mitsunaga T, Yoshida H, Kouchi K, et al. Pediatric gastroesophageal varices: treatment strategy and long-term results. *J Pediatr Surg* 2006;41:1980–3.
7. Duché M, Habéis D, Roulleau P, et al. Prophylactic endoscopic sclerotherapy of large esophagogastric varices in infants with biliary atresia. *Gastrointest Endosc* 2008;67:732–7.
8. 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;145:801–7.
9. 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.
10. 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.
11. Lampela H, Hukkinen M, Kosola S, et al. Poor performance of noninvasive predictors of esophageal varices during primary prophylaxis surveillance in biliary atresia. *J Pediatr Surg* 2020;55:2662–7.
12. Pimenta JR, Ferreira AR, Bittencourt PF, et al. Evaluation of primary prophylaxis with propranolol and elastic band ligation in variceal bleeding in cirrhotic children and adolescents. *Arq Gastroenterol* 2016;53:257–61.
13. 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 Proe* 2019;51:171–8.
14. Galand J, Ley D, Coopman S, et al. Primary prophylaxis of oesophageal variceal bleeding in children by ligation is safe and as efficient as secondary prophylaxis. *J Hepatol* 2018;68:600–1.
15. Quintero J, Juampérez J, Mercadal-Hally M, et al. Endoscopic variceal ligation as primary prophylaxis for upper GI bleeding in children. *Gastrointest Endose* 2020;92:269–75.
16. Wanty C, Helleputte T, Smets F, et al. Assessment of risk of bleeding from esophageal varices during management of biliary atresia in children. *J Pediatr Gastroenterol Nutr* 2013;56:537–43.
17. Duche M, Ducot B, Ackermann O, et al. Progression to high-risk gastroesophageal varices in children with biliary atresia with low-risk signs at first endoscopy. *J Pediatr Gastroenterol Nutr* 2015;60:664–8.
18. Cales P, Zabotto B, Meskens C, et al. Gastroesophageal endoscopic features in cirrhosis: observer variability, interassociations, and relationship to hepatic dysfunction. *Gastroenterology* 1990;98:156–62.
19. Beppu K, Inokuchi K, Koyanagi N, et al. Prediction of variceal hemorrhage by esophageal endoscopy. *Gastrointest Endose* 1981;27:213–8.
20. Sarin SK, Lahoti D, Saxena SP, et al. Prevalence, classification and natural history of gastric varices: a long-term follow-up study in 568 portal hypertension patients. *Hepatology* 1992;16:1343–9.
21. Kleber G, Sauerbruch T, Ansari H, et al. Prediction of variceal hemorrhage in cirrhosis: a prospective follow-up study. *Gastroenterology* 1991;100:1332–7.
22. Horigome H, Nomura T, Saso K, et al. Endoscopic injection sclerotherapy for esophagogastric variceal bleeding in children with biliary atresia. *Hepatogastroenterology* 1999;46:3060–2.
23. Pimenta JR, Ferreira AR, Fagundes ED, et al. Factors associated with bleeding secondary to rupture of esophageal varices in children and adolescents with cirrhosis. *J Pediatr Gastroenterol Nutr* 2017;64:e44–8.
24. Sohn H, Park S, Kang Y, et al. Predicting variceal bleeding in patients with biliary atresia. *Scand J Gastroenterol* 2019;54:1385–90.
25. Cales P, Desmorat H, Vinel JP, et al. Incidence of large oesophageal varices in patients with cirrhosis: application to prophylaxis of first bleeding. *Gut* 1990;31:1298–302.
26. Desai MS, Zainuer S, Kennedy C, et al. Cardiac structural and functional alterations in infants and children with biliary atresia, listed for liver transplantation. *Gastroenterology* 2011;141:1264–72.
27. De Vries W, de Langen ZJ, Aronson DC, et al. Mortality of biliary atresia in children not undergoing liver transplantation in the Netherlands. *Pediatr Transplant* 2011;15:176–83.
28. van Heurn LW, Saing H, Tam PK. Portoenterostomy for biliary atresia: Long-term survival and prognosis after esophageal variceal bleeding. *J Pediatr Surg* 2004;39:6–9.
29. Samyn M, Davenport M, Jain V, et al. Young people with biliary atresia requiring liver transplantation: a distinct population requiring specialist care. *Transplantation* 2019;103:e99–107.
30. Sanada Y, Mizuta K, Urahashi T, et al. Indication of liver transplantation for jaundice-free biliary atresia with portal hypertension. *Ann Transplant* 2011;16:7–11.
31. D'Souza R, Grammatikopoulos T, Pradhan A, et al. Acute-on-chronic liver failure in children with biliary atresia awaiting liver transplantation. *Pediatr Transplant* 2019;23:e13339.
32. Jayakumar S, Odulaja A, Patel S, et al. Surviving Sengstaken. *J Pediatr Surg* 2015;50:1142–6.
33. Carneiro de Moura M, Chen S, Kamath BM, et al. Acute variceal bleeding causes significant morbidity. *J Pediatr Gastroenterol Nutr* 2018;67:371–6.
34. Howard ER, Stringer MD, Mowat AP. Assessment of injection sclerotherapy in the management of 152 children with oesophageal varices. *Br J Surg* 1988;75:404–8.
35. Khanna V, Bhatnagar V, Agarwala S, et al. Portal pressure and blood nitric oxide levels as predictors of outcome in biliary atresia. *J Indian Assoc Pediatr Surg* 2016;21:49–53.
36. Duche M, Fabre M, Kretzschmar B, et al. Prognostic value of portal pressure at the time of Kasai operation in patients with biliary atresia. *J Pediatr Gastroenterol Nutr* 2006;43:640–5.
37. Kasai M, Okamoto A, Ohi R, et al. Changes of portal vein pressure and intrahepatic blood vessels after surgery for biliary atresia. *J Pediatr Surg* 1981;16:152–9.
38. van Wessel DB, Witt M, Bax N, et al. Variceal bleeds in patients with biliary atresia. *Eur J Pediatr Surg* 2018;28:439–44.

39. Fagundes ED, Ferreira AR, Roquete ML, et al. Clinical and laboratory predictors of esophageal varices in children and adolescents with portal hypertension syndrome. *J Pediatr Gastroenterol Nutr* 2008;46:178–83.
40. Altman RP. Portal decompression by interposition mesocaval shunt in patients with biliary atresia. *J Pediatr Surg* 1976;11:809–14.
41. Luoto TT, Koivusalo AI, Pakarinen MP. Long-term outcomes and health perceptions in pediatric-onset portal hypertension complicated by varices. *J Pediatr Gastroenterol Nutr* 2020;70:628–34.
42. Hasegawa T, Tamada H, Fukui Y, et al. Distal splenorenal shunt with splenopancreatic disconnection for portal hypertension in biliary atresia. *Pediatr Surg Int* 1999;15:92–6.
43. Shneider BL, Abel B, Haber B, et al. Portal hypertension in children and young adults with biliary atresia. *J Pediatr Gastroenterol Nutr* 2012;55:567–73.
44. Huppert PE, Goffette P, Astfalk W, et al. Transjugular intrahepatic portosystemic shunts in children with biliary atresia. *Cardiovasc Intervent Radiol* 2002;25:484–93.
45. Chiou FK, Ong C, Low Y, et al. Non-invasive predictors for the first variceal hemorrhage in children with biliary atresia after Kasai portoenterostomy. *J Clin Exp Hepatol* 2019;9:581–7.
46. Tomita H, Ohkuma K, Masugi Y, et al. Diagnosing native liver fibrosis and esophageal varices using liver and spleen stiffness measurements in biliary atresia: a pilot study. *Pediatr Radiol* 2016;46:1409–17.
47. Yokoyama S, Ishigami M, Honda T, et al. Spleen stiffness by 2-D shear wave elastography is the most accurate predictor of high-risk esophagogastric varices in children with biliary atresia. *Hepatol Res* 2019;49:1162–8.