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ORIGINAL ARTICLE

Validating the BAVENO VI criteria to identify low risk biliary atresia patients without endoscopy for esophageal varix

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Summary
Background and aims. — Portoenterostomy is the initial surgical treatment for biliary atresia (BA); however, no curative therapy exists for BA. Varix bleeding is a major complication of end-stage liver disease and must be determined in patients with BA, necessitating routine surveillance using esophagogastroduodenoscopy (EGD). We attempted to validate criteria to identify BA patients requiring EGD.
Methods. — From January 2007 to December 2017, we selected BA patients who underwent Kasai surgery, transient elastography (TE), and EGD at Severance hospital. In total, 190 cases were included; laboratory tests and EGDs were carried out from 3 months before TE to 3 months after TE.
Results. — Based on the cut-off value (< 10) of the liver stiffness measurement (LSM), 35 (81.4%) patients with low-risk varix (LRV) and 8 (18.6%) with high-risk varix (HRV) were identified. Based on platelet counts (> 150,000), 87 (77.68%) patients with LRV and 25 (22.32%) with HRV were identified. Based on this, the BAVENO VI criteria, which identify patients who can safely avoid screening EGD, missed 9/68 (13.24%) of HRV patients. The expanded BAVENO VI criteria missed 21/68 (30.88%) of HRV patients. However, the criteria using LSM <10 and platelet count > 150,000 missed identifying only 4/68 (5.88%) HRV patients.

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Conclusions. — The BAVENO criteria may be as useful in children with BA as in adults with liver cirrhosis. Regular laboratory tests, imaging studies, and EGD may avoid missing diagnoses of varices in BA patients. However, LSM < 10 and platelet count > 150,000 may provide more accurate criteria and help identify patients who does not need endoscopy.

Introduction

Biliary atresia (BA) is an idiopathic progressive obliteration of the hepatic or common bile duct that can cause neonatal obstructive cholangiopathy in the first month of life [1,2]. BA is a rare disease with unknown etiology; it occurs in approximately 1.06 of 10,000 live births in Korea [3]. The portoenterostomy (Kasai) procedure was introduced as the initial surgical treatment for BA. However, no curative therapy still exists for BA [4]. BA is the leading cause of end-stage liver disease and an indication for liver transplantation in children [4,5]. Sequential surgical management with the Kasai operation followed by liver transplantation is the current standard of care for patients who progress to end-stage liver disease. Moreover, esophageal varix is a major complication of end-stage liver disease to be determined in BA patients. Therefore, it is essential to perform routine surveillance such as esophagogastroduodenoscopy (EGD) to evaluate for esophageal varix [6—8]. However, since EGD is invasive procedure, even risk is mainly related to anesthesia in patients with high American Society of Anesthesiologists class, a non-invasive test to identify patients requiring EGD may be beneficial in children [9,10].

Degree of hepatic fibrosis status can be assessed through laboratory tests and liver stiffness measure (LSM) using transient elastography (TE) [11]. Platelet count (PLT), protein, and albumin decrease when hepatic fibrosis increases. Moreover, aspartate transaminase, alanine aminotransferase (ALT), total bilirubin, direct bilirubin, gamma-glutamyl transferase (GGT), and prothrombin time (international normalized ratio; INR) may be increased in BA patients with poor hepatic fibrosis. In adults, the BAVENO VI criteria (LSM < 20 kPa and PLT > 150,000 cells/μL) are used to identify low esophageal varix risk in patients with liver cirrhosis who do not require EGD [12—14]. However, there are no validated criteria for pediatric patients, especially those with BA. If the BAVENO VI criteria can be applied in patients with BA to minimize EGD use, continuous follow-up may be possible while reducing EGD-related risks.

This study aimed to validate the BAVENO VI criteria for BA patients who have undergone Kasai surgery to safely avoid EGD for esophageal varix surveillance. Moreover, we aimed to identify whether alternative combinations of LSM and PLT should be recommended for BA patients.

Methods

Study population

We selected BA patients who had undergone Kasai surgery and transient elastography (TE) between January 2007 and December 2017. The cases were included if the laboratory tests and EGD were done from 3 months before TE to 3 months after TE. BA patients in whom TE was performed after undergoing treatment for esophageal bleeding (band ligation, sclerotherapy, splenic vessel embolization, or LT) were excluded (Fig. 1).

Transient elastography

Patients who underwent TE were included only if the LSM was measured with a success rate > 60% or interquartile range < 30%. All TE procedures were performed using the FibroScan (Echosens, Paris, France) by a professionally trained specialist at Severance hospital. The median value of successful LSM was recorded in kilopascals (kPa). All TE procedures were performed with the patient in the decubitus position, through the intercostal spaces, to measure the right lobe of the liver.

Esophagogastroduodenoscopy

All EGD procedures were performed by the endoscopists at Severance hospital. The varices' status was described according to the shape and size. The red color sign, presence of gastric varix, and evidence of bleeding were recorded according to the endoscopist's judgement. A low-risk varix (LRV) was defined as the absence of varix or grade 1 esophageal varix, whereas a high-risk varix (HRV) was defined as grade 2 or higher esophageal varix, any gastric varix or red mark, or a lesion with actual bleeding.

Laboratory tests

We retrospectively reviewed patient records; the laboratory test (PLT, TB, DB, AST, ALT, GGT, and INR) results closest to the TE date were selected.

Statistical analysis

The demographic data, laboratory values, and LSMs were compared between patients with and without the risk of varix bleeding. The normality of data was assessed by Shapiro-Wilk test. In the case of continuous variables that satisfy the normal distribution, mean ± SD and independent *t*-test were used for comparison. In the case of non-normal distribution, the medians were expressed as median (Q1, Q3). For categorical variables, we used the chi-square test or Fisher's exact test for analysis. Statistical analyses were performed using the software R package, version 3.4.4.

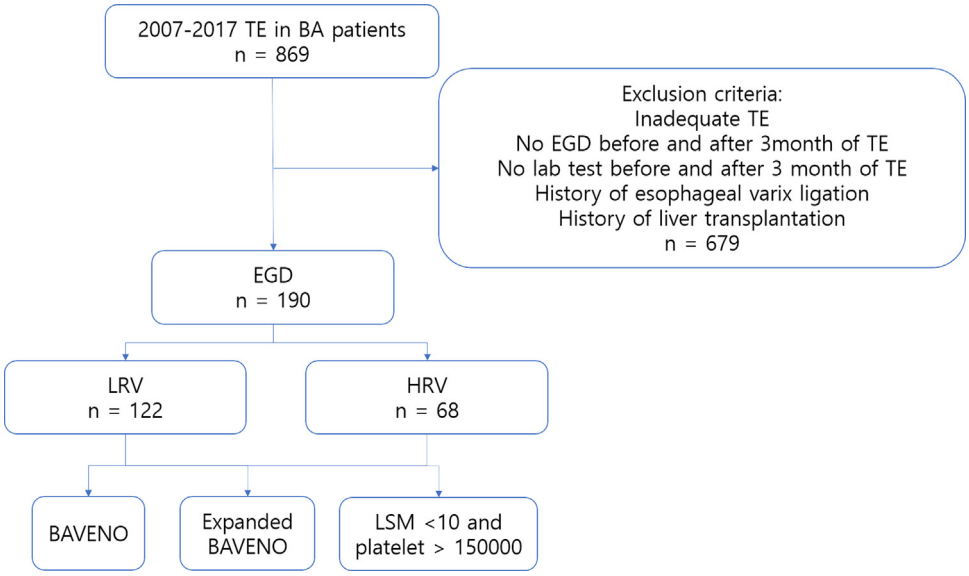

Figure 1 Flowchart of the study.

Ethics statement

The Yonsei Severance Hospital Institutional Review Board approved the study protocol (No. 4-2018-0768).

Results

Baseline characteristics

A total of 190 TE were performed, with EGD and blood tests. The HRV group had significantly higher birth-to-OP and OP-to-FibroScan lengths and higher INR than the LRV group ($P < 0.05$).

The PLT, ALT, and GGT levels were significantly lower in the HRV group than in the LRV group ($P < 0.05$) (Table 1).

Prevalence of patients with various criteria

Several LSM and PLT criteria were used to identify the number of patients included in each risk group. Based on the LSM (cut-off value < 10), 43 cases were included, of which 35/43 (81.4%) LRV patients and 8/43 (18.6%) HRV patients were identified. Based on the criteria of PLT > 150,000, 87 (77.68%) LRV patients and 25 (22.32%) HRV patients were included. Consequently, based on the BAVENO VI criteria to identify patients who can safely avoid screening with EGD, 48 (84.21%) LRV and 9 (15.79%) HRV patients were included. The expanded BAVENO VI criteria identified 63 (75.00%) LRV and 21 (25.00%) HRV patients. The criteria using LSM < 10 and PLT > 150,000 identified 33 (89.19%) LRV and 4 (10.81%) HRV patients (Table 2).

Diagnostic performance of each criterion

Table 3 demonstrates the usefulness of the criteria combining LSM and PLT to predict HRV in BA patients. We missed diagnosis in 9/68 (13.24%) and 21/68 (30.88%) HRV patients on using the BAVENO VI and expanded BAVENO VI criteria, respectively. However, on using the combined LSM <10 and PLT > 150,000 criteria, we missed diagnosis in only 4 patients (5.88%) with HRV. The sensitivity of the BAVENO VI criteria was 86.76, while that of the new combination criteria was 94.12. The negative predictive values were 84.12, 75.00, and 89.19 for the BAVENO VI, expanded BAVENO IV, and new combined criteria, respectively.

Discussion

Despite the introduction of the reasonably successful Kasai procedure as a surgical treatment, BA is today the most common cause for liver transplantation in children. Moreover, the Kasai operation is not a curative treatment for BA, but is known as a bridge therapy, which is performed to buy time before liver transplantation.

Although liver transplantation itself is a high-risk operation, bleeding due to esophageal varices carries a much higher risk of mortality [4]. If blood tests, TE, and EGD can be performed every 3 or 6 months every year, the risk of bleeding from esophageal varices can be minimized and the need for liver transplantation can be evaluated closely. Although EGD is the most accurate method of identifying varices, EGD itself is risky because of the sedation process that is required to perform this procedure in children. The risk of side effects is not high if a single EGD is performed. However, the risk can increase if EGD is repeatedly performed to identify varices. Therefore, the best results will be achieved by minimizing the number of EGDs required; this can be achieved by performing EGD only in those with an absolute indication. The BAVENO VI criteria are used in adult patients with cirrhosis to identify the need for endoscopic examinations. However, to the best of our knowledge, no such criteria exist for use in pediatric patients.

In the present study, we could identify the basic features of patients, which are provided in Table 1. Similar to the results of a previous study, HRV was higher in patients

Table 1 Baseline characteristics.

	Total ($n = 190$)	Low-risk varix ($n = 122$)	High-risk varix ($n = 68$)	*P*-value
Birth_OP_Day	62.00 (52.25, 73.75)	60.50 (47.75, 70.00)	64.00 (60.00, 82.25)	0.0038
OP_FibroScan_Day	955.50 (341.50, 2154.75)	594.50 (264.75, 1932.50)	1314.00 (614.00, 2563.25)	0.0044
Gender				0.2475
Male	68 (35.79%)	40 (32.79%)	28 (41.18%)	
Female	122 (64.21%)	82 (67.21%)	40 (58.82%)	
PLT	180.00 (105.75, 254.00)	221.00 (145.50, 272.50)	125.50 (92.50, 177.50)	< .0001
AST	90.00 (48.25, 148.75)	92.50 (54.00, 157.25)	79.00 (43.75, 130.25)	0.1512
ALT	68.50 (36.25, 121.75)	81.50 (40.25, 151.00)	55.00 (27.50, 92.75)	0.0046
Protein	6.30 (5.70, 6.70)	6.35 (5.70, 6.80)	6.30 (5.70, 6.53)	0.214
Albumin	3.71 ($\pm$0.58)	3.75 ($\pm$0.63)	3.64 ($\pm$0.49)	0.1532
TB	1.35 (0.60, 2.90)	1.20 (0.60, 3.00)	1.40 (0.60, 2.45)	0.7883
DB	0.80 (0.30, 2.20)	0.80 (0.30, 2.38)	0.70 (0.30, 1.65)	0.5267
GGT	145.50 (65.50, 315.50)	192.00 (82.75, 405.75)	100.00 (51.75, 222.25)	0.0050
INR	1.06 (0.98, 1.17)	1.04 (0.95, 1.14)	1.09 (1.03, 1.24)	0.0010
Esophageal varix				< .0001
None	83 (43.68%)	68 (55.74%)	15 (22.06%)	
Mild	67 (35.26%)	54 (44.26%)	13 (19.12%)	
Moderate	27 (14.21%)	0 (0.00%)	27 (39.71%)	
Severe	13 (6.84%)	0 (0.00%)	13 (19.12%)	
Gastric varix				< .0001
No	137 (72.11%)	122 (100.00%)	15 (22.06%)	
Yes	53 (27.89%)	0 (0.00%)	53 (77.94%)	
Red mark				< .0001
No	179 (94.21%)	122 (100.00%)	57 (83.82%)	
Yes	11 (5.79%)	0 (0.00%)	11 (16.18%)	
Bleeding				< .0001
No	180 (94.74%)	122 (100.00%)	58 (85.29%)	
Yes	10 (5.26%)	0 (0.00%)	10 (14.71%)	
LSM	20.45 (10.80, 37.40)	20.00 (8.32, 34.70)	21.35 (12.45, 46.42)	0.0638
LSM.IQR	15.91 (8.71, 21.97)	16.00 (9.05, 21.00)	15.80 (7.72, 22.65)	0.6626

Continuous variables data that satisfy the normal distribution are presented as mean $\pm$ SD. In the case of non-normal distribution data are presented as median (Q1, Q3). PLT: platelet; AST: aspartate transaminase; ALT: alanine aminotransferase; TB: total bilirubin; DB: direct bilirubin; GGT: gamma-glutamyl transferase; INR: international normalized ratio; LSM: liver stiffness measurement.

Table 2 Prevalence of patients with various criteria.

	n	Low-risk varix	High-risk varix
LSM < 10	43	35 (81.40%)	8 (18.60%)
LSM $\geq$ 10	147	87 (59.18%)	60 (40.82%)
LSM < 15	67	46 (68.66%)	21 (31.34%)
LSM $\geq$ 15	123	76 (61.79%)	47 (38.21%)
LSM < 20	92	61 (66.30%)	31 (33.70%)
LSM $\geq$ 20	98	61 (62.24%)	37 (37.76%)
LSM < 25	110	72 (65.45%)	38 (34.55%)
LSM $\geq$ 25	80	50 (62.50%)	30 (37.50%)
PLT > 150,000	112	87 (77.68%)	25 (22.32%)
PLT $\leq$ 150,000	78	35 (44.87%)	43 (55.13%)
PLT > 110,000	140	101 (72.14%)	39 (27.86%)
PLT $\leq$ 110,000	50	21 (42.00%)	29 (58.00%)
Within BAVENO VI criteria	57	48 (84.21%)	9 (15.79%)
Outside BAVENO VI criteria	133	74 (55.64%)	59 (44.36%)
Within expanded BAVENO VI criteria	84	63 (75.00%)	21 (25.00%)
Outside expanded BAVENO VI criteria	106	59 (55.66%)	47 (44.34%)
Within new criteria	37	33 (89.19%)	4 (10.81%)
Outside new criteria	153	89 (58.17%)	64 (41.83%)

Data are presented as *n* and percentage (%). LSM: liver stiffness measurement; PLT: platelet. New criteria: LSM < 10 and PLT > 150,000.

Table 3 Diagnostic performance of each criterion.

	BAVENO VI criteria	Expanded BAVENO VI criteria	New criteria
HRV missed	9 (13.24%)	21 (30.88%)	4 (5.88%)
Sensitivity	86.76 (78.71, 94.82)	69.12 (58.14, 80.10)	94.12 (88.53, 99.71)
Specificity	39.34 (30.68, 48.01)	51.64 (42.77, 60.51)	27.05 (19.17, 34.93)
PPV	44.36 (35.92, 52.80)	44.34 (34.88, 53.80)	41.83 (34.01, 49.65)
NPV	84.21 (74.74, 93.68)	75.00 (65.74, 84.26)	89.19 (79.18, 99.19)
LR+	1.43 (1.21, 1.70)	1.43 (1.12, 1.82)	1.29 (1.14, 1.46)
LR−	0.34 (0.18, 0.64)	0.60 (0.40, 0.89)	0.22 (0.08, 0.59)

Data are presented as median (Q1, Q3). HRV: High-risk varix; PPV: positive predictive value; NPV: negative predictive value; LR+: positive likelihood ratio; LR−: negative likelihood ratio. New criteria: LSM < 10 and PLT > 150,000.

who were older at the time of Kasai operation [15]. In addition, the risk of HRV increased with time after surgery. The duration from Kasai operation to FibroScan was significantly lower in the LRV group than in the HRV group. As seen in this study, the time passed after the Kasai operation was positively associated with HRV [16].

Adami et al. [17], with a study design that differs from our own, showed platelet count/spleen size z score ratio can be used to screen children who should be considered for EGD. The result was similar with our study. The platelet counts were significantly lower in the HRV group than in the LRV group in this study. Thrombocytopenia might be caused by liver cirrhosis and splenomegaly. The ALT was high in the LRV group. Liver damage can lead to elevated ALT levels, but if liver cirrhosis progresses, ALT levels may decrease, which may lead to the above results.

Protein and albumin levels were lower in the HRV group than in the LRV group, although the difference was not statistically significant. However, as we could not exclude patients with IV albumin replacement, albumin levels might be further decreased in the HRV group.

In Table 2, we present several criteria to determine their usefulness in BA patients. The lower the value of LSM, the fewer the HRV patients were included. In addition, the higher the value of PLT, the fewer the HRV patients included. Similarly, the higher the value of the standard, the lesser the HRV patients included. In addition, when using the criteria LSM < 10 and PLT > 150,000, which are more stringent than the BAVENO criteria, only 4 HRV patients were included [12,18]. Table 3 confirms the diagnostic performance of each criterion. Among the HRV patients, the diagnosis was missed in 9, 21, and 4 when using the BAVENO criteria, expanded BAVENO criteria, and combined criteria of LSM < 10 and PLT > 150,000, respectively. The negative predictive value, which is considered to be the most important among these criteria, was also very high (89.19) while using the new criteria.

In adults, validation of the BAVENO criteria was performed on patients with cirrhosis. Approximately 2% of the BAVENO criteria were mis-classified. In Korea, HRV were mis-classified in 3.8% when using the BAVENO criteria for people with cirrhosis among those who underwent TE, and approximately 6.8% were mis-classified using expanded BAVENO criteria. In this study, the BAVENO criteria were applied to BA children and mis-classified 5.88% of HRV patients and missed 13.24% of HRV when the expanded BAVENO criteria were applied. However, when applying the LSM < 10 and PLT > 150,000 criteria, only 5.88% of HRV patients were mis-classified. However, 5.88% is higher than 2% and 3.8%, which were the rates of mis-classification in adult cirrhosis patients and Korean adult patients with cirrhosis, respectively. However, the new criteria may be used as an objective method to identify the BA patients who can avoid EGD screening.

Some limitations were present in this study. First, this study only involved retrospective reviewing of the records of a single institution. Hence, the actual usefulness of the new criteria cannot be confirmed without a prospective study. Second, the results of the FibroScan and EGD performed multiple times in one patient was included as a single case, reflecting individual characteristics. Third, the EGD, FibroScan, and laboratory tests were not performed regularly in patients. Moreover, patients with problems, such as cholangitis or infection may have undergone EGD and FibroScan more times, which might have caused a selection bias.

However, despite these limitations, this is the first study, to the best of our knowledge, to confirm the usefulness of the BAVENO criteria in children with BA, and it seems to be an objectively groundbreaking study for identifying patients who need EGD. However, it is not recommended to use only these criteria because it can be fatal if we miss diagnosing patients with varices. Moreover, patients who need EGD can be more accurately selected if patients with known poor prognostic factors (e.g., Kasai operation done in patients older than 2 months, recurrent cholangitis) are examined carefully.

In conclusion, the BAVENO criteria could be as useful in children with BA as in adults. However, regular laboratory tests, imaging studies, and EGD must be performed so that varices in BA patients are not missed. Further, basing patient classification on the criteria of LSM < 10 and PLT > 150,000 would be more accurate and objective for identifying patients who does not need endoscopy.

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Author contributions

Conceptualization: Kang Y. Data curation: Kang Y. Formal analysis: Kang Y. Investigation: Kang Y. Methodology: Koh H,

Han S. Software: Kim S, Park S. Validation: Kim S, Park S. Writing — original draft: Kang Y. Writing — review & editing: Kang Y, Kim S, Park S, Han S, Koh H.

Disclosure of interest

The authors declare that they have no competing interest.

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