

Multicenter Retrospective Risk Assessment of Esophageal Variceal Bleeding in Patients with Cirrhosis: An Acoustic Radiation Force Impulse Elastography-Based Prediction Model

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Background/Aims: Acoustic radiation force impulse (ARFI) elastography predicts the presence of esophageal varices (EVs). We investigated whether an ARFI-based prediction model can assess EV bleeding (EVB) risk in patients with cirrhosis. **Methods:** The records of 262 patients with cirrhosis who underwent ARFI elastography and endoscopic surveillance at two institutions in 2008 to 2013 were retrospectively reviewed, and ARFI-spleen diameter-to-platelet ratio scores (ASPS) were calculated. **Results:** The median patient age (165 men, 97 women) was 56 years. The median ARFI velocity, spleen diameter, platelet count, and ASPS were 1.7 m/sec, 10.1 cm, $145 \times 10^9/L$, and 1.16, respectively. During the median 38-month follow-up, 61 patients experienced EVB. Among all patients (179 without EVs and 83 with EVs), the cutoff value that maximized the sum of the sensitivity (73.1%) and specificity (78.4%) (area under receiver operating characteristic curve [AUROC], 0.824) for predicting EVB was 2.60. The cumulative EVB incidence was significantly higher in patients with ASPS ≥ 2.60 than in those with ASPS < 2.60 ($p < 0.001$). Among patients with EVs ($n = 83$), 49 had high-risk EVs (HEVs), and 22 had EVB. The cumulative EVB incidence was significantly higher in HEV patients than in low-risk EV patients ($p = 0.037$). At an ASPS of 4.50 (sensitivity, 66.7%; specificity, 70.6%; AUROC, 0.691), the cumulative EVB incidence was significantly higher in patients with a high ASPS than in those with a low ASPS ($p = 0.045$). A higher ASPS independently predicted EVB (hazard ratio, 4.072; $p = 0.047$). **Conclusions:** ASPS can assess EVB risk in patients with cirrhosis. Prophylactic management should be considered for patients with HEVs and ASPS ≥ 4.50 . (*Gut*

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Key Words: Acoustic radiation force impulse; Esophageal varix; Liver cirrhosis

INTRODUCTION

Esophageal varices (EVs) are an important complication affecting approximately 50% of patients with cirrhosis depending on the clinical stage.¹ EVs are present in 30% to 40% of patients with compensated cirrhosis and in up to 85% of patients with decompensated cirrhosis.² In patients with compensated cirrhosis, new varices develop at a rate of 7% to 8% per year.³ Small varices can progress to large varices at a rate of 10% to 12% per year; therefore, patients with small varices are at a higher risk of bleeding.⁴

Esophageal variceal bleeding (EVB) occurs at a rate of 10% to 15% yearly,⁵ and acute EVB reportedly has a 6-week mortality rate of 15% to 25%.⁶⁻⁸ Since EVB is a life-threatening complication of patients with cirrhosis, the current guidelines recommend both screening endoscopy for high-risk patients with cirrhosis to identify whether primary prophylactic treatment should be considered and repeated endoscopic surveillance.^{1,9,10} To determine EVB risk, the presence and size of varices and presence of the color red requires endoscopy, an invasive and expensive procedure that is not risk-free.^{5,11} Thus, based on the current European (Baveno VI) and American (American Association for the Study of Liver Diseases) recommendations, patients with liver stiffness (LS) < 20 kPa and platelet count $> 150,000/mm^3$ were suggested to avoid endoscopy by undergoing annual

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surveillance of platelet count and EVs via transient elastography (TE).^{1,9} Similarly, Kim *et al.*,¹² showed a measurement-based, noninvasive prediction model of LS, the LS-spleen diameter to platelet ratio score (LSPS), that reliably detected high-risk EVs (HEVs).

Recently, acoustic radiation force impulse (ARFI) imaging has been suggested as an alternative method for noninvasive assessments of liver fibrosis and portal hypertension.^{13,14} Some studies have shown that ARFI elastography is a reliable technique for predicting portal hypertension.^{15,16} Morishita *et al.*¹⁶ reported that the ARFI value can predict the presence of EVs and HEVs among patients with HCV-related cirrhosis, with area under the receiver operating characteristic curve (AUROC) values of 0.890 and 0.868, respectively. Most recently, Park *et al.*¹⁷ suggested a noninvasive ARFI-based prediction model called the ARFI-spleen diameter-to-platelet ratio score (ASPS), which accurately identifies HEVs in patients with compensated cirrhosis. In this study, the ASPS predicted HEVs with an AUROC value of 0.946, and an ASPS value of 5.28 was suggested as the cutoff for considering endoscopic examinations or appropriate prophylactic treatment. However, no study has investigated whether an ARFI-based prediction model can assess the forthcoming risk of EVB in patients with cirrhosis.

Here, we investigated the predictive role of the ASPS in assessing the risk of EVB in patients at two tertiary academic institutions in Korea.

MATERIALS AND METHODS

1. Patients

Between 2010 and 2013, we retrospectively recruited 291 patients with compensated cirrhosis who underwent ARFI elastography and endoscopic surveillance at Severance Hospital, Yonsei University College of Medicine, Seoul, Korea (n=143) and at Kyungpook National University Hospital, School of Medicine, Kyungpook National University, Daegu, Korea (n=148). This study cohort included patients described in our previous study.¹⁷ Compensated cirrhosis was defined as evident cirrhosis in the absence of any previous or current known complications of portal hypertension, including ascites, variceal bleeding, and/or hepatic encephalopathy.^{18,19} Cirrhosis was diagnosed using standard laboratory, radiological, and physical examination findings or by liver histology in equivocal cases.

Exclusion criteria were as follows: (1) >6 months between ARFI elastography and endoscopic surveillance, (2) Child-Pugh C class, (3) hepatic decompensation including current or past history of EVs, (4) current or past history of hepatocellular carcinoma, (5) previous or current history of treatment for portal hypertension, (6) history of splenectomy, (7) ARFI measurement failure or unreliable measurement, (8) presence of portal vein thrombosis, and (9) right-sided heart failure.

The study protocol was performed according to the ethical

guidelines of the 1975 Declaration of Helsinki. Written informed consent was not required due to the retrospective nature of this multicenter study. This study was approved by the Institutional Review Board of Severance Hospital, Yonsei University College of Medicine (IRB No. 2012-0015-001) and Kyungpook University Hospital (IRB No. 2015-09-030).

2. Clinical and laboratory variables

Demographic data, including age, sex, body mass index, and other clinical and laboratory parameters were recorded for each patient at the time the ARFI measurements were taken. Clinical parameters included a previous history of treatment for EVs or portal hypertension, and laboratory parameters included hemoglobin, alanine aminotransferase, aspartate aminotransferase, serum albumin, total bilirubin, prothrombin time, and platelet count. The Child-Pugh class was assessed based on these parameters.

3. Imaging techniques

Standard ultrasonographic scanning of the abdomen, including measurement of the maximum spleen diameter and ARFI elastography, were performed under fasting conditions. The spleen diameter was defined as the bipolar diameter at the crossing point of the spleen hilum²⁰ and was measured using electronic calipers. ARFI elastography was performed on each patient using a Siemens Acuson S2000 ultrasound system (Siemens Healthcare GmbH, Erlangen, Germany) by expert sonographers at each institute (all had performed >500 examinations) who were blinded to the endoscopy results. LS was measured with ARFI elastography, similar to the protocol of our previous study.¹⁷ ARFI shear wave velocity was measured in meters per second (m/sec). The median value of 10 valid measurements was calculated. ARFI failure was defined as zero valid shots, and unreliable measurements were reported as an interquartile range (IQR) to a median value ratio >30% or success rate <60%.¹⁵

4. Endoscopic evaluation and grading of EVs

Endoscopic evaluation and grading of EVs was performed by expert endoscopists at each institute (>1,000 examinations) who were blinded to the ARFI elastography results. EVs were classified as small (veins minimally elevated above the esophageal mucosal surface), medium (tortuous veins occupying less than one-third of the esophageal lumen), or large (veins occupying more than one-third of the esophageal lumen). HEVs were defined as medium to large EVs and small EVs with red signs, while low-risk EVs were defined as small EVs without red signs.^{21,22}

5. Calculation of the ASPS

The ASPS was calculated as follows: (ARFI velocity [m/sec] × spleen diameter [cm]) / platelet count [$10^9/L$]).

6. Patient follow-up

All patients underwent periodic surveillance with annual endoscopy, ultrasonography, and laboratory assessments for EV screening and follow-up. Patients with HEVs took the nonselective β -blocker propranolol as a prophylaxis for EVB after the diagnosis of HEV was made if not contraindicated. The dose of propranolol was titrated according to the resting pulse rates or side effects. Any patient suspected of having upper gastrointestinal bleeding underwent an emergency endoscopy within 12 hours of presentation to ensure accurate diagnosis and appropriate treatment. EVB was defined when hematemesis, hematochezia, or melena was confirmed by endoscopy to originate from EVs.

7. Statistical analysis

The primary aim of this longitudinal study was to assess the predictive value of the ASPS for assessing the risk of future EVB. Continuous variables were compared using the Student *t*-test or the Mann-Whitney *U*-test, whereas categorical variables were compared using the chi-square test or Fisher exact test. To assess the predictive value of the model for cumulative bleeding events during follow-up, time-dependent ROC curves for the time to the first EVB event were constructed, and the AUROC was also computed.²³ The cutoff values, sensitivity, specificity, negative predictive value (NPV), positive predictive value (PPV), positive likelihood ratio, and negative likelihood ratio were also calculated.

The Kaplan-Meier method was used to examine the time to the first occurrence of EVB, the primary end point. The log-rank test was used to assess variations in EVB episodes. The Cox proportional hazards model was used for the multivariate analyses. Variables with *p*-values <0.10 in the univariate analysis were included in the multivariate analysis, and *p*-values <0.05 were considered statistically significant. The data were analyzed using SPSS 20.0 for Windows (IBM Corp., Armonk, NY, USA) and MedCalc Software version 12.7.2 (MedCalc Software bvba, Ostend, Belgium).

RESULTS

1. Baseline characteristics

Of 291 patients screened by the inclusion criteria, 29 were excluded, leaving a total of 262 patients who were ultimately enrolled (Supplementary Fig. 1). The median interval between ARFI elastography and endoscopy was 112 days (IQR, 14 to 154 days).

Baseline patient characteristics are summarized in Table 1. The mean age was 56.0 years, and 165 patients (63.0%) were men. Hepatitis B virus was the most common etiology of cirrhosis (*n*=166, 63.3%). A total of 244 patients (93.1%) were classified as Child-Pugh class A, whereas 18 (6.9%) were classified

as Child-Pugh class B. A total of 83 patients (31.7%) had EVs (38 small, 27 medium, and 18 large), and 49 (18.7%) had HEVs. Portal hypertensive gastropathy was observed in 24 patients (9.9%). The median ARFI velocity, platelet count, spleen diameter, and ASPS were 1.7 m/sec, $145 \times 10^9/L$, 10.1 cm, and 1.16, respectively.

2. Comparison of patients with and without EVs or HEVs

When patients with and without EVs were compared (Table 2), those with EVs were significantly older (median: 57 years vs 56 years) and were more likely to be male (72.3% vs 58.7%) than those without EVs (all *p*<0.05). In addition, the proportion of patients with hypertensive gastropathy was significantly higher in the EV group than in the non-EV group (73.5% vs 3.4%, respectively; *p*<0.001). Patients with EVs had a significantly lower hemoglobin level (median: 12.7 g/dL vs 13.7 g/dL), a lower serum albumin level (3.9 g/dL vs 4.2 g/dL), a higher international

Table 1. Baseline Characteristics of the Entire Population (*n*=262)

| Variable | Value |
|------------------------------------|---------------------|
| Demographic data | |
| Age, yr | 56.0 (48.0–64.0) |
| Male sex | 165 (63.0) |
| Body mass index, kg/m ² | 23.6 (21.2–25.7) |
| Etiology | |
| HBV | 166 (63.3) |
| HCV | 24 (9.2) |
| Alcoholic | 40 (15.3) |
| Others | 32 (12.2) |
| Laboratory data | |
| Hemoglobin, g/dL | 13.6 (11.8–14.8) |
| Platelet count, 10 ⁹ /L | 145 (94–186) |
| Serum albumin, g/dL | 4.2 (3.7–4.4) |
| Prothrombin time, INR | 1.0 (1.0–1.2) |
| Aspartate aminotransferase, IU/L | 35 (25–46) |
| Alanine aminotransferase, IU/L | 25 (15–37) |
| Total bilirubin, mg/dL | 0.8 (0.6–1.2) |
| Child-Pugh class A/B | 244 (93.1)/18 (6.9) |
| Esophageal varix | 83 (31.7) |
| Small/medium/large | 38/27/18 |
| High-risk esophageal varix | 49 (18.7) |
| Portal hypertensive gastropathy | 24 (9.9) |
| ARFI velocity, m/sec | 1.7 (1.3–2.5) |
| Spleen diameter, cm | 10.1 (9.0–12.0) |
| ASPS | 1.16 (0.66–2.84) |

Data are presented as the median (interquartile range), number (%), or number.

HBV, hepatitis B virus; HCV, hepatitis C virus; INR, international normalized ratio; ARFI, acoustic radiation force impulse; ASPS, ARFI-spleen diameter-to-platelet ratio score.

Table 2. Comparison between Patients with and without EV or HEV

| Variable | Patients without EV (n=179, 68.3%) | Patients with EV (n=83, 31.7%) | p-value | Patients without HEV (n=213, 81.3%) | Patients with HEV (n=49, 18.7%) | p-value |
|------------------------------------|---------------------------------------|-----------------------------------|---------|--|------------------------------------|---------|
| Demographic data | | | | | | |
| Age, yr | 56 (46–63) | 57 (49–65) | 0.047 | 56 (47–63) | 57 (49–65) | 0.083 |
| Male sex | 105 (58.7) | 60 (72.3) | 0.028 | 130 (61.0) | 35 (71.4) | 0.176 |
| Body mass index, kg/m ² | 23.7 (21.2–25.6) | 23.6 (21.2–26.4) | 0.580 | 23.9 (21.2–25.7) | 23.4 (21.2–25.5) | 0.932 |
| Etiology | | | | | | |
| Viral/non-viral | 134 (74.9)/45 (25.1) | 56 (67.5)/27 (32.5) | 0.142 | 161 (75.6)/52 (24.4) | 29 (59.2)/20 (41.8) | 0.100 |
| EVs | | | | | | |
| Small-medium/large | - | 65 (78.3)/18 (21/7) | - | 34 (16.0)/0 | 31 (63.3)/18 (36.7) | <0.001 |
| Portal hypertensive gastropathy | 6 (3.4) | 61 (73.5) | <0.001 | 18 (8.5) | 10 (20.4) | 0.014 |
| Laboratory data | | | | | | |
| Hemoglobin, g/dL | 13.7 (12.0–14.8) | 12.7 (10.5–15.0) | 0.012 | 13.8 (12.0–15.0) | 12.0 (10.5–14.1) | 0.006 |
| Aspartate aminotransferase, IU/L | 31 (23–42) | 40 (30–50) | 0.159 | 32 (24–42) | 42 (32–51) | 0.293 |
| Alanine aminotransferase, IU/L | 26 (14–37) | 22 (15–37) | 0.206 | 25 (15–37) | 22 (15–37) | 0.099 |
| Serum albumin, g/dL | 4.2 (3.9–4.4) | 3.9 (3.5–4.3) | <0.001 | 4.2 (3.8–4.4) | 3.9 (3.2–4.2) | <0.001 |
| Total bilirubin, mg/dL | 0.8 (0.6–1.1) | 1.1 (0.8–1.8) | 0.252 | 0.8 (0.6–1.1) | 1.2 (0.7–1.7) | 0.221 |
| Prothrombin time, INR | 1.0 (1.0–1.1) | 1.1 (1.0–1.3) | <0.001 | 1.0 (1.0–1.1) | 1.1 (1.0–1.2) | 0.003 |
| Platelet count, 10 ⁹ /L | 159 (125–214) | 89 (61–125) | <0.001 | 153 (107–202) | 73 (55–125) | <0.001 |
| ARFI, m/sec | 1.5 (1.2–2.0) | 2.5 (1.8–2.8) | <0.001 | 1.5 (1.3–2.2) | 2.5 (1.9–2.9) | <0.001 |
| Spleen diameter, cm | 9.5 (8.5–10.8) | 12.8 (10.1–14.5) | <0.001 | 9.9 (8.7–11.0) | 13.0 (10.5–14.5) | <0.001 |
| ASPS | 0.85 (0.54–1.47) | 3.58 (2.06–5.28) | <0.001 | 1.00 (0.62–1.97) | 3.68 (1.85–5.42) | <0.001 |

Data are presented as the median (interquartile range) or number (%).

EV, esophageal varix; HEV, high-risk EV; INR, international normalized ratio; ARFI, acoustic radiation force impulse; ASPS, ARFI-spleen diameter-to-platelet ratio score.

normalized ratio (INR; 1.1 vs 1.0), a lower platelet count ($89 \times 10^9/L$ vs $159 \times 10^9/L$), a higher ARFI velocity (2.5 m/sec vs 1.5 m/sec), a larger spleen diameter (12.8 cm vs 9.5 cm), and a higher ASPS score (3.58 vs 0.85) (all $p < 0.05$). The AUROC of the ASPS for predicting the presence of EVs at enrollment was 0.880 (95% confidence interval [CI], 0.838 to 0.923; $p < 0.001$).

When patients with and without HEVs were compared (Table 2), the proportion of patients with large EVs and hypertensive gastropathy was significantly higher in the HEV group than in the non-HEV group (36.7% vs 0%, 20.4% vs 8.5%, respectively; all $p < 0.05$). Patients with HEVs showed significantly lower hemoglobin levels (median: 12.0 g/dL vs 13.8 g/dL), lower serum albumin level (3.9 g/dL vs 4.2 g/dL), higher INR (1.1 vs 1.0), lower platelet count ($73 \times 10^9/L$ vs $153 \times 10^9/L$), higher ARFI velocity (2.5 m/sec vs 1.5 m/sec), larger spleen diameter (13.0 cm vs 9.9 cm), and a higher ASPS score (3.68 vs 1.00) (all $p < 0.05$). The AUROC of the ASPS for predicting the presence of HEV at enrollment was 0.790 (95% CI, 0.720 to 0.860; $p < 0.001$).

3. Incidence of EVB in the entire study population

The median follow-up period of the whole population was 38 months (IQR, 31 to 51 months). During the study period, 22 patients experienced their first EVB episodes. The cumulative incidence of EVB at 1 and 3 years was 0.76% and 4.96%, respec-

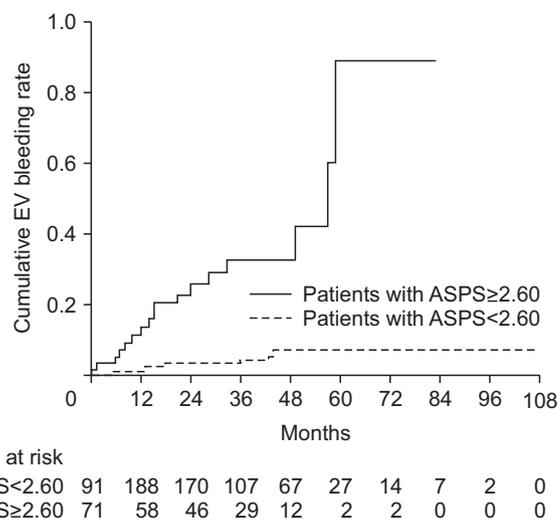


Fig. 1. Cumulative EVB incidence according to the ASPS cutoff value of 2.60 in the entire population. The cumulative EVB incidence in patients with ASPS ≥ 2.60 was significantly higher than in patients with an ASPS ≥ 2.60 in the entire population ($p < 0.001$ by the log-rank test).

EV, esophageal varices; EVB, EV bleeding; ASPS, ARFI-spleen diameter-to-platelet ratio score.

Table 3. Comparison between Patients with and without EVB

| Variable | Patients without EVB (n=240, 91.6%) | Patients with EVB (n=22, 8.4%) | p-value |
|------------------------------------|--|-----------------------------------|---------|
| Demographic data | | | |
| Age, yr | 55 (48–63) | 64 (54–72) | 0.005 |
| Male sex | 146 (61.9) | 16 (72.7) | 0.324 |
| Body mass index, kg/m ² | 23.9 (21.2–25.8) | 23.1 (21.9–25.2) | 0.963 |
| Etiology | | | |
| Viral/non-viral | 179 (75.4)/58 (24.6) | 10 (45.5)/12 (54.5) | 0.002 |
| EVs | | | |
| Small-medium/large | 49 (20.8)/30 (12.7) | 16 (72.8)/6 (27.2) | <0.001 |
| Portal hypertensive gastropathy | 18 (7.6) | 10 (45.5) | <0.001 |
| Laboratory data | | | |
| Hemoglobin, g/dL | 13.7 (12.0–14.9) | 12.0 (9.9–14.4) | 0.031 |
| Aspartate aminotransferase, IU/L | 34 (25–45) | 41 (34–71) | 0.107 |
| Alanine aminotransferase, IU/L | 25 (15–37) | 23 (15–43) | 0.441 |
| Serum albumin, g/dL | 4.2 (3.7–4.4) | 3.7 (3.5–4.2) | 0.009 |
| Total bilirubin, mg/dL | 0.8 (0.6–1.2) | 1.2 (0.8–2.1) | 0.282 |
| Prothrombin time, INR | 1.0 (1.0–1.1) | 1.2 (1.0–1.3) | <0.001 |
| Platelet count, 10 ⁹ /L | 149 (99–195) | 81 (56–108) | <0.001 |
| ARFI, m/sec | 1.7 (1.3–2.2) | 2.8 (2.3–3.4) | <0.001 |
| Spleen diameter, cm | 10.0 (8.8–11.9) | 12.5 (10.0–14.5) | 0.001 |
| ASPS | 1.07 (0.63–2.49) | 4.79 (2.54–7.16) | <0.001 |

Data are presented as the median (interquartile range) or number (%).

EV, esophageal varix; EVB, EV bleeding; ARFI, acoustic radiation force impulse; ASPS, ARFI–spleen diameter-to-platelet ratio score.

tively. The AUROC of the ASPS for predicting the presence of EVB at enrollment was 0.824 (95% CI, 0.742 to 0.908; $p < 0.001$). The ASPS cutoff value for predicting EVB was 2.60, a point at which the sum of the sensitivity (73.1%) and specificity (78.4) was maximized. The cumulative EVB incidence in patients with an ASPS ≥ 2.60 was significantly higher than that in those with an ASPS < 2.60 ($p < 0.001$) (Fig. 1).

When patients with and without EVB were compared (Table 3), patients with EVB were significantly older ($p = 0.005$). In addition, the proportion of patients with non-viral etiology, large EV, and hypertensive gastropathy was significantly higher in the EVB group (54.5% vs 24.6%, 27.2% vs 12.7%, 45.5% vs 7.6%, respectively; all $p < 0.05$). Patients with EVB had significantly lower hemoglobin levels (median: 12.0 g/dL vs 13.7 g/dL), lower serum albumin level (3.7 g/dL vs 4.2 g/dL), higher INR (1.2 vs 1.0), lower platelet count ($81 \times 10^9/L$ vs $149 \times 10^9/L$), higher ARFI velocity (2.8 m/sec vs 1.7 m/sec), larger spleen diameter (12.5 cm vs 10.0 cm), and a higher ASPS score (4.79 vs 1.07) (all $p < 0.05$).

4. Risk assessment of EVB in the subgroup with pre-existing EVs

Among patients with EVs ($n = 83$), 49 had HEVs, 22 (15 with HEV, seven with low-risk EV) of whom experienced EVB during

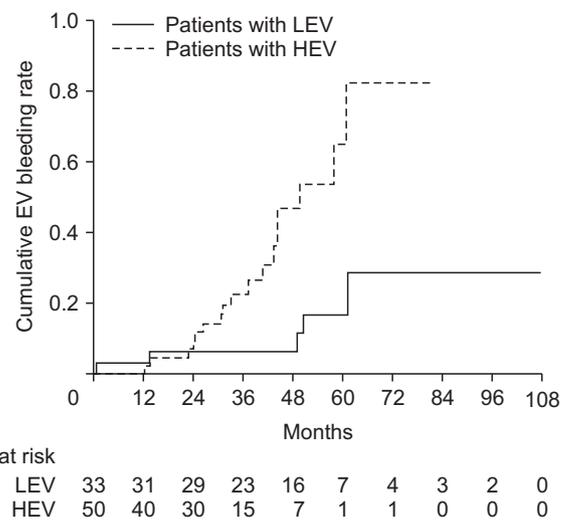


Fig. 2. Cumulative EVB incidence in patients with LEV and HEV. The cumulative incidence of EBV of patients with HEV was significantly higher than that of patients with LEV ($p = 0.037$, log-rank test). EV, esophageal varices; EVB, EV bleeding; LEV, low-risk; HEV, high-risk EV.

the follow-up period. In this subgroup, the cumulative incidence rate of EVB at 1 and 3 years was 11.30% and 24.51%, respectively. When patients with EVs were stratified into low-risk EV

Table 4. Comparison of Patients with EVs According to ASPS Value

| Variable | Patients with ASPS <4.50 (n=55, 66.2%) | Patients with ASPS ≥4.50 (n=28, 33.8%) | p-value |
|------------------------------------|---|---|---------|
| Age, yr | 59 (48–66) | 56 (51–61) | 0.739 |
| Male sex | 29 (70.9) | 21 (75.0) | 0.694 |
| Body mass index, kg/m ² | 23.7 (20.5–26.5) | 23.3 (22.3–25.9) | 0.419 |
| Hemoglobin, g/dL | 14.0 (10.5–15.0) | 11.5 (10.1–14.0) | 0.047 |
| Aspartate aminotransferase, IU/L | 39 (29–49) | 41 (31–55) | 0.814 |
| Alanine aminotransferase, IU/L | 21 (15–37) | 25 (19–45) | 0.422 |
| Serum albumin, g/dL | 4.0 (3.5–4.3) | 3.7 (3.5–4.2) | 0.284 |
| Total bilirubin, mg/dL | 1.0 (0.6–1.6) | 1.5 (1.0–2.5) | 0.090 |
| Prothrombin time, INR | 1.1 (1.0–1.2) | 1.2 (1.0–1.4) | 0.159 |
| Platelet count, 10 ⁹ /L | 107 (84–141) | 58 (45–72) | <0.001 |
| High-risk EV | 28 (50.9) | 22 (78.6) | 0.034 |
| Portal hypertensive gastropathy | 9 (16.4) | 13 (46.4) | 0.006 |
| ARFI velocity, m/sec | 2.3 (1.7–2.8) | 2.6 (2.3–3.1) | 0.022 |
| Spleen diameter, cm | 11.4 (9.9–13.3) | 14.5 (12.9–15.5) | <0.001 |

Data are presented as the median (interquartile range) or number (%).

EVs, esophageal varices; ARFI, acoustic radiation force impulse; ASPS, ARFI–spleen diameter–to–platelet ratio score; INR, international normalized ratio.

and HEV groups, the incidences at 1 and 3 years in patients with low-risk EVs were 8.83% and 17.87%, respectively, (n=34), while in patients with HEV, they were 13.12 and 30.52, respectively (n=49) (p=0.037 on the log-rank test) (Fig. 2).

5. Risk assessment of EVB in the subgroup with pre-existing HEVs

Based on the Korean management guidelines for liver cirrhosis, 49 patients with high-risk EV were treated with a nonselective β -blocker (n=14, 28.6%) or endoscopic variceal ligation (n=35, 71.4%). However, during the follow-up period, 15 of these patients experienced their first EVB. When an ASPS of 4.50, the point at which the sum of the sensitivity (66.7%) and specificity (70.6%) was maximized (AUROC, 0.691; 95% CI, 0.516 to 0.866; PPV of 17.2%; NPV of 50.0%; negative likelihood ratio, 0.5; positive likelihood ratio, 2.3) was selected, patients with an ASPS ≥ 4.50 showed significantly lower hemoglobin levels (median: 11.5 g/dL vs 14.0 g/dL), lower platelet count (median: $58 \times 10^9/L$ vs $107 \times 10^9/L$), higher proportion of HEV (78.6% vs 50.9%) and portal hypertensive gastropathy (46.4% vs 16.4%), higher ARFI velocity (median: 2.6 m/sec vs 2.3 m/sec), and larger spleen diameter (median: 14.5 cm vs 11.4 cm) (all p<0.05) (Table 4).

Among patients with HEV, those with a high ASPS showed a significantly higher cumulative EVB incidence than those with a low ASPS (p=0.045 by log-rank test); the incidence at 1 and 3 years was 7.72% versus 20.17% and 20.56% versus 45.36%, respectively (Fig. 3). In addition, a higher ASPS independently predicted EVB among patients with HEV (hazard ratio, 1.330;

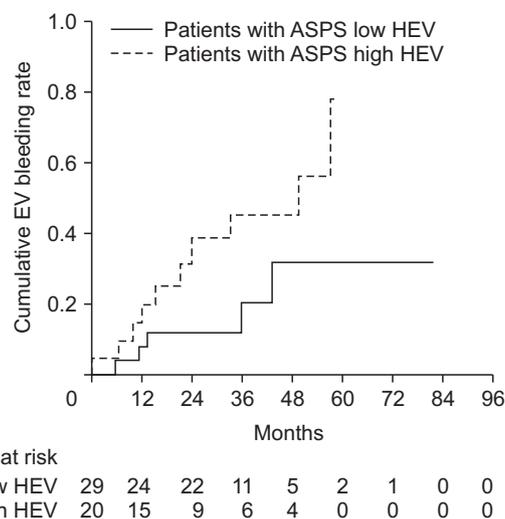


Fig. 3. Among patients with HEV, the cumulative EVB incidence of patients with a high ASPS was significantly higher than that of patients with a low ASPS (p=0.045, log-rank test).

EV, esophageal varices; HEV, high-risk EV; ASPS, acoustic radiation force impulse–spleen diameter–to–platelet ratio score.

p=0.017), together with age and the presence of portal hypertensive gastropathy (Table 5).

DISCUSSION

Advances in noninvasive methods for assessing liver fibrosis have enabled the diagnosis of cirrhosis in the early compensated stage. Despite being asymptomatic, all cirrhosis patients are recommended to undergo screening endoscopy to

Table 5. Independent Predictors of EVB among Patients with HEV

| Variable | Univariate analysis | | Multivariate analysis | |
|--|---------------------|----------------------|-----------------------|-----------------------|
| | p-value | HR (95% CI) | p-value | HR (95% CI) |
| Age, yr | 0.034 | 1.072 (1.005–1.143) | 0.008 | 1.136 (1.034–1.248) |
| Male gender | 0.625 | 1.389 (0.372–5.181) | - | - |
| Use of nonselective β -blocker (vs no use) | 0.382 | 0.523 (0.122–2.239) | - | - |
| Large EV (vs small-medium EV) | 0.753 | 1.222 (0.350–4.265) | - | - |
| Child-Pugh class A (vs B) | 0.818 | 1.058 (0.652–1.717) | - | - |
| Hemoglobin, g/dL | 0.965 | 0.994 (0.752–1.313) | - | - |
| Aspartate aminotransferase, IU/L | 0.410 | 1.005 (0.993–1.019) | - | - |
| Alanine aminotransferase, IU/L | 0.461 | 1.010 (0.983–1.038) | - | - |
| Serum albumin, g/dL | 0.449 | 1.471 (0.541–3.997) | - | - |
| Total bilirubin, mg/dL | 0.903 | 1.035 (0.597–1.792) | - | - |
| Platelet count, $10^9/L$ | 0.169 | 0.990 (0.975–1.004) | - | - |
| NSBB (vs EVL) | 0.378 | 0.565 (0.159–2.011) | - | - |
| Portal hypertensive gastropathy | 0.032 | 5.000 (1.152–21.706) | 0.017 | 11.067 (1.535–79.805) |
| ASPS | 0.028 | 1.330 (1.032–1.715) | 0.017 | 1.466 (1.070–2.008) |

EV, esophageal varix; EVB, EV bleeding; HEV, high-risk EV; HR, hazard ratio; CI, confidence interval; NSBB, nonselective beta-blocker; EVL, endoscopic varix ligation; ASPS, acoustic radiation force impulse-spleen diameter-to-platelet ratio score.

determine whether primary prophylactic treatment should be considered.^{1,9,10} Moreover, repeated endoscopic surveillance is also recommended to monitor the potential risk of HEVs.^{5,11} If there is a noninvasive way to determine the presence of HEVs that require prophylactic therapy, many low-risk patients could avoid unnecessary endoscopy screening. Thus, Park *et al.*¹⁷ recently suggested a noninvasive ARFI-based prediction model for diagnosing HEVs in patients with compensated cirrhosis. In that study, the ARFI-based prediction model, named the ASPS, exhibited accurate diagnostic performance in predicting HEVs with an AUROC of 0.946. Additionally, the study also showed acceptable performance for the validation set with an AUROC of 0.814. However, no study has investigated the predictive value of an ARFI-based prediction model to assess the risk of predicting EVB in patients with cirrhosis. Here, we assessed the risk of EVB using ASPS cutoffs. Among patients with a high ASPS >4.50, those with HEV comprised a significantly higher percentage than those with an ASPS below the cutoff (59.2% vs 40.8%; $p=0.045$). In addition, a higher ASPS independently predicted EVB among patients with HEV (hazard ratio, 4.072; $p=0.047$).

LS by TE has represented a major advancement in the noninvasive prediction of EVB. Most studies have shown that patients with an LS of 20 to 21 kPa are at high risk of developing EVB.^{23,24} Kim *et al.*¹² developed an LS-based prediction model, the LSPS. A high LSPS (≥ 6.5) was a significant predictor of EVB. Spleen stiffness (SS) assessed by TE was recently proposed as an indicator closely related to portal hypertension.^{25,26} Buechter *et al.*²⁴ showed that patients with a high SS levels (>42.6 kPa) are at higher risk for EVB. Furthermore, that study suggested an algorithm combining LS and SS to identify patients at low risk for

bleeding; this algorithm showed an NPV up to 1.0. Few studies have assessed the risk of EVB, compared to studies focused on LS or SS, in patients with cirrhosis based on ARFI imaging, which is why we conducted this study. ARFI imaging can be obtained during ultrasonography examinations performed by the same sonographer and thus does not require additional equipment or personnel. ARFI-based risk evaluations may be helpful in a medical environment without TE or for patients who are limited to examinations by TE because of obesity or abundant ascites.²⁷

This study has several limitations. First, because of its retrospective design, it was susceptible to potential selection bias. It was also difficult to strictly control the interval between ARFI and endoscopy. Compared to our previous prospective study that limited the time between ARFI and endoscopy to within 3 months,¹⁷ this study limited the interval to within 6 months. Another problem is that patients in our study population with an ASPS <4.50 still had many HEVs compared with patients with ASPS ≥ 4.50 (50.9% vs 78.6%). Although we selected a point that maximize the sum of the sensitivity and specificity, the small size of our study population might have limited targeting a clinically significant cutoff. Thus, further large-scale studies might enable the establishment of an accurate cutoff. In addition, the study lacks a comparison with LS and SS, the latter of which is a highly suspected noninvasive parameter used to predict the effect of portal hypertension and EVB.¹⁵ Second, we could not propose a management strategy for patients with low-risk EVs but a high ASPS due to the extremely small sample size. However, more careful follow-up strategy to detect the progression to HEV might be required for the patients with

LEV but a high ASPS, although further studies are required to validate this hypothesis. Finally, because the hepatic venous pressure gradient was not obtained invasively (the gold standard for diagnosing portal hypertension), quantitative analysis of various parameters, including ARFI elastography, could not be performed.

In conclusion, the ASPS, an ARFI-based noninvasive prediction model, was helpful in assessing the risk of EVB in patients with cirrhosis. Prophylactic management should be considered for patients with HEV and an ASPS ≥ 4.50 .

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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