Case Reports in Gastroenterology

Case Rep Gastroenterol 2022;16:179–185
DOI: 10.1159/000523757
Received: September 28, 2021
Accepted: February 11, 2022
Published online: March 28, 2022

Case Series

A Novel Splenic Vein Flow Volume to the Portal Vein Flow Velocity Index as a Predictor for the Degree of Esophageal Varices in Liver Cirrhosis Patients

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Keywords
Esophageal varices · Doppler ultrasound · Splenoportal ratio · Portal vein flow velocity · Splenic vein flow volume · Liver cirrhosis

Abstract
Bleeding esophageal varices (EV) have the highest mortality rate from all complications of liver cirrhosis (LC). Several Doppler ultrasound (DUS) studies have been done on the splenic or portal vein (PV) to evaluate the hemodynamic of the esophageal vein. Our study focused on finding a better index using the ratio from two parameters correlated with EV, splenic vein flow volume (SFV), and PV flow velocity. In this study, 28 patients with LC were evaluated using DUS to compare the SFV to PV flow velocity/speed (Sv/Ps) index and other measured DUS parameters with the EV degree. Afterward, the receiver operating characteristic (ROC) curve analysis was performed on statistically significant DUS parameters. Mean Sv/Ps index value in the group of nonvarices was 9.89 ± 3.56; 19.50 ± 5.56 in the small esophageal varices (SEV) and 74.12 ± 29.37 in the large esophageal varices (LEV) group with $p < 0.001$. ROC curve analysis generated an optimal cutoff point of 16.5 (90% sensitivity and 100% specificity) to predict the presence of EV and the cutoff point of 46.7 (100% sensitivity and specificity) to predict the presence of LEV. In conclusion, the Sv/Ps index measured using DUS can be used as a noninvasive method to predict the presence of EV, especially in predicting LEV.

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Introduction

Bleeding of esophageal varices (EV) is one of the fatal complications in liver cirrhosis (LC), and it is the most common cause of upper gastrointestinal bleeding (10–30%) [1–4]. When the EV is underdiagnosed, the mortality rate can be 20%. The risk of EV bleeding is also related to its size, where large esophageal varices (LEV) are at a greater risk for variceal rupture. Therefore, screening and monitoring the degree of EV in LC patients become very important [5, 6].

The most routine examination in daily practice for EV screening is upper gastrointestinal endoscopy, which has been recommended for every LC patient. Unfortunately, endoscopy is not widely available, especially in rural areas and is still considered a semi-invasive procedure [7, 8]. Other examinations such as hepatic venous pressure gradient, a gold standard for portal hypertension (PH) measurement, might also help predict the presence of varices. However, it has been considered an invasive procedure, and it is not widely available due to a lack of expertise [9, 10].

Doppler ultrasound (DUS) has been widely used to explore the relationship between PH and EV [11–13]. Several DUS parameters such as portal vein (PV) velocity, PV congestion index, and hepatic vein waveform, which show an abnormality on PH, have been used to predict the presence of EV. However, most of the studies still used a single parameter and did not consider the degree of EV [14, 15].

One parameter associated with EV is the PV velocity [16–18]. Unfortunately, the association seemed not strong enough and even showed insignificant in some studies, especially on SEV [18–20]. Another parameter is splenic vein flow volume (SFV), which is relatively easy to measure but not yet frequently used in clinical practice [21]. Therefore, this study was aimed to combine these two parameters to bolster the power of each variable, which might result in a better index for predicting and evaluating the degree of EV.

Material and Methods

Patients' Selections

The university institutional review board approved this cross-sectional study (IRB), and all adult subjects have been given written informed consent and the details about the study. We reviewed all the medical records from those willing to participate to exclude any history of liver mass, portal or hepatic vein thrombus, liver resection, pancreatic disease, post-transjugular intrahepatic portosystemic shunt or balloon-occluded retrograde transvenous obliteration. We also collected the etiology data of LC and the Child-Pugh (CP) grade of each patient from the medical record.

Imaging Technique and Analysis

Transabdominal ultrasound was performed using Medison Accuvix V20 (Samsung Healthcare, Seoul, Republic of Korea) with curvilinear transducer 3.5–5 MHz performed by a radiologist who has experienced more than 15 years in performing this procedure. The gray-scale abdominal screening was first evaluated before the Doppler mode to exclude any liver mass and portal or hepatic thrombus. Splenic length, diameter, and velocity of the portal and splenic veins were measured 3 times which average will be used for statistical analysis.

Spectral-wave Doppler was performed to measure the maximum flow velocity of the main PV with sampling location in the mid-part of the PV (gate: 50% vein diameter, insonation angle: ≤60°). Maximum splenic-vein flow velocity was measured in the splenic hilum region (gate: 50% vein diameter, insonation angle: ≤60°). The flow volume is acquired using the area × flow velocity × 60-s equation. The index was a division of SFV to PV flow velocity/speed (Sv/Ps).

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Table 1. Subjects' distribution based on the EV group

Variables	LEV	SEV	Non-EV	*p* value
Gender				
Male	8	8	6	0.958
Female	2	2	2	
Etiology				
Hepatitis B	9	8	4	0.132
Hepatitis C	1	1	4	
Others	0	1	0	
CP score				
CP score A	3	9	8	0.007
CP score B	4	0	0	
CP score C	3	1	0	

LEV, large esophageal varices; SEV, small esophageal varices; EV, esophageal varices.

Endoscopy was performed in the Hepatobiliary division endoscopy unit using a video endoscope (EG-3870UTK; Pentax system, Tokyo, Japan) on the same day of the DUS examination. The EV were graded as large (size more than 5 mm) or small (equal or less than 5 mm), based on the consensus made by the American Association for the Study of Liver Diseases (AASLD) [22].

Data Analysis

All statistical analysis was performed using commercial software (SPSS version 21; IBM Corporation, Armonk NY, USA). ANOVA (normal distribution showed by the Shapiro-Wilk test) was used to test the association between the Sv/Ps index and grade of EV (no varices, small esophageal varices [SEV], and LEV). The repeatability of measured DUS parameters was calculated using the coefficient of variance. Cutoff points were acquired with the receiver operating characteristic curve method between EV and non-EV groups and between LEV and non-LEV groups.

Results

Thirty LC patients who underwent endoscopy procedures for EV screening between January 2018 and February 2018 were asked to participate in the study. However, 2 patients refused to participate in the study. A final total of 28 patients (22 males and 6 females, with a mean age of 55 years old) were assessed in this study. Medical records showed that 75% of the patients have hepatitis B virus infection and 21% hepatitis C virus infection. Four percent of the patients had a history of nonmalignant biliary obstruction, which was considered the most likely cause of cirrhosis (biliary cirrhosis). Seventy-two percent of patients were diagnosed with CP class A, fourteen percent of patients with CP class B, and the rest with CP class C. Endoscopy examination revealed 36% of patients had LEV, 36% of patients with SEV, and 28% of patients without EV. No gastric varices were found among patients. Higher CP grade showed a significant association with the higher degree of EV (p 0.007) (Table 1).

The typical images of DUS measurements are shown in Figure 1. Each DUS parameter measurement showed a coefficient of variance of less than 10%, indicating good repeatability. Those parameters were then calculated and compared with the degree of EV (Table 2). Parameters associated with EV degree were splenic length, splenic vein diameter, splenic flow velocity,

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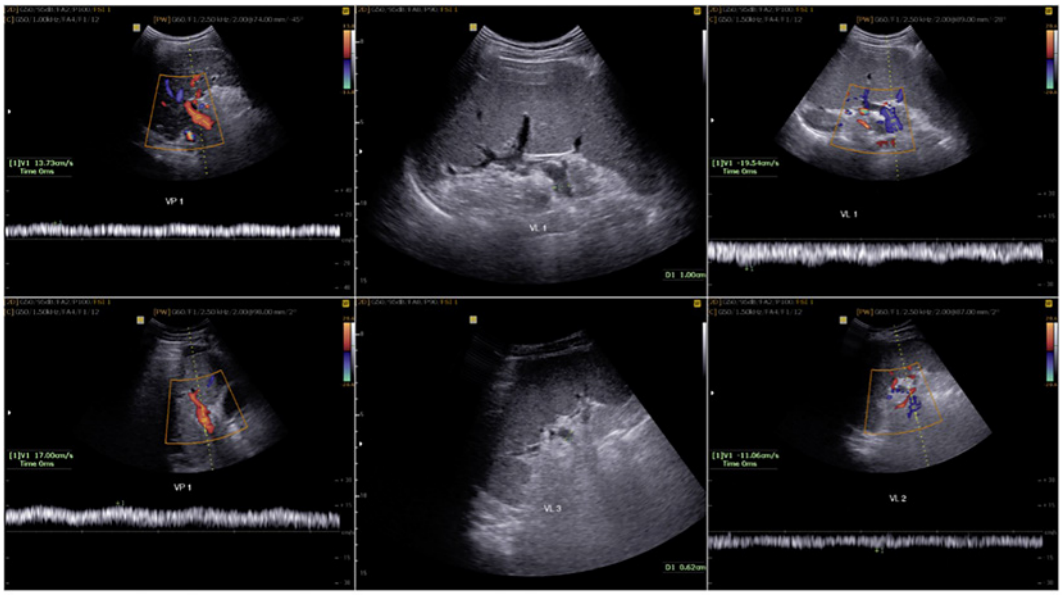

Fig. 1. Representative images from patients with the Sv/Ps index of 67.03 (top) and 11.77 (bottom). On endoscopy, it was revealed that the former had LEV, and the latter had no varices. From left to right are PV flow velocity, splenic vein diameter, and splenic vein flow velocity measurements as the components to calculate Sv/Ps index.

Table 2. Ultrasound parameters with the degree of EV

Parameter	Repeatability (CoV), %	LEV		SEV		Non-EV		*p* value
		mean	SD	Mean	SD	mean	SD	
Splenic length, cm	4.9	14.44	3.55	11.58	1.07	9.55	0.59	0.003[+]
PV diameter, cm	7.7	1.02	0.27	0.82	0.18	0.78	0.25	0.074*
PV flow velocity, cm/s	9.5	13.58	4.80	18.53	5.10	16.65	3.13	0.065*
Splenic vein diameter, cm	5.6	0.99	0.21	0.73	0.09	0.52	0.09	0.000*
Splenic vein flow velocity, cm/s	8.2	21.28	6.67	13.94	3.20	12.51	1.77	0.001[+]
SFV, mL/min	N/A	1,045	677	346	89	159	46	0.000[+]
Sv/Ps index	N/A	74.12	29.37	19.50	5.56	9.89	3.56	0.000[+]

CoV, coefficient of variation; SD, standard deviation; LEV, large esophageal varices; SEV, small esophageal varices; EV, esophageal varices; Sv/Ps, splenic flow volume divided by portal flow velocity; cm, centimeter; cm/s, centimeter per second; mL/min, milliliter per minute.

*ANOVA.

[+]Kruskal-Wallis.

and Sv/Ps index (Table 3), with the highest sensitivity and specificity for the Sv/Ps index for differentiating LEV with non-LEV (100% for both sensitivity and specificity).

Discussion

To our knowledge, this is the first proof-of-concept study in Southeast Asia, looking at the Sv/Ps index as a predictor for predicting the EV in LC patients. Our study showed that a single DUS parameter of the PV could not accurately predict EV degree, which was

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Table 3. The cutoff point, sensitivity, specificity, and AUC for each significant DUS parameter in predicting EV and LEV

EV versus Non-EV	Cutoff	Sensitivity	Specificity	AUC
Splenic length, cm	11.70	0.70	1.00	0.90
Splenic vein diameter, cm	0.64	0.90	1.00	0.98
Splenin vein flow velocity, cm/s	14.5	0.55	0.88	0.78
SFV, mL/min	271.6	0.95	1.00	0.99
Sv/Ps index	16.5	0.90	1.00	0.94
LEV versus Non-LEV				
Splenic length, cm	14.87	0.60	1.00	0.79
Splenic vein diameter, cm	0.82	0.90	0.94	0.96
Splenin vein flow velocity, cm/s	15.1	0.80	0.94	0.92
SFV, mL/min	452.9	1.00	0.94	0.99
Sv/Ps index	46.7	1.00	1.00	1.00

LEV, large esophageal varices; EV, esophageal varices; Sv/Ps, splenic flow volume divided by portal flow velocity; cm, centimeter; cm/s, centimeter per second; mL/min, milliliter per minute; AUC, area under the curve.

supported by Rezayat et al. [18] and Shabestari et al. [20]. Gupta et al. [23] also described a PV having too many collaterals other than the left gastric vein (LGV), which is the primary feeding vein of EV. Therefore, it might be unreliable to be used as a single predictor for detecting the presence of EV.

Most of those collaterals are located at the distal part of the PV, far from the splenic vein. Hence, the splenic vein hemodynamic measurement might be more reliable and relatable to the hemodynamic of LGV, which is known to regulate and contribute to the development of EV. Prior studies using endoscopic ultrasound demonstrated that the blood flow velocity of LGV correlated with the size of EV [24].

The association of splenic parameters to the presence of EV has been studied by Mahmoud et al. [13] and Liu et al. [25], where the splenic size can be used as a predictor of EV. They managed to use it as a predictor but failed to show the correlation with a higher degree of EV. It was concluded that the more severe cirrhosis, the more collaterals were created, resulting in the less consistent result. Their investigation likewise identified SFV as the best single parameter for predicting EV, which is aligned with our findings.

Our study incorporated two DUS parameters to create a single index to enhance the sensitivity and specificity of the examination. Liu et al. [25] attempted a similar technique by employing the splenoportal index (splenic index divided by mean PV velocity) to supplement each parameter. Compared to their study, the Sv/Ps index demonstrated similar accuracy to the splenoportal index (AUC 0.94) in predicting EV. In addition, we extended our investigation that the proposed index showed better accuracy (AUC 1) in predicting the large varices group with a higher risk of rupture.

We acknowledged several limitations in this study. First, we have a small sample size. However, we hope this study can serve as a "proof-of-concept" study to foster subsequent validation studies with bigger sample size. Also, as 96% of our subjects comprised viral LC, we could not infer our proposed index on alcoholic or nonviral LC. Second, it was a single-observer within a single-institution study. Future multiobserver and institution studies might be necessary to warrant the generalizability of our findings. Third, we only included patients with EV, and the presence of collaterals was not thoroughly evaluated.

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For example, large short gastric vein collaterals (as commonly present in gastric varices cases) would significantly divert flow from the splenic vein, thus reducing the reliability of the index measurement.

In conclusion, the Sv/Ps index measured using DUS demonstrated excellent accuracy as a noninvasive method to predict the presence of EV, especially in predicting LEV. Once validated in more extensive studies, this index might be clinically useful, especially in monitoring known EV in cirrhotic patients.

Acknowledgments

The authors would like to express special thanks to Dr. Fiona Amelia MD, MPH, from Boxplot Consultant, for proofreading the final draft of the manuscript.

Statement of Ethics

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975 (revised in 2008). This cross-sectional study was approved by our institutional review boards (the Ethics Committee of the Faculty of Medicine Universitas Indonesia No:938/UN2.F1/ETIK/2015; October 26th, 2015). Written informed consent was obtained from all the patients as the patients were given complete information about the research before the examination was performed. All patients in this study had agreed and signed the participation agreement letter. Written informed consent was also obtained from the patient for publication of the details of their medical case and accompanying images.

Conflict of Interest Statement

The authors of this manuscript (Krishna Pandu Wicaksono, Sahat Matondang, Christopher Silman, Joedo Prihartono, and Cosmas Rinaldi Adithya Lesmana) have no conflicts of interest and declare no relationship with any companies whose products or services may be or will be related to the subject matter of the article.

Funding Sources

No funding received.

Author Contributions

Krishna Pandu Wicaksono and Sahat Matondang come with the research idea. Krishna Pandu Wicaksono performed DOS under the supervision of Sahat Matondang, and Cosmas Rinaldi Adithya Lesmana performed or supervised the endoscopy procedure. Joedo Prihartono collected and analyzed all the data. All the authors (Krishna Pandu Wicaksono, Sahat Matondang, Christopher Silman, Joedo Prihartono, Cosmas Rinaldi Adithya Lesmana) significantly contributed to this research. All the authors read and approved the final manuscript.

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Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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