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ORIGINAL ARTICLE

A strategy for varices screening based on acoustic radiation force impulse combined with platelet (CHESS2001): An alternative of Baveno VI criteria

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Abstract

Few studies have reported on acoustic radiation force impulse (ARFI) for varices screening. Our study aimed to identify a strategy based on liver stiffness measurement (LSM) and spleen stiffness measurement (SSM) by ARFI combined with platelet count (PLT), named the ARP strategy, for ruling out high-risk varices (HRV) and avoiding unnecessary esophagogastroduodenoscopy (EGD) in patients with compensated cirrhosis. We retrospectively reviewed patients who underwent ARFI from a previous cohort (NCT04307264). Of them, patients between 2017 and 2019 composed the training cohort to develop the ARP strategy. The validation cohort consisted of others between 2015 and 2016 to validate and compare it with Baveno VI criteria about the performance for varices screening. Primary outcomes were the rates of spared EGDs and HRV missed. A total of 741 consecutive patients were included in the final analysis. Of them, 576 patients were included in the training cohort and 165 patients in the validation cohort. In the training cohort, ARP strategy was defined as LSM < 1.805 m/s or SSM < 2.445 m/s and PLT > 110×10^9/L. ARP strategy could spare 234 (40.6%) EGDs with a missed HRV rate of 3.4% (8 of 234). In the validation cohort, compared with Baveno VI criteria, the ARP strategy improved the proportion of avoided EGDs (49.7% vs. 34.5%; $p < 0.001$) and lowered the rate of misclassified HRV (1.2% vs. 3.5%; $p < 0.001$). *Conclusion*: The ARP strategy was an efficient and safe tool for varices screening in compensated cirrhosis, and it might be an auxiliary or even alternative to Baveno VI criteria.

Yifei Huang, Lili Zhao, and Ruiling He contributed equally to this work.

INTRODUCTION

Variceal hemorrhage is one of the most severe and immediate life-threatening complications in patients with cirrhosis and portal hypertension, with the risk of 5%–15% per year. Despite improvement in management, overall mortality with each episode of variceal hemorrhage remains about 15%–25% at 6 weeks.[1–4] Current guidelines recommend early identification of high-risk varices (HRV) and primary prophylaxis with an esophagogastroduodenoscopy (EGD) to prevent variceal hemorrhage and to improve outcomes in patients with cirrhosis.[1–4] However, EGD is invasive and resource-intensive; thus, its routine use for identification of HRV is limited. Particularly, a high proportion of patients with compensated cirrhosis undergoing screening do not have gastroesophageal varices (GEV) or have only small varices without high-risk features. These patients do not directly benefit from EGD and yet are exposed to the risks of sedation-related and procedure-related complications.[5] Therefore, it is significant to develop a better way of identifying the population with HRV and reducing the burden of unnecessary EGD, and the use of simple and noninvasive tools is desirable.[6]

Baveno VI criteria (liver stiffness measurement [LSM] < 20 kPa by transient elastography [TE] with platelet count (PLT) > 150×10^9/ L) has been recommended and fully validated for triaging patients who might avoid EGD safely.[1,4,7,8] A possible limitation of Baveno VI criteria is related to a relatively low number of spared EGD.[6,7] Spleen stiffness measurement (SSM) by TE shows a similar or even better value than LSM to rule out patients with HRV.[9,10] Nevertheless, the failure rate of SSM using the standard probe of TE is high. A dedicated probe (100 Hz instead of 50 Hz frequency) with a significantly higher success rate than the standard probe (92.5% vs. 76.0%) has recently been commercialized but not widely used.[6,10] Meanwhile, TE is limited by its high rate of unreliable results (15%–20%), primarily caused by obesity.[11]

Acoustic radiation force impulse (ARFI) has been proposed as an alternative method to assess tissue stiffness, both quantitatively and qualitatively. It is categorized as a displacement imaging technique, which uses a deep focused radiation force, induced by ultrasound. The displacement is measured by comparing the locations of tissue echoes emitted before and immediately after the impulse.[12] 2016 practice guidance by the American Association for the Study of Liver Diseases has demonstrated that SSM is more feasible with ARFI.[2] The recent Baveno VII guideline recommends the validation of LSM thresholds for HRV obtained from devices other than TE to improve the performance for varices screening.[1] Thus, this technology is a promising tool in diagnosing and ruling out HRV and compares favorably to other noninvasive tools in Asian studies.[13,14]

Our study aimed to develop and validate a strategy based on LSM and SSM by ARFI combined with PLT, named the ARP strategy, for ruling out HRV and avoiding unneeded EGD in patients with compensated cirrhosis.

METHODS

Patients

This study was conducted based on the database of a multicenter, observational trial (CHESS2001; ClinicalTrials.gov identifier: NCT04307264) to evaluate the performance of CHESS criteria, based on LSM by TE and PLT, for varices screening in compensated cirrhosis. From the database, we selected patients who underwent LSM and SSM by ARFI between November 2015 and December 2019. Of them, patients between 2017 and 2019 comprised the training cohort to develop the ARP strategy. The validation cohort consisted of other patients between 2015 and 2016 to validate and compare the ARP strategy with Baveno VI criteria about the performance for varices screening. Routine blood tests, including PLT, aspartate aminotransferase, alanine aminotransferase, γ-glutamyl transpeptidase, albumin, total bilirubin, prothrombin time and international normalized ratio, were measured. Two independent investigators (Y.H. and R.H.) reviewed the medical records, including demographic, laboratory, and endoscopic data.

Inclusion criteria were (1) age > 18 years; (2) confirmed cirrhosis based on previous compatible clinical, biochemical, and radiology findings; (3) without decompensated events (e.g., ascites, bleeding, overt encephalopathy); (4) with LSM and SSM by ARFI and PLT measurement; and (5) with written informed consent. Patients were excluded for the following: (1) the time frame between ARFI, PLT, other demographic, laboratory data, and EGD > 14 days; (2) accepted primary prevention (nonselective beta blockers or endoscopic variceal ligation); (3) Child-Pugh score > 9; (4) hepatocellular carcinoma; and (5) splenectomy.

The study was performed in accordance with the ethical guidelines of the Declaration of Helsinki and was approved by the institutional review board. Written informed consent was obtained from all study patients. All authors had access to the study data and reviewed and approved the final manuscript.

LSM and SSM

Patients needed to fast for at least 6 h before ARFI examination, and it was performed using a Siemens Acuson S2000 ultrasound system by an experienced operator with more than 10 years of experience who

was blinded to clinical data and EGD. LSM was measured in the right lobe using the seventh to ninth rib intercostal approach, with the right arm in maximum abduction. SSM was measured using the intercostal approach in the left quarter rib area, with the left arm in maximum abduction. A 10 × 5 mm region-of-interest box was placed on the liver and spleen parenchyma without large blood vessels or abnormal lesions at a depth of 2 to 5 cm below the liver and spleen capsule. People should hold their breath for a few seconds when a suitable image was obtained. LSM or SSM was expressed as shear wave velocity (meters per second). In the validation cohort, LSM was also assessed using TE (FibroScan; Echosens) by an independent operator who was blinded to other clinical data. TE was obtained in accordance with the standard procedure.[15] LSM by TE was expressed as shear wave Young's Modulus (kilopascals). For each patient, 10 repetitive measurements were performed for the liver and/or spleen, and the median values were calculated. Acceptable values were defined as the ratio of the interquartile range to the median value ≤30%.[12]

Endoscopic evaluation of GEV

EGD was performed by two independent expert gastroenterologists (L.Z. and J.L.) in all patients. A flexible EVIS EXERA video gastroscope (Olympus Europa Medical Systems) was used. HRV was defined as large varices (varix size ≥ 5 mm) or small varices (varix size < 5 mm) combined with red wale or Child-Pugh C.[4] Spared EGDs and the rates of and missed HRV were used to assess the efficacy and safety of ARP strategy for varices screening. Spared EGDs were defined as the number of patients classified as a non-HRV group by noninvasive methods among all patients who received EGDs. The missed HRV was calculated by dividing the number of missed HRV by the number of spared EGDs.

Statistical analysis

Continuous variables were reported as median with interquartile range (IQR) or mean with SD, and were compared using the Mann–Whitney test or the Student's *t* test. Categorical data, presented as number and frequencies (%), were compared using the chi-square test or the Fisher's exact test. Receiver operating characteristic (ROC) curve and the area under the ROC curve (AUC) analysis of LSM, SSM, and PLT were used to assess the diagnostic value for the presence of HRV. The cutoff values of LSM, SSM, and PLT were selected according to negative predictive value >95% of identifying HRV in the training cohort, respectively, to develop the optimal strategy for ruling out HRV. The data analysis was performed using the R language (Version 4.0.3, R Core Team, 2020). A p value < 0.05 was considered statistically significant.

RESULTS

Patients

A total of consecutive 741 patients from Tianjin Second People's Hospital between November 2015 and December 2019 were included in the final analysis (Figure S1). The characteristics of the patients are presented in Table 1. Of them, 576 patients between 2017 and 2019 were included in the training cohort and 165 patients between 2015 and 2016 in the validation cohort. The characteristics of the patients assigned to the training cohort (n = 576) and to the validation cohort (n = 165) were not statistically different.

Overall, the main etiology (518 [69.9%]) of cirrhosis was hepatitis B infection, and 709 (95.7%) patients were Child-Pugh class A.

LSM, SSM, and PLT in the training and validation cohort

LSM and SSM by ARFI were successfully carried out in all enrolled patients. In the training cohort, the median (IQR) LSM, SSM, and PLT were 1.880 (0.720) m/s, 2.660 (0.630) m/s, and 134.5 (80.0) × 10^9/L, respectively (Table 1). The median (IQR) LSM for patients with non-HRV and with HRV were 1.840 (0.708) m/s and 2.060 (0.628) m/s and LSM for patients with HRV were significantly higher than that with non-HRV ($p < 0.05$) (Figure 1A). The SSM for patients with HRV was significantly higher than that with non-HRV ($p < 0.05$) with a median (IQR) of 2.930 (0.685) m/s and 2.630 (0.628) m/s, respectively (Figure 1A). The median (IQR) PLT for patients with non-HRV and with HRV was 140.0 (76.0) ×10^9/L and 94.0 (67.0) × 10^9/L, and PLT was higher in patients with non-HRV than that with HRV ($p < 0.05$) (Figure 1A).

In the validation cohort, the median (IQR) LSM, SSM, and PLT were 1.840 (0.938) m/s, 2.620 (0.643) m/s, and 142 (80.3) × 10^9/L, respectively (Table 1). Comparing patients with non-HRV and HRV, the latter had a higher LSM (median [IQR], 1.815 [0.910] m/s vs. 2.160 [0.818] m/s), a higher SSM (median [IQR], 2.615 [1.110] m/s vs. 2.700 [1.110]) m/s, and a lower PLT (median [IQR], 142.0 [83.0] × 10^9/L vs. 110.0 [69.0] × 10^9/L) (Figure 1B). However, the differences were not significance (p = 0.06, p = 0.36, and p = 0.23, respectively), probably due to small sample size of patients with HRV.

TABLE 1 Baseline characteristics of study cohort

Parameters	Total (n = 741)	Training cohort (n = 576)	Validation cohort (n = 165)	*p* value
Age (years), mean (SD)	49.3 (11.9)	49.7 (11.9)	48.0 (12.2)	0.05
Male, n (%)	460 (62.1)	359 (62.3)	101 (61.2)	0.92
BMI, mean (SD)	24.9 (5.1)	24.9 (5.1)	24.7 (5.2)	0.15
LSM, median (IQR)	1.870 (0.773)	1.880 (0.720)	1.840 (0.938)	0.83
SSM, median (IQR)	2.660 (0.640)	2.660 (0.630)	2.620 (0.643)	0.67
Etiology, n (%)				
Hepatitis B infection	518 (69.9)	401 (69.6)	117 (70.9)	
Hepatitis C infection	91 (12.3)	69 (12.0)	22 (13.3)	
Alcohol-associated liver disease	29 (3.9)	23 (4.0)	6 (3.6)	
Primary biliary cirrhosis	22 (3.0)	20 (3.5)	2 (1.2)	
Autoimmune	15 (2.0)	13 (2.3)	2 (1.2)	
Other	66 (8.9)	52 (9.0)	14 (8.5)	
Child-Pugh Class, n (%)				0.75
Class A	709 (95.7)	561 (97.4)	148 (89.7)	
Class B	32 (4.3)	15 (2.6)	17 (10.3)	
Laboratory, median (IQR)				
PLT (10^9/L)	137.0 (76.0)	134.5 (80.0)	142 (80.3)	0.20
ALT (U/L)	52.0 (97.0)	50.0 (92.5)	61.0 (135.5)	0.91
AST (U/L)	46.0 (77.0)	45.0 (76.0)	50.0 (90.8)	0.98
GGT (U/L)	65.0 (99.3)	66.0 (107.0)	62.0 (79.3)	0.52
Alb (g/L)	43.4 (4.1)	43.4 (6.4)	43.1 (7.0)	0.17
TBIL (μmol/L)	17.3 (10.8)	17.4 (11.0)	16.4 (11.6)	0.43
PT (s)	13.7 (1.6)	13.6 (1.6)	13.8 (1.4)	0.72
INR	1.1 (0.1)	1.1 (0.2)	1.1 (0.1)	0.49
Varices, n (%)				
Any varices	311 (42.9)	252 (43.8)	59 (35.8)	0.07
HRV	76 (10.3)	65 (11.3)	11 (6.7)	0.30

Abbreviations: Alb, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body index; GGT, gamma-glutamyl transpeptidase; INR, international normalized ratio; IQR, interquartile range; PT, prothrombin time; TBIL, total bilirubin.

Performance of ARP strategy for screening varices

In the training cohort (n = 576), 65 (11.3%) patients had HRV. The AUC for LSM, SSM, and PLT for the detection of HRV was 0.63 (95% confidence interval [CI] 0.59–0.67), 0.66 (95% CI 0.62–0.70), and 0.72 (95% CI 0.68–0.76), respectively (Table S1). With the aim of identifying, by ROC curves, the LSM, SSM and PLT, the most accurate cutoffs to rule out patients with HRV (corresponding to negative predictive value [NPV] of 95%), the cutoffs of LSM < 1.805 m/s, SSM < 2.445 m/s, and PLT > 110×10^9/L were chosen, respectively. The diagnostic performance of LSM, SSM, and PLT for HRV was demonstrated in Tables S1 and S2. The ARP strategy to rule out HRV was defined as LSM < 1.805 m/s or SSM < 2.445 m/s and PLT > 110×10^9/L. The ARP strategy could spare 234 (40.6%) EGD with a risk of missed HRV of 3.4% (8 of 234) (Table 2).

In the validation cohort (n = 165), 11 (6.7%) patients had HRV. The ARP strategy spared 82 (49.7%) EGD with a risk of missed HRV of 1.2% (1 of 82). Meanwhile, Baveno VI criteria (LSM < 20 kPa + PLT > 150×10^9/L) was verified. Baveno VI criteria could spare 57 (34.5%) EGD with a risk of missed HRV of 3.5% (2 of 57). Comparing Baveno VI criteria, the ARP strategy improved the proportion of avoided EGD (49.7% vs. 34.5%; $p < 0.001$) and lowered the rate of misclassified HRV (1.2% vs. 35%; $p < 0.001$) (Figure S2).

Subgroup analysis in the validation cohort stratified by etiology and Child-Pugh class

The main etiology (69.9%) of cirrhosis was hepatitis B infection, and most of our patients were Child-Pugh class A (95.7%); thus, we did a subgroup analysis in the validation cohort to explore the varices screening

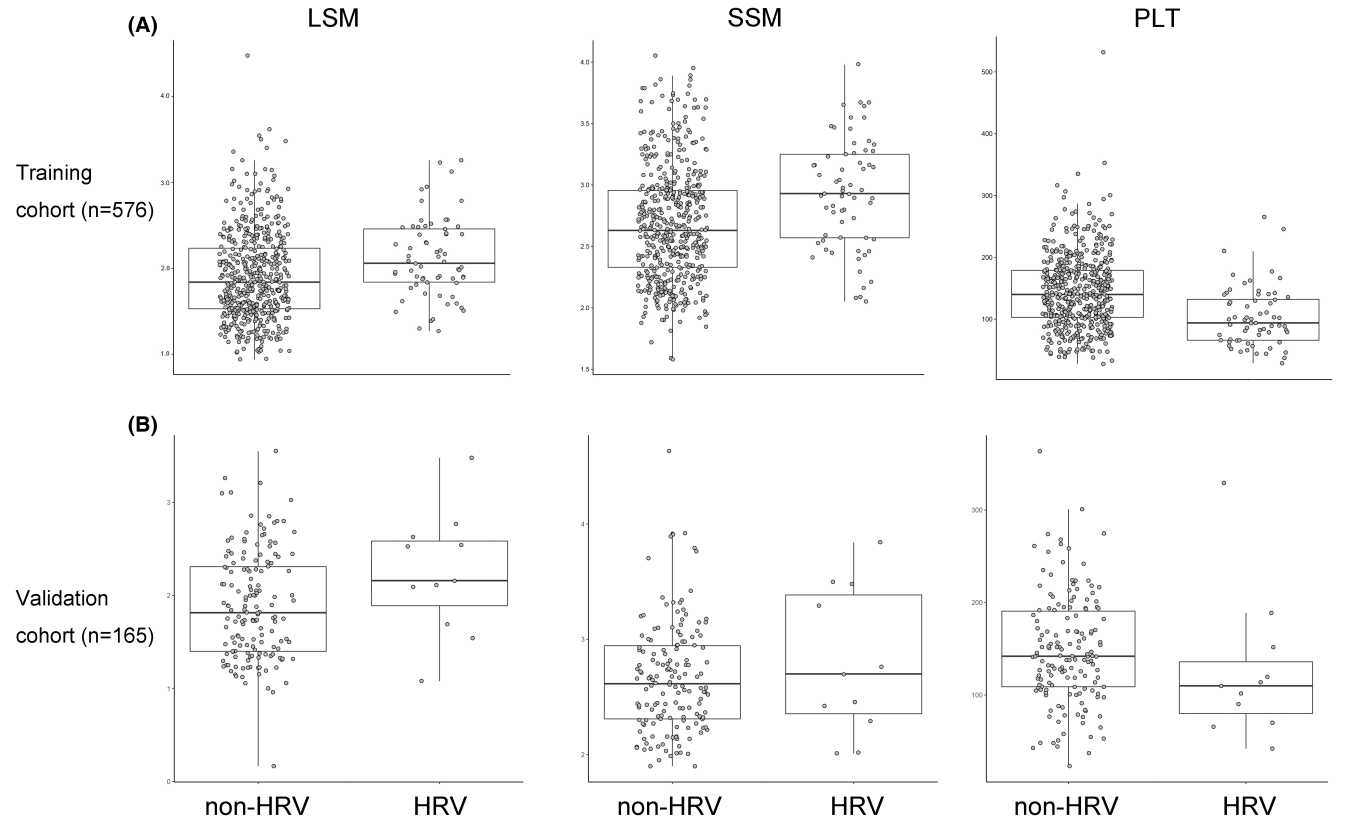

FIGURE 1 Distribution of liver stiffness measurement (LSM), spleen stiffness measurement (SSM), and platelet count (PLT) according to the presence of non–high-risk varices (HRV) and HRV. (A) Distribution in the training cohort. (B) Distribution in the validation cohort. Each dot represents a patient, and bars indicate mean values.

TABLE 2 Performance of ARP strategy for varices screening in the training and validation cohort

	Missed HRV	Spared EGD
Training cohort (n = 576)		
ARP strategy		
(LSM < 1.805 m/s or SSM < 2.445 m/s) and PLT > 110 × 10^9/L	8 of 234 (3.4%)	234 (40.6%)
Validation cohort (n = 165)		
ARP strategy		
(LSM < 1.805 m/s, or SSM < 2.445 m/s) and PLT > 110 × 10^9/L	1 of 82 (1.2%)[a]	82 (49.7%)[b]
Baveno VI criteria		
LSM < 20 kPa + PLT > 150 × 10^9/L	2 of 57 (3.5%)[a]	57 (34.5%)[b]

Note: Data are presented as n (%) or n/N (%), where N is the total number of related cases; the unit of platelets was ×10^9/L.

[a]$p < 0.001$.

[b]$p < 0.001$.

value of the ARP strategy in the two specific groups. In the validation cohort, 117 (70.9) patients had a hepatitis B infection and 148 (89.7) patients were Child-Pugh class A. Examining only patients with hepatitis B infection, the ARP strategy spared 58 (49.6%) with a risk of missed HRV of 0% (0 of 58) (Table 3). As for patients with Child-Pugh class A, the ARP strategy spared 68 (45.9%) with a risk of missed HRV of 1.5% (1 of 68) (Table 3). Compared with Baveno VI criteria, the ARP strategy improved the proportion of avoided EGD (hepatitis B infection, 49.6% vs. 33.3%, $p < 0.001$; Child-Pugh class A, 45.9% vs. 37.2%, $p < 0.001$), and the rates of misclassified HRV were similar or lower (hepatitis B infection, 0% vs. 0%; Child-Pugh class A, 1.5% vs. 3.6%, $p < 0.001$).

DISCUSSION

Liver cirrhosis is generally characterized by a long phase of compensated disease. However, when it progresses to decompensation, the survival of these patients drops sharply.[16] Therefore, it is very important to achieve appropriate risk stratification in patients with compensated cirrhosis, and this should be particularly focused on identifying and staging portal hypertension and its main complications.[4,5] Because EGD is invasive and resource-intensive, there is increasing interest in the development of rapid and accurate noninvasive tools.

TABLE 3 Performance of ARP strategy in patients with hepatitis B infection and patients with Child-Pugh class A in the validation cohort

	Missed HRV	Spared EGD
Hepatitis B infection (n = 117)		
ARP strategy		
(LSM < 1.805 m/s or SSM < 2.445 m/s) and PLT > 110 × 10^9/L	0 of 58 (0.0%)[a]	58 (49.6%)[b]
Baveno VI criteria		
LSM < 20 kPa + PLT > 150 × 10^9/L	0 of 39 (0.0%)[a]	39 (33.3%)[b]
Child-Pugh class A (n = 148)		
ARP strategy		
(LSM < 1.805 m/s or SSM < 2.445 m/s) and PLT > 110 × 10^9/L	1 of 68 (1.5%)[c]	68 (45.9%)[d]
Baveno VI criteria		
LSM < 20 kPa + PLT > 150 × 10^9/L	2 of 55 (3.6%)[c]	55 (37.2%)[d]

Note: Data are presented as n (%) or n/N (%), where N is the total number of related cases; the unit of platelets was ×10^9/L.

[a]$p < 0.001$.

[b]$p < 0.001$.

[c]$p < 0.001$.

[d]$p < 0.001$.

In this study, the screening model, named the ARP strategy, was developed by LSM and SSM by ARFI combined with PLT and validated to rule out HRV and avoid EGD in patients with compensated cirrhosis. In the training cohort and validation cohort, the proportions of ARP strategy ([LSM < 1.805 m/s or SSM < 2.445 m/s] and PLT > 110 × 10^9/L) to avoid EGD were 40.6% and 49.7%, respectively, and the misclassification rates were low (<5%). Furthermore, we compared the ARP strategy with Baveno VI criteria in the validation cohort, and the data demonstrated that the ARP strategy allowed an improvement of spared EGD proportion (49.7% vs. 34.5%) and a reduction of missed HRV rate (1.2% vs. 3.5%).

Ultrasound-based tissue elastography was accomplished by either TE, two-dimensional shear wave elastography (2D-SWE), or ARFI.[11] TE was currently the most widely used elastography technique in clinical practice (LSM by TE in particular).[6] Several studies[7,8] and one meta-analysis[17] validated Baveno VI criteria (LSM < 20 kPa by TE with PLT > 150 × 109/L) as safe for screening HRV in patients with compensated cirrhosis, with <5% of HRV missed overall. The proportion of spared EGD with Baveno VI criteria, however, was relatively low (15%–25%). Baveno VI criteria in this study provided a little higher spare EGD rate (34.5%) in the validation cohort, probably due to the difference of percentage of patients with HRV (6.7%), Child-Pugh class A (89.7%), and hepatitis B infection (70.9%). Many authors proposed different cutoffs and models to increase the number of EGDs that could be avoided, such as well-conducted expanding Baveno VI criteria.[18,19] However, this would be at a lower rate of spared EGDs than the ARP strategy, and most importantly, with a controversial rate of HRV missed above the accepted threshold of 5%.[20–23]

Previous studies showed that LSM by TE had a significant correlation with the severity of portal hypertension. Nevertheless, LSM only had a good correlation with portal pressure in the early stage of portal hypertension, because liver fibrosis was the main cause of portal hypertension in this period.[24–27] With advanced cirrhosis and increased portal vein inflow due to splanchnic vasodilation and hyperdynamic circulation, SSM might have a better correlation with portal pressure than that of LSM.[28–30] Therefore, SSM might provide a reliable basis for the hemodynamic changes during the development of liver cirrhosis and avoid the limitations caused by the measurement of LSM. A noninvasive prediction model combining SSM with Baveno VI criteria (satisfying Baveno VI and SSM ≤46 kPa) was useful to rule out HRV and could make it possible to avoid a significantly larger number of unnecessary EGD compared with Baveno VI criteria only.[9] However, there were at least two limitations for TE: The failed measurements percentage was high (15%–20%), primarily caused by obesity, ascites, and narrow intercostal spaces; and there is one more limitation regarding the upper limit of the cutoff value of 75 kPa, considering that SSM frequently exceeds this value.[31]

Other than TE, several studies explored LSM and SSM by 2D-SWE for varices screening. Yan et al. suggested that the new criteria (LSM by 2D-SWE < 16 kPa and PLT > 100 × 10^9/L) could be a potential model to spare more EGD screening with a HRV missed rate < 5%.[32] In addition, Qi et al. conducted a CHESS2004 trial (NCT 04546360) to establish a standard for predicting HRV that is more suitable in patients with hepatitis B infection–compensated cirrhosis. With regard to ARFI, it might have some technical advantages over TE. ARFI measured the displacement by comparing the locations of tissue echoes emitted before and immediately after the impulse; thus, it was not limited by obesity, ascites, and narrow intercostal spaces. It was reported that the rate of unsuccessful measurements was only about 2.9%, and ARFI could be successfully performed in all patients in the present study.[31] Moreover, performers could choose the regions of interest while performing real-time B-mode imaging to avoid nearby interfering structures such as blood vessels and minimize the measurement error.[14] Several studies show the ability of this technique for predicting the presence of varices and HRV. Takuma et al. obtained SSM by ARFI to predict HRV, and the results showed that the SSM cutoff value of 3.3 m/s had a sensitivity of 98.4%, specificity of 63.4%, and accuracy of 73.0% in patients with

compensated cirrhosis.[13] Takuma et al. reported that both SSM and LSM by ARFI were linearly correlated with portal pressure. The SSM cutoff value of 3.51 m/s was selected to rule out the presence of HRV, and the sensitivity, specificity, and accuracy of diagnosis are 93.8%, 84.1%, and 86.7%, respectively.[33] However, a few studies reported on ARFI combined with PLT for varices screening and avoiding unneeded EGD.

The present study uses a large ARFI cohort to report on a varices screening model to rule out HRV and avoid EGD in patients with compensated cirrhosis. Applying the ARP strategy, it was possible to achieve appropriate varices risk stratification in patients with compensated cirrhosis (Figure 2). Low PLT has been defined as a significant high-risk factor of HRV and variceal bleeding in cirrhosis and portal hypertension.[34] The results suggest that the ARP strategy made it possible to increase the number of avoided unnecessary endoscopies, and the risk of missed HRV was lower compared with Baveno VI criteria (i.e., the ARP strategy benefited more patients with lower PLT than Baveno VI criteria [110×10^9/L vs. 150×10^9/L]). With good performance, the ARP strategy can serve as the promising application direction and effective complementary or even an alternative noninvasive tool of Baveno VI for screening varices and avoiding EGD. Moreover, we conducted a subgroup analysis in the validation cohort stratified by etiology and Child-Pugh class. The results verified the greater value for varices screening of ARP strategy than Baveno VI criteria in the two specific cohort: patients with hepatitis B infection (EGD spared proportion, 49.6% vs. 33.3%; missed HRV rate, 0% vs. 0%) and patients with Child-Pugh class A (EGD spared proportion, 45.9% vs. 37.2%; missed HRV rate, 1.5% vs. 3.6%), respectively.

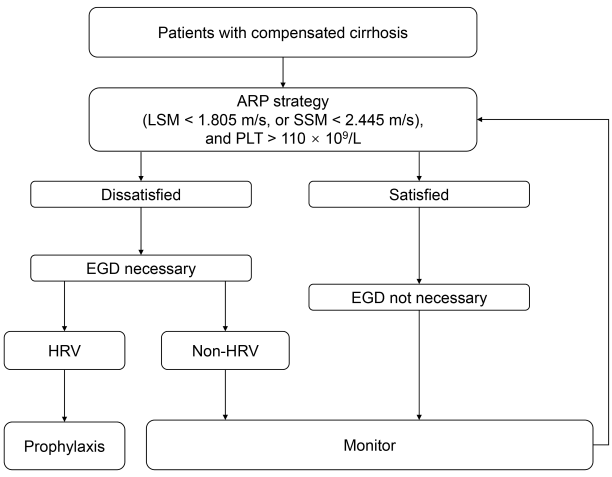

FIGURE 2 ARP strategy, a varices screening strategy based on LSM and SSM by acoustic radiation force impulse (ARFI) combined with PLT to rule out HRV and avoid esophagogastroduodenoscopy (EGD) in patients with compensated cirrhosis.

Our study had some limitations. First, the data from this single-center cohort were acquired retrospectively, and therefore could lead to unavoidable selection bias. For example, those whose LSM and SSM by ARFI were not successfully carried out might be excluded because of retrospective analysis. It prevented wider extrapolation of results to the real-world population, and fewer EGDs would be spared in clinical practice due to an unreported technical failure rate. Although this weakness is likely offset by the design and by the inclusion of a substantial sample size, multicenter prospective studies should be conducted to further evaluate the performance of the ARP strategy. Second, we defined the training and validation according to the examination time of enrolled patients, not via random allocation, which could lead to a time-associated difference such as experience of operators or population recruitment. However, patients were enrolled consecutively and there were no differences of baseline characteristics between the two cohorts, which reduced the potential bias. Meanwhile, our study uses an uneven distribution of cirrhosis etiology, having only a few cases with non-virus-infected cirrhosis. Subgroup analysis verified the efficacy of the ARP strategy in patients with compensated cirrhosis with hepatitis B infection. However, whether the ARP strategy is appropriate in cirrhosis caused by other etiologies requires furthermore evaluation.

CONCLUSIONS

Our study developed and validated a varices screening strategy, called the ARP strategy, based on LSM and SSM by ARFI combined with PLT to rule out HRV in patients with compensated cirrhosis. The data indicated that the ARP strategy was an efficient and safe model for avoiding unnecessary EGD, and it might be an auxiliary or even alternative tool to the Baveno VI criteria.

AUTHOR CONTRIBUTIONS

Study concept and design: Xiaolong Qi and Yifei Huang. *Data collection and analysis*: Yifei Huang, Lili Zhao, Shuang Li, and Chuan Liu. *Manuscript draft*: Yifei Huang and Ruiling He. *Manuscript review*: Xiaolong Qi and Jia Li. All authors read and approved the final manuscript.

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CONFLICT OF INTEREST

Nothing to report.

DATA AVAILABILITY STATEMENT

Deidentified individual participant data will not be shared. Researchers can apply for data by submitting a proposal to the corresponding author.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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