

# Validation of the EVendo score for the prediction of varices in cirrhotic patients

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**Abstract** **Background:** Screening endoscopy for varices may be deferred when the calculated EVendo score is  $\leq 3.90$ . This novel score has not been validated in an external cohort. This study aimed to assess the performance of the EVendo score and compare it with the Baveno VI criteria.

**Methods:** We identified and calculated this score in all cirrhotic patients who underwent screening endoscopy for the first time with laboratory tests and liver stiffness measurements within 6 months of the endoscopy date.

**Results:** In total, 103 patients were included. An EVendo score of  $\leq 3.90$  identified patients with no gastroesophageal varices (GEV) and varices needing treatment (VNT) with sensitivities of 82% and 83% and specificities of 57% and 34%, respectively. The negative predictive value for VNT was 94%. A comparison with the Baveno VI criteria in Child–Turcotte–Pugh–A patients showed spared endoscopy and missed VNT rates with EVendo score cutoffs of  $\leq 3.9$  and  $\leq 4.5$  and the Baveno VI criteria of 25%, 33%, and 16.6% and 1.7%, 1.7%, and 0%, respectively.

**Conclusions:** EVendo score is reliable in clinical practice for predicting GEV and VNT. The number of spared endoscopies was higher than that with the Baveno VI criteria; however, there were more missed VNT cases.

**Keywords:** Baveno VI criteria, cirrhosis, EVendo score, noninvasive, varices

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**Submitted:** 09-Dec-2021 **Revised:** 10-Jan-2022 **Accepted:** 16-Jan-2022 **Published:** 18-Feb-2022

## INTRODUCTION

Variceal bleeding is one of the leading causes of liver-related mortality in cirrhotic patients.<sup>[1]</sup> The prevalence of gastroesophageal varices (GEV) increases with the severity of liver cirrhosis; approximately 30%–40% of compensated cirrhosis patients have GEV, and only a minority (10%–20%) have varices needing

treatment (VNT). However, most decompensated cirrhosis patients (approximately 85%) have GEV as the majority have clinically significant portal hypertension (CSPH).<sup>[2–4]</sup> Therefore, screening cirrhotic patients to diagnose GEV, especially VNT, is recommended so that prophylactic bleeding measures can be applied pharmacologically or endoscopically. Until recently, guidelines recommended

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**How to cite this article:** Alswat K, Alanazi M, Bashmail A, Alkhamash M, Alqahtani SA, Al-Hamoudi W, *et al.* Validation of the EVendo score for the prediction of varices in cirrhotic patients. Saudi J Gastroenterol 2022;28:378-84.

Access this article online	
Quick Response Code:	Website: www.saudijgastro.com
	DOI: 10.4103/sjg.sjg_624_21

using esophagogastroduodenoscopy (EGD) to screen GEV in all cirrhotic patients.<sup>[5,6]</sup> However, several studies have shown that a significant proportion of cirrhotic patients subjected to screening endoscopies had negative exams with no GEV identified with EGD, in addition to the sedation risk of cirrhotic patients and higher costs.<sup>[7,8]</sup>

Therefore, efforts have been made to develop and investigate the performance of several noninvasive tools that can serve as primary screening methods to limit unnecessary screening of EGD in cirrhotic patients. Examples of these include platelet count-to-spleen diameter ratio, liver or spleen stiffness, combination algorithms, and scores such as aspartate aminotransferase (AST)-to-platelet ratio index (APRI), AST-to-alanine aminotransferase (ALT) ratio (AAR), fibrosis 4 index (FIB-4), and the King, Lok, and Liaoning scores.<sup>[9-12]</sup> One of the recommended modalities in the new guidelines and most validated method is the Baveno VI consensus criteria, which rely on liver stiffness measurement (LSM) and platelet counts. This suggests that in compensated cirrhosis, patients with both LSM <20 kPa and platelet count >150 × 10<sup>9</sup> cells/L can safely avoid screening EGD.<sup>[13]</sup> These criteria have been validated and showed good sensitivity with low specificity but still had high rates of unnecessary endoscopy.<sup>[14,15]</sup> The refinement of these criteria was made in the expanded Baveno VI criteria, which allows for more spared endoscopy rates (SER); however, this was at the expense of a higher missed VNT rate, which is above the accepted threshold of 5%.<sup>[15,16]</sup> Therefore, despite the better performance of these criteria compared to other methods, these criteria are not perfect and require the availability of LSM, which is not available in all clinical settings. For these reasons, there is an unmet need for better noninvasive GEV screening methods.

Recently, a new score formula named the EVendo score was developed using a machine-learning algorithm to identify factors significantly associated with GEV and VNT. The formula is based on readily available laboratory tests: hemoglobin (Hgb), platelet counts, international normalized ratio (INR), level of AST, blood urea nitrogen (BUN), and presence of ascites.<sup>[17]</sup> This score showed robust performance characteristics across a broad array of liver disease etiologies and is readily available using a published online calculator.<sup>[18]</sup> This novel score has not been validated by an independent group other than the inventors. Therefore, the primary aim of our study was to validate the performance of the EVendo score for the prediction of GEV and VNT in cirrhotic patients. The secondary aim was to compare the performance of the EVendo score with the Baveno VI criteria in the subgroup of patients with compensated cirrhosis.

## PATIENTS AND METHODS

### Study design and settings

This was a retrospective cohort study conducted at King Saud University Medical City and included all adult patients with cirrhosis (age >18) with laboratory investigations and LSM within 6 months of screening EGD, from January 2018 to July 2020. Data were collected using the endoscopy unit's database and medical records. The exclusion criteria included patients with a history of GEV bleeding or varices, endoscopic interventions, noncirrhotic portal hypertension, portal vein thrombosis, splenectomy, or hepatocellular carcinoma. Similarly, patients undergoing dialysis or using beta-blockers or anticoagulants were excluded from the study. The variables collected included age, sex, etiology of liver diseases, hepatic encephalopathy, ascites, platelet count, total bilirubin (TBIL), albumin (ALB), Hgb, ALT, AST, alkaline phosphatase,  $\gamma$ -glutamine transferase, presence of ascites, BUN, serum sodium, serum creatinine, prothrombin time, activated partial thromboplastin time, and INR. The EVendo score was calculated using the equation in the original study and rechecked with calculation results from the Med calculator for every patient.<sup>[17,18]</sup> LSM was performed by FibroScan<sup>®</sup> (Echosens, Paris) based on the standard procedure.<sup>[19]</sup> Cirrhosis diagnoses were reviewed in all cases, including patients diagnosed based on LSM >15 kPa and/or by histology, regardless of LSM values or the presence of liver decompensation in patients who met other inclusion criteria. VNT in our study was defined as the presence of esophageal varices with grade  $\geq$ F2, varices of any size with high-risk stigmata, or any size of gastric varices. Other varices not requiring treatment were named varices not needing treatment (VNNI).

The study was approved by the Institutional Ethical Review Board for Health Sciences Colleges Research on Human Subjects at King Saud University Medical City (E-21-5759). The requirement for informed consent was waived by the same ethics committee as we retrospectively reviewed de-identified information available in database and medical records and did not cause affect patients and their rights adversely. The study was conducted in accordance with the relevant guidelines and regulations stipulated by the King Saud University Medical City.

### Statistical analysis

We used absolute numbers and percentages to summarize categorical variables and used means and standard deviations (SDs) or medians and interquartile ranges (IQRs) to summarize continuous data. Comparisons of categorical variables between groups were made using the

Chi-square test or Fisher’s exact test, whereas comparisons of continuous data were made using Student’s *t* test or the Mann–Whitney U test. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and positive and negative likelihood ratios (LR+, LR–) with 95% confidence intervals (CIs) were estimated to study the diagnostic accuracy of the EVendo score. Receiver operating characteristic (ROC) analysis was performed to examine the overall diagnostic performance of the EVendo score and other markers. The missed VNT rate was calculated as false-negative cases/the total number of patients. The SER was calculated as (false-negative cases + true negative cases)/the total number of patients. An association with  $P \leq 0.05$  was considered statistically significant. All analyses were performed using SAS version 9.4 (SAS Institute, Inc., Cary, NC) and R software (R foundation for statistical computing, Vienna, Austria).

## RESULTS

The study cohort included 103 patients who underwent GEV screening [Figure 1]. The etiology distribution among the included patients was as follows: hepatitis C virus 33 (32%), nonalcoholic steatohepatitis 20 (19.5%), hepatitis B virus (HBV) 13 (12.5%), cryptogenic cirrhosis 13 (12.5%), autoimmune liver disease 9 (8.7%), alcoholic liver disease 3 (2.9%), and others 12 (11.6%). The majority of patients in this cohort, 60 (58.2%), had Child–Turcotte–Pugh (CTP)-A cirrhosis, and 40 (38.8%) and 3 (2.9%) patients had CTP-B and CTP-C cirrhosis, respectively.

GEV and VNT were present in 66 (64%) and 12 (11.65%) patients, respectively. The prevalence of GEV based on CTP class showed that GEV was present in all CTP-C patients and present in 26 (65%) CTP-B patients and 37 (61.6%) CTP-A patients. We found that patients with GEV had significantly lower platelet counts and ALB and higher APRI, FIB4, LSM, and EVendo scores than those with no GEV. Comparing patients with VNT with those with VNNI, patients with VNT were younger; otherwise, there were no significant differences in the basic laboratory parameters, such as ALT, AST, ALB, TBIL, INR, and platelet count. The same observation was found for noninvasive parameters, including EVendo score, APRI, FIB4, and LSM [Table 1].

### Performance of the EVendo score

The overall performance of the EVendo score for the detection of GEV and VNT showed areas under the receiver operating characteristic curves (AUROCs) of 0.75 (95% CI: 0.65–0.85) and 0.59 (95% CI: 0.54–0.63), respectively. A comparison of the performance based on CTP scores showed that the AUROCs for GEV and VNT were 0.75 (95% CI: 0.62–0.87) and 0.65 (95% CI: 0.54–0.73) for CTP-A and 0.78 (95% CI: 0.62–0.94) and 0.59 (95% CI: 0.52–0.66) for CTP-B and CTP-C.

Using an EVendo score of  $\leq 3.90$  identified patients with no GEV and patients with no VNT with sensitivities of 82% and 83% and specificities of 57% and 34%, respectively. The NPV of EVendo score  $\leq 3.90$  for ruling out VNT in the study cohort was 94%. Within all performed EGDs, an EVendo score of  $\leq 3.90$  could potentially spare 21 (20.38%)

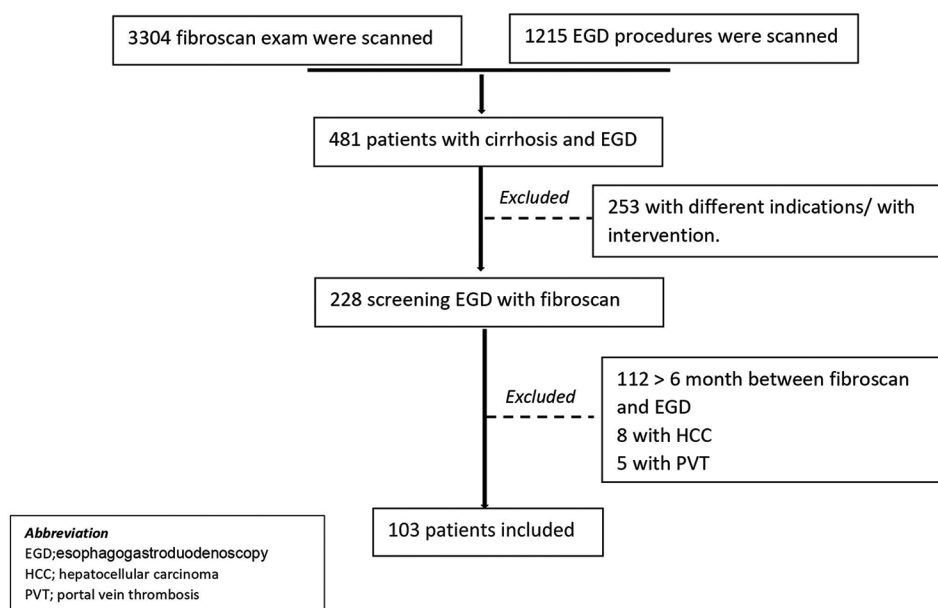


Figure 1: Enrollment Flowchart

**Table 1: Characteristics of the study patients**

	GEV presence			GEV needing treatment		
	Not Present n=37 (35.92%)	Present n=66 (64.08%)	P	Non/VNNT n=91 (88.34%)	VNT n=12 (11.65%)	P
Age, year, mean (SD)	59.59±10.29	55.67±16.85	0.201	58.18±14.34	48.75±17.00	0.039
BMI (kg/m <sup>2</sup> )	27.52±5.05	27.65±6.04	0.906	27.77±5.51	26.37±6.96	0.427
Female (n=51) n (%)	18 (48.65%)	33 (50.00%)	0.895	43 (47.25%)	8 (66.67%)	0.206
Laboratory data, mean (SD)						
ALT (U/L)	47.23±32.71	43.44±22.20	0.486	44.95±26.99	43.67±21.90	0.875
AST (U/L)	42.46±36.39	51.11±30.05	0.198	48.50±34.03	44.25±18.47	0.673
ALB (g/L)	34.76±5.79	31.53±5.18	0.004	32.78±5.71	32.02±4.77	0.660
TBIL (mmol/L)	15.57±13.82	29.53±46.42	0.078	25.16±40.65	19.62±15.01	0.642
INR	1.18±0.52	1.24±0.22	0.417	1.22±0.37	1.26±0.24	0.723
Cr (mmol/L)	138.4±227.8	70.97±25.35	0.019	99.42±149.1	63.25±15.44	0.405
BUN (mmol/L)	6.47±5.16	4.69±2.42	0.019	5.46±3.89	4.34±1.90	0.331
Hgb (mg/dL)	129.8±22.34	123.9±21.03	0.179	127.7±21.32	113.3±20.12	0.030
PLT (10 <sup>3</sup> /mm <sup>3</sup> )	176.3±82.12	130.2±79.72	0.006	146.6±79.87	148.1±109.5	0.955
Disease severity and complications, n (%)						
CTP-A, (n=60)	23 (62.16%)	37 (56.06%)	0.397	53 (58.24%)	7 (58.33%)	0.809
CTP-B, (n=40)	14 (37.84%)	26 (39.39%)		35 (38.46%)	5 (41.67%)	
CTP-C, (n=3)	0 (0.00%)	3 (4.55%)		3 (3.30%)	0 (0.00%)	
Ascites (n=21)	6 (16.22%)	15 (22.73%)		19 (20.88%)	2 (16.67%)	0.734
Encephalopathy (n=21)	2 (5.41%)	7 (10.61%)		8 (8.79%)	1 (8.33%)	0.958
Noninvasive tests, mean (SD)						
EVendo score	4.26±2.06	5.70±1.81	<.001	5.14±2.07	5.52±1.60	0.537
APRI	0.98±1.16	1.54±1.05	0.013	1.34±1.15	1.33±0.92	0.972
FIB4	2.64±2.28	4.31±2.90	0.003	3.77±2.87	3.24±2.26	0.535
LSM (kPa)	13.75±9.20	34.01±20.75	<.001	26.59±20.66	27.77±14.64	0.850
MELD score	9.83±4.69	10.53±4.06	0.430	10.36±4.44	9.65±2.89	0.596

GEV: Gastroesophageal varices, VNT: Varices Needing Treatment, VNNT: Varices Not Needing Treatment, BMI: Body Mass Index, ALT: Alanine Aminotransferase, AST: Aspartate Aminotransferase, ALB: Albumin, TBIL: Total Bilirubin, INR: International Normalized Ratio, Cr: Serum Creatinine, BUN: Blood Urea Nitrogen, Hgb: Hemoglobin, PLT: Platelet count, CPT: Child-Turcotte-Pugh Class, APRI: AST to Platelet Ratio Index, FIB4: Fibrosis 4 index, LSM: Liver Stiffness Measurement, MELD: Model for End-stage Liver Disease

patients, with a risk of missing VNT in two patients (1.9%). In our analysis, we identified another potential cutoff value for the EVendo score of 4.5. The performance of this cutoff was close to that of 3.9 [Table 2]. However, with this cutoff point, an EVendo score of ≤4.50 could potentially spare more EGDs in 27 patients (26.21%), with a similar risk of missing VNT in two patients (1.9%) [Table 3].

**Comparison of the performance of the EVendo score and Baveno VI criteria in CTP-A patients**

The performance of the Baveno VI criteria was assessed in the whole cohort and then in CTP-A patients and compared to that of the EVendo score. The Baveno VI criteria ruled out GEV and VNT with sensitivities of 92% and 100% and specificities of 46% and 24%, respectively, for the whole cohort.

When the analysis was restricted to CTP-A patients, the Baveno VI criteria were able to rule out GEV and VNT with sensitivities of 89% and 100%, specificities of 43% and 26%, and NPVs of 71% and 100%, respectively [Table 4]. The Baveno VI criteria were able to spare 22 (21.35%) endoscopies with a missing rate of VNT of 0%. However, the number of spared endoscopies in CPT-A was less than the number spared using the EVendo score with cutoff points of 3.9 and 4.5: 16.6% versus 25% and 33.3% [Table 3].

**DISCUSSION**

The need for high-performing, noninvasive screening tests to identify cirrhotic patients with GEV, especially VNT, cannot be underscored. In this study, we validated the

**Table 2: Comparison of the performance of EVendo score with two cutoff values\***

EVendo score	Sensitivity	Specificity	PPV	NPV	LR+	LR-
Cutoff ≤3.9						
GEV	0.82 (0.70, 0.90)	0.57 (0.39, 0.73)	0.77 (0.66, 0.86)	0.64 (0.45, 0.80)	1.89 (1.29, 2.78)	0.32 (0.18, 0.57)
VNT	0.83 (0.52, 0.98)	0.34 (0.24, 0.45)	0.14 (0.07, 0.25)	0.94 (0.80, 0.99)	1.26 (0.94, 1.69)	0.49 (0.13, 1.79)
Cutoff ≤4.5 all						
GEV	0.76 (0.64, 0.85)	0.73 (0.56, 0.86)	0.83 (0.71, 0.92)	0.63 (0.47, 0.77)	2.80 (1.62, 4.84)	0.33 (0.21, 0.53)
VNT	0.83 (0.52, 0.98)	0.45 (0.35, 0.56)	0.17 (0.08, 0.29)	0.95 (0.84, 0.99)	1.52 (1.11, 2.08)	0.37 (0.10, 1.34)

\*Data was expressed as the mean with 95%CI (confidence interval). GEV: Gastroesophageal varices; VNT, Varices Needing Treatment; PPV, positive predictive value; NPV, negative predictive values; LR+, positive likelihood ratio; LR- negative likelihood ratio

**Table 3: Number of spared endoscopies and VNT\***

	All patients		CTP-A		CTP-B and C	
	Spared Endoscopies	Missed VNT	Spared Endoscopies	Missed VNT	Spared Endoscopies	Missed VNT
EVendo score ≤3.9	21/103 (20.38%)	2/103 (1.9%)	15/60 (25%)	1/60 (1.67%)	6 (13.95%)	1 (2.32%)
EVendo score ≤4.5	27/103 (26.21%)	2/103 (1.9%)	20/60 (33.34%)	1/60 (1.67%)	7 (16.27%)	1 (2.32%)
Baveno VI	17/103 (16.5)	3/103 (2.9)	10/60 (16.6%)	0		

\*Data was expressed as the mean with 95%CI (confidence interval). VNT, Varices Needing Treatment; CTP, Child-Turcotte-Pugh classification; GEV, Gastroesophageal varices; PPV, positive predictive value; NPV, negative predictive values; LR+, positive likelihood ratio; LR- negative likelihood ratio

performance of the novel EVendo score as a noninvasive screening tool for predicting GEV and VNT in a cohort of cirrhotic patients in a real-world clinical setting. In addition, we proposed a new cutoff value and compared this score’s performance with that of the recommended Baveno VI criteria in the subgroup of CTP-A patients, which is more clinically relevant for noninvasive screening recommendations. We used similar parameters and cutoff points of the EVendo score as in the original work for validation.<sup>[17]</sup>

In our study, the proportion of disease etiologies was comparable to that in the Dong *et al.*<sup>[17]</sup> study. However, we had more HBV patients (12% vs. <1%) and very few alcohol-related cirrhosis patients (3% vs. 23%). In addition, our population age was younger, with more female patients. Several studies have shown that most patients who undergo screening EGD have no varices.<sup>[20,21]</sup> The prevalence of GEV in our study was comparable to that in several studies; however, wide variation exists in the literature. In a recent large meta-analysis for varices screening that included 30 studies, the prevalence of any GEV ranged from 15% to 72%, and that of VNT ranged from 6% to 26%.<sup>[15]</sup> In our cohort, we had a higher prevalence of GEV than that in the Dong *et al.*<sup>[17]</sup> study (64% vs. 45%), but we had a lower VNT (12% vs. 16%). This finding was observed even when the analysis was restricted to CTP-A patients. This variation in the reported prevalence of varices in these studies may be related to differences in demographic and clinical factors and the tools used to diagnose cirrhosis.<sup>[22,23]</sup> Furthermore, in our cohort, which was gathered from a tertiary care referral center, a higher proportion of CTP-B patients were included in the EVendo performance analyses, which may explain the higher GEV prevalence.

We found that patients with GEV had significantly lower platelet counts and ALB and higher APRI, FIB4, EVendo score, and LSM values than those without GEV. These findings are clinically plausible as most of these parameters are associated with CSPH and consistent with the findings of previous studies.<sup>[4,7]</sup> Similar to the original work of the EVendo score, most of the laboratory parameters and noninvasive scores in our study could not segregate the degree of varices and categorize patients who had VNT from those who had VNT.

The reported performance of the EVendo score was promising, with a score of ≤3.90 cutoff giving high NPVs of 95.8% and 100% to rule out VNT in the training and validation cohorts, respectively.<sup>[17]</sup> In our analysis, we tested the performance of two cutoff points, and both points had lower sensitivity than the original EVendo score performance. However, both demonstrated high NPVs of approximately 94%–95% to rule out VNT. The advantage of our proposed cutoff of 4.5 compared to 3.9 is the potential of sparing more endoscopies (26% vs. 20%) without compromise in the missing rates of VNT (1.9% with both cutoff values). This finding also holds for the subanalysis of CTP-A patients. These findings are close, albeit lower than the reported figure in the original work of the EVendo score, and can be attributed to patient profile and sample size differences.

The reported sensitivity and specificity of the Baveno VI criteria in previous studies were 97% and 41%, respectively, with a pooled missed VNT rate of 0.3% and a pooled SER of 32.8%.<sup>[15]</sup> Our analysis showed the excellent performance of the Baveno VI criteria, with the highest sensitivity and NPV (i.e., 100%) in CTP-A patients compared to the EVendo score and with a missing rate of

**Table 4: Comparison of the performance of EVendo score with Baveno VI criteria in Child A cirrhosis patients\***

Variable (Cutoff value)	Sensitivity	Specificity	PPV	NPV	LR+	LR-
EVendo score ≤3.9 (All GEV)	0.73 (0.56, 0.86)	0.65 (0.43, 0.84)	0.77 (0.60, 0.90)	0.60 (0.39, 0.79)	2.10 (1.16, 3.80)	0.41 (0.23, 0.76)
EVendo score ≤3.9 (VNT)	0.86 (0.42, 1.00)	0.45 (0.32, 0.60)	0.17 (0.07, 0.34)	0.96 (0.80, 1.00)	1.57 (1.06, 2.31)	0.32 (0.05, 1.98)
EVendo score ≤4.5 (All GEV)	0.65 (0.47, 0.80)	0.87 (0.66, 0.97)	0.89 (0.71, 0.98)	0.61 (0.42, 0.77)	4.97 (1.69, 14.67)	0.40 (0.25, 0.64)
EVendo score ≤4.5 (VNT)	0.86 (0.42, 1.00)	0.60 (0.46, 0.74)	0.22 (0.09, 0.42)	0.97 (0.84, 1.00)	2.16 (1.38, 3.39)	0.24 (0.04, 1.47)
Baveno VI (All GEV)	0.89 (0.75, 0.97)	0.43 (0.23, 0.66)	0.72 (0.57, 0.84)	0.71 (0.42, 0.92)	1.58 (1.08, 2.30)	0.25 (0.09, 0.70)
Baveno VI (VNT)	1.00 (0.59, 1.00)	0.26 (0.15, 0.40)	0.15 (0.06, 0.29)	1.00 (0.77, 1.00)	1.36 (1.16, 1.60)	0.00 (0.00, NaN)

\*Data was expressed as the mean with 95%CI (confidence interval). GEV, Gastroesophageal varices; VNT, Varices Needing Treatment; PPV, positive predictive value; NPV, negative predictive values; LR+, positive likelihood ratio; LR- negative likelihood ratio

0% VNT. However, the SER of EGD (17%) was less than that obtained by applying the EVendo score. This low SER is related to the lower specificity of these criteria in most studies assessing and validating these criteria.<sup>[14,21,24]</sup>

This low SER with the use of the Baveno VI criteria, in addition to the limited access of LSM in many clinical settings, favors the use of an easily accessible tool potentially with a better SER such as the EVendo score, which uses parameters readily available in most clinical settings, including primary care and low-income countries. Furthermore, several challenges with the Baveno VI criteria limit their use and are worth considering. LSM is affected by the degree of concomitant inflammation, cholestasis, and technical factors. Some experts have suggested repeated measurements in two settings, but this may not be convenient and may be challenging in busy clinical practice. Furthermore, LSM is not available in every clinical setting.<sup>[25-28]</sup>

In conclusion, our analysis shows that the EVendo score has excellent and reliable performance as a screening tool for GEV and VNT in cirrhotic patients. The two cutoff points of the EVendo score have comparable sensitivity; however, an EVendo score of 4.5 has a higher SER. We demonstrated excellent performance of the Baveno VI criteria to rule out VNT; however, the SER was lower than that in previous studies. The EVendo score has the advantages of using easily accessible clinical and laboratory data and having a better SER than the Baveno VI criteria. A large prospective study is required to validate the performance of the EVendo score and compare it with other noninvasive tools.

The strength of our study is that it is the first validation study for the EVendo score in an external cohort. In addition, we included patients from real clinical practice with strict criteria and performed a detailed analysis with a proposal of a new cutoff point and a comparison to the Baveno VI criteria in CTP-A cirrhosis. Although the cohort included CTP-B and CTP-C patients, these patients were a minority. Moreover, they were included in only the EVendo score analysis and excluded from the Baveno VI criteria comparison analysis.

Our study has some limitations. The study is retrospective with potential for bias, especially referral bias. However, we applied strict criteria; our findings are consistent with those of the original work of the EVendo score, and the Baveno VI criteria results are consistent with those of several earlier studies. In addition, the majority of studies assessing varices screening were retrospective in

design,<sup>[21,24,29]</sup> with similar results among several prospective and retrospective studies.<sup>[17,24,30]</sup> Another limitation that exists in most studies assessing varices is the interobserver variability in assessing varices.

### Acknowledgements

The authors thank and acknowledge the support and fund from the National Plan for Science, Technology, and Innovation (MAARIFAH), King Abdulaziz City for Science and Technology, Riyadh, Kingdom of Saudi Arabia, grant Number 08-MED512-02. The authors also thank and acknowledge the efforts and contribution from the staff of Liver Disease Research Center at the College of Medicine, King Saud University.

### Financial support and sponsorship

This work is funded by the National Plan for Science, Technology, and Innovation (MAARIFAH), King Abdulaziz City for Science and Technology, Riyadh, Kingdom of Saudi Arabia.

### Conflicts of interest

There are no conflicts of interest.

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