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ORIGINAL ARTICLE

Usefulness of validation of EV-endo calculator in chronic liver disease patients in Liaquat National Hospital, Karachi, Pakistan.

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ABSTRACT… Objective: To validate the EVendo score to predict esophageal varices (EV) by confirming the presence of EV on upper gastrointestinal (GI) endoscopy at tertiary care hospital, Karachi, Pakistan. **Study Design:** Cross-sectional, Validation study. **Setting:** Department of Gastroenterology at Liaquat National Hospital and Medical College, Karachi, Pakistan. **Period:** October 2022 to June 2023. **Methods:** Total 412 patients with chronic liver disease (CLD) of any etiology who were underwent upper GI endoscopy for variceal screening were included. Demographic, laboratory and clinical information were recorded. By verifying the existence of EV on upper GI endoscopy, the validity and reliability of the EVendo score in predicting EV were assessed. SPSS V 22 was used for data analysis. **Results:** Out of 412 patients the ratio of men to women was 1.16:1. The average age was 55.67±11.21 years, and 191 patients (46.4%) had hepatic encephalopathy and 344 patients (83.5%) had ascites. The average score for EVendo was 7.26±3.05. Eighty-three percent of patients received positive findings for varices during upper GI endoscopy. The EVendo score's area under the curve for identifying variations was 0.908. 5.28 (sensitivity = 84.6%, specificity = 92.6%), 4.85 (sensitivity = 85.5%, specificity = 91.4%), and 5.71 (sensitivity = 84.3%, specificity = 92.6%) were the ideal cuff off values. The diagnostic accuracy for the EVendo score, using upper GI endoscopy as the gold standard, was 86.2%. **Conclusion:** The EVendo score showed excellent diagnostic accuracy, sensitivity, and specificity in predicting esophageal varices among patients with chronic liver disease.

Key words: EVendo Score, Endoscopy, Esophageal Varices, Hepatic Encephalopathy, Non-invasive.

INTRODUCTION

Diffuse hepatic fibrosis with nodules replacing the normal liver architecture with cirrhosis over a longer than six-month timeframe is known as "chronic liver disease (CLD)".[1] The average age of cirrhosis patients is increasing due to "non-alcoholic fatty liver disease (NAFLD)".[2,3] Although the burden of "hepatitis C virus (HCV)" is declining as a result of very effective antiviral drugs, cirrhosis mortality increased by 65% between 2008 and 2016 and is expected to double by 2030.[2]

Pathologic scarring of the liver tissue, or cirrhosis, results in diminished liver function. Compensated cirrhosis may decompensate if liver disease worsens, leading to variceal bleeding, hepatic encephalopathy, or ascites.[4] A series of experiences, a real evaluation, and non-invasive testing, including laboratory tests and imaging are usually used to diagnose cirrhosis. The reference standard for determination is still liver biopsy.[5,6]

According to a research, cirrhotic individuals have an estimated 50% worldwide prevalence of esophageal varices (EV). Compared to Child-Pugh class A patients, it is more prevalent in class C patients (40% versus 85%). Among cirrhotic patients tested at the KBTH, a high rate of 90.6% OV was observed. According to earlier studies, EV occurred in 80% of individuals with liver cirrhosis.[7,8] It has been proposed that upper endoscopy should be used for variceal screening in all cirrhotic patients. Techniques for detecting EVs in cirrhotic patients who might not have clinically severe portal hypertension have gained attention and, as a result, are unlikely to have varices that need upper endoscopy or mediation.[7,8]

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The development of methods to accurately restrict the population undergoing endoscopic variceal screening and painlessly identify individuals with cirrhosis for the presence of high-risk EV is thus being investigated.

Prior to screening endoscopy, the EVendo score predicts the size and existence of EV.[9] Recently, 238 cirrhosis patients participated in multi-center research that validated the EVendo score. In order to find characteristics that are substantially linked to the existence of high-risk EVs (HREVs) and EV, a machine-learning algorithm was used to construct the score. The EV endo score was mentioned by James Tabibian in his 2019 paper, "Machine learning-based development and validation of a scoring system for screening high-risk EV." The idea was that he created a screening tool to identify the stage of EV in individuals with liver cirrhosis who needed therapy. If the EVendo score technique can be verified, it may be utilized to remove the need of low-yield endoscopy in the most common situations, which can significantly cut health care spending.[10] This study was done to validate the EVendo score to predict EV by confirming the presence of EV on upper gastrointestinal endoscopy at tertiary care hospital, Karachi, Pakistan.

METHODS

The Department of Gastroenterology at Liaquat National Hospital and Medical College in Karachi was the site of this cross-sectional investigation. The Liaquat National Hospital's Research and Ethics Committee provided its approval to the study idea (Ref: App No. 0798-2022 LNH-ERC). The study was performed during October 2022 to June, 2023. Participants were explained about the study purpose and its associated risk and benefits, before obtaining written and informed consent from participants. The sample size was calculated by using prevalence of EV as 65%[24], sensitivity of albumin bilirubin-platelet (ALBI-PLT) score 77.34%, specificity 72.93%[11], and 95% confidence interval. A non-probability consecutive sampling was applied. Total 412 patients with CLD of any etiology who were underwent upper GI endoscopy for variceal screening were included in current research study.

Demographic information, such as name, age, sex, medical record number, and clinical history pertaining to the cause of the chronic liver disease, were briefly collected. Laboratory investigations were done, child Pugh score was calculated. The EVendo score was based on parameters including international normalized ratio (INR), aspartate transaminase (AST), platelet count (PLT), blood urea nitrogen (BUN), hemoglobin level (Hb) and ascites. The calculation is based on multiplying INR by 9.5 and adding it to the AST level and then dividing by sum of 35. Next, dividing the PLT by 150, BUN by 150 and Hb by 150 and adding all these values. Finally, dividing the sum product of 9.5 INR and AST by the second result of PLT, BUN and HB and adding a point of 1 if ascites were present to reach to the final score. If the EVendo score is less than 3.90, EGD variceal screening can be postponed and the patient can be followed; however, if the score is greater than 3.90, there is a greater than 5% chance of EV, hence EGD variceal screening should be carried out. By verifying the existence of EV on upper GI endoscopy, the validity and reliability of the EVendo score in predicting EV were assessed. The gold standard for EV, upper GI endoscopy was used to figure out the validity of the EVendo score.

SPSS V 22 was used for analysis. Simple descriptive statistics were used to show the demographic data, including the mean and standard deviation, or frequency and percentages. EVendo score using Wilcoxon Rank matched-pair testing compared the EVendo score and presence of EV, which was diagnosed on upper GI endoscopy. Effect modifiers were controlled through stratification, while independent sample t-test or chi-square test were used for comparisons taking $p \leq 0.05$ as significant.

RESULTS

The study included 412 patients in total. The ratio of males with females was 1.16:1. 55.67±11.21 years was the average calculated age of our study patients. However, 81.1% were older than 45 years. The mean body mass index was 25.21±4.51 kg/m2, and 23.3% of the patients were found to be obese. Out of the 412 patients,

344 (83.5%) had ascites, of which 34% had mild, 64.8% had moderate, and 1.2% had severe ascites. In terms of hepatic encephalopathy, 191 (46.4%) had hepatic encephalopathy, of which 19.9% had grade I, 56% had grade II, and 24.1% had grade III. The majority of patients (52%) had Child Turcotte Pugh Class C. The mean child Turcotte Pugh Class Score was 9.29±2.63. The mean levels of hemoglobin, INR, AST, platelet, BUN, and total bilirubin were 2.98±3.57 mg/dl, 106.17±54.09 x 103/mcl, 74.07±67.12 U/L, 11.17±1.79 g/dl, and 1.50±0.38, respectively. EVendo mean score was 7.26±3.05. During upper gastrointestinal endoscopy, 331 (80.3%) patients had positive results for varices (Table-I).

Variables		Frequency (%)
Gender	Male	221 (53.6)
	Female	191 (46.4)
Age (years)	≤45 years	78 (18.9)
	>45 years	334 (81.1)
Obesity		96 (23.3)
Comorbidities	None	142 (34.5)
	Single	167 (40.5)
	Double	103 (25.0)
Hepatitis B surface antigen Positive		87 (21.1)
Anti hepatitis C virus positive		195 (47.3)
Ascites	No ascites	68 (16.5)
	Mild	117 (34)
	Moderate	223 (64.8)
	Severe	4 (1.2)
Hepatic encephalopathy grade	No Hepatic encephalopathy	221 (53.6)
	Grade-I	38 (19.9)
	Grade-II	107 (56)
	Grade-III	46 (24.1)
Child Turcotte Pugh Class	Class A	89 (21.6)
	Class B	108 (26.2)
	Class C	215 (52.2)
Varices by Upper GI endoscopy	Yes	331 (80.3)
	No	81 (19.7)

Table-I. Descriptive statistics of demographic and clinical profile of study population

The area under the curve for the EVendo score in detecting varies was 0.908. The optimal cuff off values were 5.28 (sensitivity = 84.6%, specificity = 92.6%), 4.85 (sensitivity = 85.5%, specificity = 91.4%), and 5.71 (sensitivity = 84.3%, specificity = 92.6%), as shown in Figure-1.

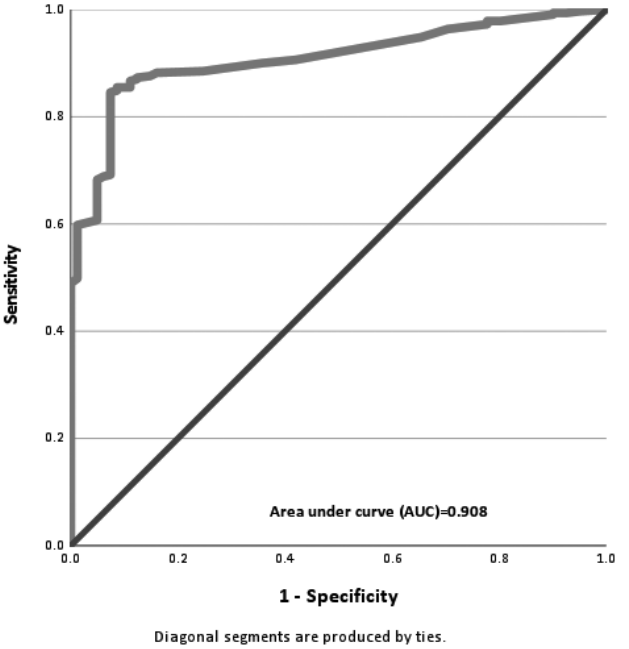

Figure-1. Receiver-operating characteristic (ROC) curve for EVendo in detection of Varices

Using upper gastrointestinal endoscopy as the gold standard, the overall diagnostic accuracy for the EVendo score was 86.2%. Detailed results are shown in Table-II, and Table-III, respectively.

A significant association of varices by upper GI endoscopy was found with ascites ($p<0.001$), hepatic encephalopathy ($p<0.001$) and Child Turcotte Pugh Class C ($p<0.001$) whereas significant mean difference was found for Child Turcotte Pugh Class Score ($p<0.001$), INR ($p<0.001$), AST($p<0.001$), Platelet Count ($p<0.001$), BUN ($p=0.003$), total bilirubin($p<0.001$) and EVendo Score($p<0.001$). Detailed results of associations and mean comparisons are presented in Table-IV.

DISCUSSION

According to earlier research, the majority of newly diagnosed cirrhotic patients having endoscopy do not exhibit any EVs on screening endoscopy.[12-16] According to a comprehensive meta-analysis of

S. No	Cutt Off Values	Sensitivity (%)	Specificity (%)	Youden's Index
1	5.28	84.6	92.6	0.772
2	4.85	85.5	91.4	0.769
3	5.71	84.3	92.6	0.769
4	5.00	85.2	91.4	0.766
5	6.10	84.0	92.6	0.766

Table-II. Optimal cuff-off values for EVendo in detection of Varices

Variables	Varices by Upper gastrointestinal endoscopy		Sensitivity	Specificity	PPV	NPV	Diagnostic Accuracy
	Positive (n)	Negative (n)					
EVendo ≥5.28	280	6	84.6%	92.6%	97.9%	59.5%	86.20%
EVendo<5.28	51	75					

Table-III. Diagnostic accuracy of EVendo score taking Upper GI endoscopy as gold standard

PPV; Positive predictive value, NPV; Negative predictive value

Variables		Varices By Upper Gastrointestinal Endoscopy		P-Value
		Positive (n=331)	Negative (n=81)	
Gender	Male	183 (55.3)	38 (46.9)	0.176
	Female	148 (55.3)	38 (46.9)	
Age (years)	Mean± SD	55.49±11.24	56.39±11.10	0.520
	≤45 years	65 (19.6)	13 (16)	0.460
	>45 years	266 (80.4)	68 (84)	
Body mass index (kg/m^2)	mean±SD	25.26±4.54	24.98±4.37	0.609↕
Obesity		76 (23.0)	20 (24.7)	0.741
Comorbidity	None	114 (34.4)	28 (34.6)	0.413
	Single	130 (39.3)	37 (45.7)	
	Double	87 (26.3)	16 (19.8)	
Hepatitis B surface antigen Positive		69 (20.8)	18 (22.2)	0.786
Anti hepatitis C virus positive		152 (46.1)	42 (51.9)	0.350
Ascites		296 (89.4)	48 (59.3)	<0.001*
Hepatic encephalopathy		171 (51.7)	20 (24.7)	<0.001*
Child Turcotte Pugh Class Score	Mean±SD	9.97±2.41	6.49±1.32	<0.001↕*
Child Turcotte Pugh Class	A	34(10.3)	55(67.9)	<0.001*
	B	87(26.3)	21(25.9)	
	C	210(63.4)	5(6.2)	
Haemoglobin (g/dl)	Mean±SD	11.10±1.85	11.42±1.50	0.161↕
International normalised ratio	Mean±SD	1.59±0.34	1.10±0.27	<0.001↕*
Aspartate aminotransferase (U/L)	Mean±SD	83.41±71.42	35.90±16.26	<0.001↕*
Platelet Count (x 10^3/ul)	Mean±SD	93.32±44.29	158.70±58.84	<0.001↕*
Blood urea nitrogen (mg/dl)	Mean±SD	18.62±8.80	22.12±11.78	0.003↕*
Total Bilirubin (mg/dl)	Mean±SD	3.36±3.87	1.40±0.72	<0.001↕*
EVendo Score	Mean±SD	8.14±2.69	3.67±1.28	<0.001↕*

Table-IV. Association of varices by upper gastrointestinal endoscopy

Chi-square/fisher exact test was applied. ↕Independent t-test was applied. P-value<0.05 considered significant. *Significant at 0.05 levels.

more than 30 research, the prevalence of HRVs was around 6-26% while that of EVs varied between 15-72%.[17] Similar findings were shown by data from another study, which showed that only 17.3% of patients had HRVs and only 43% of patients had EVs on screening endoscopy.[14] This highlights the necessity for non-invasive, reasonably priced evaluation instruments for EV identification and HRV prediction. In the American population, a study[18] validated and introduced a non-invasive score i.e. EVendo score, which is an evaluation technique for both HRV prediction and EV detection. INR, platelet count, AST, BUN, and hemoglobin were the characteristics that served as its foundation. Ascites and a low platelet count indicate portal hypertension, while severe liver fibrosis is linked to elevated INR and AST.[19-21] Similarly, low BUN indicates reduced urea production because of poor liver function, whereas in cirrhotic individual's hemoglobin with low levels may be caused by portal hypertensive gastropathy.[14]

In current study, there was predominance of males and the majority were older than 45 years. 23.3% of the patients were obese. Most of the patients had moderate ascites. Among patients with hepatic encephalopathy, 56% had grade II. EVendo mean score was 7.26±3.05. During upper gastrointestinal endoscopy, 80.3% of patients had positive results for varices. The area under the curve for the EVendo score in detecting varies was 0.908. The optimal cuff off values were 5.28 (sensitivity = 84.6%, specificity = 92.6%), 4.85 (sensitivity = 85.5%, specificity = 91.4%), and 5.71 (sensitivity = 84.3%, specificity = 92.6%). Using upper gastrointestinal endoscopy as the gold standard, the overall diagnostic accuracy for the EVendo score was 86.2%.

The EVendo score was created and verified in research which was conducted in multiple centers with 238 cirrhosis patients.[12] In order to determine the characteristics that are strongly linked to the occurrence of EVs and HREVs, a machine learning algorithm was used to create the score. With an AUROC of 0.84, this score was able to detect EVs among patients. It was then confirmed in a separate prospective cohort with high performance (AUROC of 0.81 in the subgroup of patients with Child-Pugh A cirrhosis, and 0.82 for EV in all patients). With an AUROC of 0.74 in the training set, 0.75 in the validation set, and 0.75 in the patients with Child-Pugh A cirrhosis, the score identified patients with HREV.[18] When it comes to ruling out EVs and HRVs, an EVendo score of less than 3.9 is helpful. Its sensitivity is around 92.3% and 100%, respectively, and its specificity is almost 66% for EVs and 49% for HRVs.[18]

Given that EV prevalence was below 50% in both populations, the Dong et al.[18] and another investigation[14] were comparable. With a higher AUROC cutoff of >7.3, the study predicted EVs with a strong diagnostic accuracy of 86.76%, outstanding sensitivity of 94.92%, and negative predictive value of 95.38%. With a slightly higher threshold of >8, the AUROC was utilised to predict HRVs with a great sensitivity of 87.23%, specificity of 83.56%, negative predictive value of 96.91%, and diagnostic accuracy of 84.19%. When compared to other concurrent non-invasive evaluation techniques, such as APRI and platelet count to splenic diameter, the EVendo score demonstrated the highest diagnostic accuracy for both HRV and EV presence prediction. There were some limitations of this study. Outcomes were not recorded in this study. Evaluation of clinical outcomes with EVendo score would have given us further insights.

CONCLUSION

The EVendo score showed excellent diagnostic accuracy, sensitivity, and specificity in predicting esophageal varices among patients with chronic liver disease. Given its strong correlation with endoscopic findings, the score may serve as a reliable non-invasive tool to aid in variceal screening and risk stratification in clinical practice.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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AUTHORSHIP AND CONTRIBUTION DECLARATION	
1	**Baby Anbreen:** Data collection, drafting, responsible for data.
2	**Shahid Karim:** Conception, design, proof reading, critical revisions.
3	**Punhal Khan:** Literature review, data analysis, proof reading.
4	**Mehreen Akmal:** Literature review, data collection, proof reading.
5	**Baseer Ahmad:** Literature review, data collection, proof reading.