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Original Article

A Novel Non-invasive Score Precisely Predicts Development of Esophageal Varices in Patients with Chronic Viral Hepatitis C

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ABSTRACT

Background:
Portal hypertension is a major complication of cirrhosis, leading to the development of gastroesophageal varices (GEVs). All patients with cirrhosis should be screened by endoscopy for esophageal varices (EVs) at the time of diagnosis. In recent years, several non-invasive methods for detecting EV have been evaluated. Our aim was to combine the imaging data, FibroScan, fibrosis markers, and blood parameters to propose a new score for the prediction of EV.

Materials and Methods:
180 HCV (Hepatitis C virus) positive patients with cirrhosis were enrolled in this cross-sectional study. APRI score, AAR score, FIB4 score, King score, and (PC\SD) (Platelet count/Spleen Diameter) were calculated. Abdominal ultrasonography and FibroScan were done for all patients. Data were collected to develop a scoring system as a non-invasive index combined from eight parameters; platelet count, serum albumin, spleen diameter, portal vein diameter, PC/SD ratio, FIB4, APRI, and FibroScan.

Results:
ROC curve analysis of different variables revealed that serum albumin had the highest AUC (0.83, cut off point 2.55) followed by PC/SD ratio (0.82, cut off 681), then came platelet count (0.77, cut off 91.0 × 103), spleen diameter (0.70, cut off 15.35), APRI (0.73, cut off 1.31), and both FIB4 (0.70, cut off 4.33) and PV diameter (0.67 cut off 13.1) and lastly FibroScan (0.69, cut off 44.6). Using ROC curve analysis to study the discrimination ability of this combination, the AUC was 0.89 (95% CI 0.81-0.98, $p < 0.001$), which gives the score a good discrimination ability at the cut off point of 4.5 (or 56.25 %), with 85% sensitivity and 95% specificity.

Conclusion:
Our novel score could be a reliable tool to predict EV instead of a single parameter.

Keywords: Platelet count, FibroScan, APRI score, FIB4 score, Spleen diameter, Score

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INTRODUCTION

Portal hypertension is a major complication of cirrhosis, leading to the development of gastroesophageal varices (GEV). Depending on the clinical stage of liver cirrhosis, GEVs are present in 30-40% of patients with compensated cirrhosis, however, they can be present in up to 85% of patients with decompensated cirrhosis. They develop at a rate of 7-8% per year in patients with compensated cirrhosis, and its progression at a rate of 10-12% per year occurs from small to large varices (1).

Despite advances in pharmacological and endoscopic

therapy, variceal bleeding is responsible for high morbidity and mortality. 60% of recurrent bleeding occurs within the first week while 30–40% of patients may rebleed within the next 2-3 days. So, the highest corresponding mortality rate for variceal bleeding is 10–20% within 6 weeks after the first episode of bleeding (2).

All patients with cirrhosis should be screened by endoscopy for esophageal varices (EVs) at the time of diagnosis according to the current guidelines. Although endoscopy is the only validated method for diagnosis of EV, it is an invasive method (2). However, in recent years, several non-invasive methods for detecting EV have been evaluated. These methods include clinical and biochemical parameters, and ultrasonographic findings (3).

Increased hepatic resistance is the most important factor contributing to the development of portal hypertension. So, non-invasive serum markers depending on the phenomena of increasing the hepatic resistance and liver fibrosis have been tested as predictors of EV in patients with cirrhosis with promising results (3,4).

One of the important scores that is constructed to predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C was the APRI score (4). Also, in the same year Giannini and colleagues, evaluated AAR score and its correlation with the histological stage and prognosis of hepatitis C virus-related liver diseases (5).

The FIB-4 score was initially developed by Sterling and colleagues in patients with HIV/HCV (Human immunodeficiency virus/Hepatitis C virus) co-infection to predict liver fibrosis (6). Then it was confirmed by Vallet-Pichard and co-workers as a simple, accurate, and inexpensive marker for the assessment of liver fibrosis in patients with hepatitis C (7).

Numerous trials had been done to detect non-invasive diagnostic tests such as aspartate aminotransferase (AST)-to-platelets (PLT) ratio index (APRI), PLT-to-spleen diameter ratio (PSR), FIB-4 index, King's score, and AST-to-alanine aminotransferase (ALT) ratio (AAR) for prediction of GEV (9). In an attempt to increase the accuracy of the diagnosis of EVs, combinations of markers were tested and some of them were validated such as AST/ALT ratio, APRI, or PSR (10).

Transient elastography (FibroScan) is a rapid, non-invasive, reliable, and accurate tool not only for diagnosis but also to assess the degree of hepatic fibrosis in patients with chronic liver disease References should be in order References should be in order(11). Recent studies have suggested TE(Transient Elastography) as a complementary technique in the assessment of PH(Portal Hypertension) that might attribute to the intimate relationships between liver fibrosis, increase intrahepatic resistance, portal hypertension, EV, and liver stiffness measurement (LSM) (12).

It has been suggested that a combination of imaging data, FibroScan, fibrosis markers, and blood parameters may provide better screening of EVs. Our aim was to propose a new score for the prediction of EV by combining them.

MATERIALS AND METHODS

This cross-sectional study was conducted on 199 patients presenting to the Department of Tropical Medicine and Infectious diseases at Tanta University Hospital. Institutional Ethics Committee approval was taken before the start of the study.

The aim of the research was made clear to all participants in the study and informed consent was signed by every patient before enrolment in the study. All authors had access to the study data and reviewed and approved the final manuscript.

A full history was taken from all the patients who fulfilled the inclusion criteria of having HCV positive cirrhosis. The patients were subjected to a full clinical examination, routine laboratory investigation, calculation of Child-Pugh class, calculation of body mass index (BMI), and esophagogastroduodenoscopy (EGD) within 2 weeks of investigation of laboratory parameters. Endoscopy was done by an expert endoscopist using Pentax EG-2985. Examination of upper gastrointestinal tract up to the proximal duodenum; wherever possible; was done (13).

Patients with renal failure (five patients), morbid obesity (four patients), endocrinal distress (six patients), and febrile illness (four patients) were excluded. So, 180 patients who met the inclusion criteria were divided into two groups: Group I included 60 patients with cirrhosis without EVs, and group II included 120 patients with cirrhosis and EVs. The patients underwent

Table 1: **Non-invasive fibrosis tests and scores for prediction of esophageal varices**

Fibrosis test	Calculation
AAR score	AST / ALT (Aspartate Transaminase / Alanine Transaminase)
APRI score	[(AST / ULN (Upper limit of normal)) / platelet count (109/L)]_100
Fibrosis score 4 (Fib 4)	(Age x AST) / (Platelets count × (square ALT)
King score	age (years) × AST (U / L) × INR (International normalized ratio) / number of platelets (10^9 / L)
Platelet count/spleen size ratio	platelet count (cell / 103) / spleen size (mm)

clinical evaluation. The grade of varices was classified according to Baveno IV classification (14).

All patients were subjected to laboratory investigations including liver function tests, prothrombin time and activity, urea and creatinine, complete blood picture, and viral hepatitis markers for HCV(HCV antibodies) and HBV(Hepatitis B virus).

Also, all patients were subjected to abdominal ultrasonography, which was done in Tropical Medicine Department Using Toshiba 770 25A with a convex probe, 3.5 MH. Portal vein diameter and maximum spleen bipolar diameter were assisted by an expert specialist.

FibroScan transient elastogram was performed for all patients using Echosens™ FibroScan 502 that was done within days following or preceding the upper gastrointestinal tract endoscopy. The operator was not aware of the results of endoscopy. The Fibroscan® probe consists of a 3.5 MHz ultrasound transducer installed on the axis of a low amplitude vibrator (frequency of 50 Hz and amplitude of 2 mm peak-to-peak). To obtain measurements of liver stiffness, the tip of the ultrasound transducer was placed in the right intercostal area, at the level of the right lobe of the liver. When activated, the vibrator generated an elastic shear wave to the liver while the ultrasound transducer performed a series of ultrasound acquisitions (transmission/reception) with a repeat frequency of 4 kHz. The median value of at least 10 successful measurements with an interquartile range (IQR) of ≤ 30% from the median and success rate of ≥ 60% was considered as a reflection of the liver stiffness or shear modulus of the liver. This value is expressed in kilopascals (kPa) (15).

Non-invasive tests and equations were performed for all patients in the study. Variables investigated in this study, which could predict EV were combinations of the age of the patient, laboratory investigation, and radiological parameters as shown in table 1.

Data were collected to develop a non-invasive scoring index combining eight parameters; platelet count, serum albumin, spleen diameter, portal vein diameter, PC/SD ratio, FIB4, APRI, and FibroScan. The intended score consisted of the combination of the previous significant eight parameters. The patient would have one mark for each of the following:

Serum albumin ≤ 2.55 mg/dL, PC/SD ratio ≤ 6.81, platelet count ≤ 94.0 ×103, spleen diameter ≥ 15.35 cm, APRI ≥ 1.32, FIB4 ≥ 4.33, PV diameter ≥ 13.1, and FibroScan ≥ 44.6. To convert the score to a ratio, we multiplied the results of the patient by 100 and then divide by eight.

Statistical Analysis:

Results were collected, tabulated, and statistically analyzed by SPSS software version 20 (SPSS Inc. Released 2011. IBM SPSS statistics for windows Armnok, NY: IBM Corp.).

ANOVA test was used for comparison of quantitative variables between more than two groups of normally distributed data with Tukey test as the post hoc test. Kruskal Wallis test was used for comparison of quantitative variables between more than two groups of non-normally distributed data with Tamhane's test as the post hoc test. Receiver operator characteristic (ROC) with respective points of maximal accuracy for sensitivity and specificity was generated to determine biomarker performance. p value < 0.05 was considered statistically significant.

RESULTS

Both groups did not show any significant difference regarding the mean age or BMI ($p > 0.05$ for each). They had very close mean Child Pough score and AST/ALT ratio ($p > 0.05$), however patients without varices had significantly lower APRI, FIB 4, and King's score ($p < 0.001$). The laboratory investigations showed that patients without varices had significantly

Table 2: Patients' characteristics, demographic, and laboratory data

Variables	Patients without varices (n = 60) Mean ± SD	Patients with varices (n = 120) Mean ± SD	t test	*p* value
Age (y):	52.90 ± 6.86	53.77 ± 8.04	0.72	0.47
BMI (Body mass index)	24.57 ± 2.31	25.08 ± 2.25	1.43	0.15
Child score:	8.55 ± 1.97	8.57 ± 1.85	0.08	0.93
APRI score	1.33 ± 0.74	2.01 ± 1.00	U = 5.03	< 0.001
AST/ALT score	1.65 ± 0.49	1.72 ± 0.66	U = 0.26	0.79
Fib 4	4.75 ± 2.48	6.93 ± 3.16	U = 4.53	< 0.001
King's score:	49.22 ± 40.43	68.89 ± 39.21	U = 3.79	< 0.001
Hb (Hemoglobin) (mg/dL)	9.99 ± 1.59	9.85 ± 1.60	0.53	0.59
RBCs (Red blood cell count) (cell/µL)	3.63 ± 0.61	3.56 ± 0.65	0.68	0.49
Platelet count: platelets/µL × 103	121.95 ± 36.70	87.90 ± 27.13	U = 6.06	< 0.001
Albumin: g/dL	2.90 ± 0.42	2.33 ± 0.39	8.82	< 0.001
INR (International Normalized Ratio):	1.61 ± 0.47	1.59 ± 0.36	0.22	0.82
FBG (Fasting Blood Sugar): mg/dL	96.90 ± 15.98	101.27 ± 20.22	1.46	0.14
2 h PP (postprandial blood sugar): mg/dl	147.95 ± 20.60	168.35 ± 47.77	3.99	< 0.001
AST (IU/L)	60.5 ± 27.57	63.47 ± 21.91	U = 0.71	0.47
ALT (IU/L)	38.30 ± 16.89	40.32 ± 16.85	U = 0.42	0.67
Child grade				
A	12 (20.0)	18 (15.0)	$X^2 = 0.90$	0.64
B	30 (50.0)	60 (50.0)		
C	18 (30.0)	42 (35.0)		

lower 2-hour postprandial (PP) blood sugar, higher platelet count, and higher serum albumin compared with group 2 ($p < 0.001$) but did not differ in other laboratory parameters or Child-Pugh grade (table 2).

The PC/SD ratio was calculated by dividing the number of platelets/µL by the maximum bipolar diameter of the spleen in millimeters, estimated with abdominal ultrasonography.

Patients with varices had significantly higher mean values of FibroScan, higher PV diameter, larger spleen diameter ($p < 0.001$), and lower PC/SD than patients without varices ($p < 0.001$) (table 3).

The following eight significant items were chosen: serum albumin, PC/SD ratio, platelet count, APRI, FIB4, PV diameter, FibroScan, and spleen diameter. ROC curve analysis of different variables revealed that serum albumin had the highest AUC (0.83, cut off point 2.55) followed by PC/SD ratio (AUC 0.82, cut off 681), then came platelet count (AUC 0.77, cut off 91.0 × 103), APRI (0.73, cut off 1.31), FIB4 (0.70, cut off 4.33), PV diameter (0.67 and cut off 13.1), FibroScan (0.69, cut off 44.6), and spleen diameter (0.70, cut off 15.35) (table 4).

Based on the univariate analysis of the different risk factors, multivariate regression analysis model for the resulted eight significant risk factors was done. It showed that only albumin and FibroScan were independently related to the presence of varices; higher albumin as a protective factor, and high FibroScan as a risk factor (table 5).

Using ROC curve analysis to study the discrimination ability of this combination, the AUC was 0.89 (95% CI: 0.81-0.98, $p < 0.001$), which gives the score of good discrimination ability at cut off point of 4.5 (or 56.25%) with 85% sensitivity and 95% specificity (tables 3,4).

Considering the eight items as a scale, Cronbach's alpha was 0.73 (acceptable after exclusion of PC/SD ratio).

In the univariate regression analysis model, the intended score was significantly related to the presence of varices ($p < 0.001$) with three times increased risk as Exp B was 3.02 (95% CI: 1.76-5.02). It gave overall correct classification 81.7%,

Table 3: Fibro scan, ultrasonography results, and score calculation in both groups

Variables	Group 1 (n=60) Mean ± SD	Group 2 (n = 120) Mean ± SD	Test of sig	*p* value
Fibroscan (kPa)	43.02 ± 19.11	55.82 ± 14.37	U = 4.32	< 0.001
PV diameter (mm)	13.30 ± 1.97	14.82 ± 2.23	t = 3.88	< 0.001
Spleen diameter (mm)	15.98 ± 2.67	18.34 ± 3.12	t = 4.97	< 0.001
PC/SD	7.95 ± 2.82	4.93 ± 1.66	U = 6.89	< 0.001
Score	10.95 ± 1.21	11.69 ± 1.11	t = 3.95	< 0.001

Table 4: ROC curve analysis of the significant risk factors and the intended score for the prediction of esophageal varices

Variables	AUC	Cut off	Sensitivity %	Specificity%	PP %	NP %	Accuracy %
Serum albumin g/dL	0.83	2.55	95.0	65.0	58.0	96	75
Platelet count (cell/µL × 103)	0.77	91.0	80.0	60.0	48	83	65
Spleen diameter (mm)	0.70	15.35	82.5	50.0	47	85	63
APRI	0.73	1.31	80.0	60.0	48	83	65
FIB 4	0.70	4.33	75.0	60.0	48	83	65
PV diameter Mm	0.67	13.1	75.0	60.0	52	84	68
Fibroscan KPa	0.69	44.60	75.0	55.0	48	83	65
PC/SD	0.82	681	75.0	82.7	68	87	80
Overall score (%)	0.89	4.5 (56.25%)	85	95	89	93	92

Table 5: Multivariate and univariate regression analysis of the intended score for prediction of esophageal varices

Variables	B	Wald	Sig	Exp (B)	95% CI for Exp (B)	
					Lower	Upper
Multivariate regression of the different variables						
Serum albumin g/dL	-3.16	20.58	< 0.001	0.04	0.01	0.16
Platelet count (cell/µL ×103)	-0.42	0.36	0.54	0.65	0.16	2.59
Spleen diameter (mm)	0.22	0.11	0.73	1.24	0.34	4.53
APRI	0.85	1.78	0.18	2.34	0.67	8.19
FIB 4	0.15	0.04	0.83	1.17	0.26	5.12
PV diameter (mm)	0.92	2.01	0.15	2.51	0.70	9.02
FibroScan (KPa)	1.23	7.03	0.008	3.44	1.38	8.58
PC/SD						
Univariate regression analysis of the intended score						
Score	1.10	16.04	< 0.001	3.02	1.76	5.02

Table 6: Calibration and discrimination of the score results for predicting of esophageal varices

	Calibration			Discrimination		
	Goodness of fit χ^2	DF	P	AUC ± SE	95% CI	*p*
Score	39.88	5	< 0.001	0.89 ± 0.02	0.84-0.94	< 0.001

Nagelkerke pseudo R2 56.2%, and highly significant goodness of fit with Hosmer Lemeshow Chi-square 39.88 ($p < 0.001$, table 4, 5, and 6).

DISCUSSION

Predicting the presence and determination of the size of varices require EGD, which is an invasive and expensive procedure that is not free of risks. In order to decrease the need for screening endoscopy, many studies have evaluated non-invasive ways for prediction of EV especially medium and large varices, which required prophylactic therapy. A rapid progression of small varices (< 5 mm) to large ones occurs at a rate of 10-12% per year (16), so, strategies to prevent the first episode of variceal bleeding (primary prophylaxis) is needed (17). This is especially important in countries with low socioeconomic state and where the availability of endoscopic units is limited (18-22). Our study aimed to propose a scoring system for prediction of EVs collecting the most important parameters that may predict and correlate the presence of EVs by combining eight parameters; platelet count, serum albumin, spleen diameter, portal vein diameter, PC/SD ratio, FIB4, APRI, and FibroScan.

In our study, the cutoff value of serum albumin was 2.55, which could significantly predict EV (AUROC = 0.83) with a sensitivity of 95%, a specificity of 65%, positive predictive value (PPV) 58%, and negative predictive value (NPV) 96%. Serum albumin reflects the synthetic function of the liver. These results are in agreement with Sarwar and colleagues who found that serum albumin level was less than 2.95 gm/dL in the variceal group with a statistically significant difference from that of the non-variceal group (23). Also, Hossain and co-workers found that serum albumin could predict the presence of EV with the specificity of 83.8%, PPV of 62.06% and NPV of 80.2% (24). On the other hand, Mandal and colleagues found serum albumin level of 2.52 gm/dL in the variceal group but the difference of this value from those of the non-variceal group was not statistically significant (25).

In our study, the platelet count below 91.0×10^3 had 80% sensitivity and 60% specificity and it was an independent risk factor for the presence of varices. The cutoff value of the platelet count that predicts the presence of EV was studied in many studies and varies widely. Thomopoulos and colleagues found that patients with varices had the platelet count of less than 118,000 /cu mm (3). Also, Gentile and others evaluated a score based on age above 50 years, and platelets count below 150,000/mm (19). The values of thrombocytopenia related to the presence of EV were different in published studies, probably due to differences in samples (20).

It was noted that there was an association between thrombocytopenia and the presence of EV because both resulted from the deterioration of liver function (20,21). The etiology of thrombocytopenia in patients with chronic liver disease may be attributed not only to portal hypertension, but also to autoantibodies against platelets, hypersplenism, and direct effect of HCV (26).

Since platelet count alone may be misleading as it cannot be solely attributed to portal hypertension (20-26), Giannini and colleagues aimed to chart a new parameter bridging thrombocytopenia to splenomegaly so as to originate a variable that takes into account the diminished platelet count probably due to hypersplenism attributed to portal hypertension (26).

In our study, PC/SD ratio cut off 681 had 75% sensitivity and 82.7% specificity and this value was lower than most approved by other studies. Our results were similar to those of Masjedizadeh and co-workers who determined the usefulness of PC/SD for the prediction of EVs and found that PC/SD ratio predicted EV with 47.1% sensitivity, 75.3% specificity, and 88.6% PPV and 25.8 % NPV with cut-off value = 663 (22). However, our results were lower than reported by most other studies. Studies performed by Giannini et al showed that a PC/SD ratio cutoff < 909 had a PPV of 96% and NPV of 100% (26). Also, a systematic review by Chawla and co-workers concluded that the test characteristics of PC/SD ratio of 909 might not be adequate to replace endoscopy as a non-invasive screening tool for EV (27). This difference might probably be influenced by racial characteristics.

The combination of the two different parameters provides theoretical advantages over the use of a single parameter, since falsely positive and/or negative results of one parameter may be overcome by the use of another one, and complementary information may lead to more accurate predictions (26-28).

In our present study, we found that portal vein diameter could significantly predict the presence of EV with a cutoff value of 13.1 with sensitivity 75.0%, specificity 60.0%, PPV 52%, NPV 84%, and accuracy of 0.68. This was in accordance with Berzigotti and colleagues who found PVD = 13 mm was 100% specific for clinically significant portal hypertension with a strong association with variceal formation (28). However; a lower diameter of PV was demonstrated by Sarwar and co-workers with a cutoff value of 11 mm (23). The difference in these values may be attributed to the discrepancy in the frequency of esophageal varices in different studies, which could be explained by the different stages of fibrosis in the recruited patients, different laboratory inclusion criteria, racial differences, and whether the diagnosis of liver disease was based on the biopsy or not.

In the present study, another ultrasonographic finding, the spleen diameter cutoff value = 15.35 mm could significantly predict EV with sensitivity 82.5%, and specificity 55%. Our results agree with those of Mandal and others who found that the average spleen size of the patients with GEV was higher than the spleen size in the patients without EV (25). So, they concluded that GEV developed in cirrhotic patients with spleen size larger than 13.1 cm. These observations were more or less similar to other studies. Thomopoulos and colleagues showed that most patients with GEVs had a spleen size of more than 13.5 cm, which is nearly similar to ours (3).

In our study, AUCs of APRI and FIB 4 scores for the prediction of varices were 0.73 and 0.70. They had the same specificity 60% but the sensitivity of APRI was 80% and for FIB4 was 75%. Our results are different from Deng and colleagues who showed in their meta-analysis study that the summary AUCs of APRI and FIB 4 scores for the prediction of varices were 0.6774 and 0.7755, respectively (29). In our study, the overall accuracy of both APRI and FIB 4 was 65% for prediction of esophageal varices. This was different from the result of Stefanescu and colleagues who concluded that Fib 4 was better than APRI in prediction of esophageal varices (OV).

In our study, AUCs of FibroScan was 0.69 with 75% sensitivity and 55% specificity. The clinical usefulness of non-invasive travsient elastography for assessing PH and prediction of OV was discussed in many studies. In our study FibroScan had moderate accuracy in prediction OV. This may be attributed to the fact that TE reflects an increase in intrahepatic resistance but not the amount of portal blood inflow and peripheral hemodynamic changes. Our finding was in accordance with LIop and colleagues who demonstrated a moderate correlation between TE and HVPG (Hepatic vein pressure gradient) however, Kim and others concluded that FibroScan was a reliable and non-invasive procedure that should be integrated into clinical practice for the evaluation of PH (30, 31). Vizzutti and colleagues gave a cut-off value for prediction of varices (17.6 kPa) which was lower than our cut off value (12).

In our score, we tried to combine the eight mentioned parameters in order to predict OV (AUROC 0.89; NPV 93%, PPV 89%, 85% sensitivity, 95% specificity and overall accuracy 92%). So, our score combined the most valuable parameters that depend on not only the increased vascular resistance but also to increased portal blood flow.

Several scores were developed to predict OV. Kim and colleagues proposed a model that used TE values and the spleen diameter to platelet ratio, which reflect PH in patients with chronic hepatitis B infection. This model showed excellent diagnostic performance for the prediction of high-risk EVs (AUROC 0.953; NPV 94.7%, PPV 93.3%) (31). El-Zanaty and colleagues proposed a novel index combining seven parameters namely platelet count, serum albumin, prothrombin concentration, right lobe of the liver diameter, portal vein diameter, splenic diameter, and ascites, which showed 100% specificity and 70% sensitivity in the prediction of OV(32).

Egypt has the highest prevalence of hepatitis C virus worldwide; with an enormous number of patients with liver cirrhosis due to chronic hepatitis C infection (33-39). Portal hypertension is a common complication of liver cirrhosis that can lead to the development of EVs (21).

In conclusion: This novel score was precisely able to predict EVs in patients with chronic hepatitis C infection. Using ROC curve analysis to study the discrimination ability of this combination, the AUC was 0.89 (95% CI: 0.81-0.98, $p < 0.001$) which gives the score good discrimination ability at cut off point of 4.5 (or 56.25 %) with 85% sensitivity and 95%

specificity. So, this novel score could be a reliable tool to predict EV instead of a single parameter.

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CONFLICT OF INTEREST

The authors declare no conflict of interests related to this work.

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