The Egyptian Journal of Hospital Medicine (October 2024) Vol. 97, Page 4373-4378

Evaluation of Non-invasive Fibrosis Markers in Predicting Esophageal Variceal Bleeding

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ABSTRACT

Background: The end stage of chronic liver disease (ESCLD), cirrhosis, causes nodule formation, fibrous tissue production, and disruption of the liver's architecture. Ascites, portal vein dilatation, splenomegaly, the formation of oesophageal and gastric varices, variceal hemorrhage, ascites, hypersplenism, and encephalopathy are among the complications that arise from cirrhosis, which impairs liver function and causes portal hypertension.

Objective: This study aimed to evaluate the use of non-invasive fibrosis markers and ultrasonographic parameters in predicting oesophageal variceal (EV) bleeding.

Subjects and methods: This Prospective cohort study was conducted at Internal Medicine Department, Ain Shams hospitals and lasted for 3 months. This study included 86 patients diagnosed with EV attending to Internal Medicine clinics.

Result: There was no statistically significant difference between two groups regarding model for end stage liver disease (MELD) score and AST/ALT. There was significant increase in EV with bleeding group than EV without bleeding regarding aspartate aminotransferase to platelet ratio index (APRI), FIB-4, and spleen diameter, while there was significant decrease in EV with bleeding group than EV without bleeding regarding platelet count splenic diameter ratio (PC/SD), and PLT.

Conclusion: The present study concluded that platelets counts, FIB-4 Index and APRI score appear to be promising markers in the prediction of EV bleeding. They can be used as screening method to predict EVB and appropriate referral to higher centers. Measuring platelets counts, FIB-4 Index and APRI score is simple, reliable, objective, and cost effective. Nevertheless, before these indicators are routinely used in clinical practice, more extensive research is required.

Keywords: Non-invasive fibrosis markers, predicting EV bleeding.

INTRODUCTION

The ESCLD that causes nodule formation, fibrous tissue production, and liver architectural disruption is cirrhosis. A hyperdynamic circulation and its associated complications, including ascites, portal vein dilatation, splenomegaly, the formation of oesophageal and gastric varices, variceal hemorrhage, ascites, hypersplenism, and encephalopathy, are caused by cirrhosis, which negatively impacts liver function and causes portal hypertension. Cirrhosis and EV patients had a hepatic venous pressure gradient of at least 10–12 mmHg during hemodynamic catheterization [(1)].

EV is more prevalent in Child-Pugh class-C patients than in Child-Pugh class-A patients (85% versus 40%), and it is present upon diagnosis in around 50% of cirrhotic individuals. Varices arise de novo at a rate of 5%/year, with a greater frequency in people who continue to drink alcohol or whose liver function deteriorates. Varices bleed 5–15% annually and grow from tiny to large at a rate of 5–12%/year after they develop. In addition to being impacted by the presence of red wale marks on varices at endoscopy and the severity of liver disease as determined by the Child-Pugh score, the most bleeding risk is observed in big varices defined as having a diameter of more than 5 mm [(2)].

Studies indicate that variceal hemorrhage has improved over the past few decades, while reports from the 1940s to the 1980s show dismal results with fatality rates ranging from 30 to 60%. A 20–30% mortality rate indicates that bleeding from EV is still of major clinical concern, even though the death rate from a bleeding episode has decreased due to advancements in endoscopic and radiographic procedures as well as novel pharmaceutical therapy [(3)]. Since trials of primary prophylaxis clearly demonstrate that the risk of variceal hemorrhage may be lowered by 50% to around 15% for large esophageal varices, early detection of varices prior to the first bleed is crucial [(4)].

There is no a universally applicable preventative therapy for EV hemorrhage at the moment. Although, they do not halt variceal development, non-selective beta blockers (NSBBs) are utilized to reduce bleeding in patients with EVs [(5)]. All cirrhotic patients should be examined for varices upon diagnosis, according to current standards. Patients without varices should be followed up with every two to three years, and those with tiny varices should be followed up with every one to two years, to see whether the varices have enlarged or whether preventative therapy is necessary. Endoscopic variceal ligation is a preventative measure for high-risk people, and esophago-gastro-duodenoscopy (EGD) is utilized to detect and quantify EVs. However, the high expense and potential risks of upper gastrointestinal (UGI) endoscopy, such as those related to intravenous sedation, are its drawbacks [(6)].

Received: 11/07/2024
Accepted: 11/09/2024

For EV screening, a number of minimally invasive or non-invasive techniques have been suggested as substitutes for EGD. Non-invasive fibrosis markers (NFM) can be helpful in identifying EV as it is caused by increased intrahepatic resistance and liver fibrosis. The WHO recommendations for assessing hepatic fibrosis advocate and validate the use of the fibrosis-4-index (FIB-4) and the aspartate aminotransferase to platelet ratio index (APRI). As EV is associated with portal vein dilatation and splenomegaly, ultrasonographic parameters including portal vein and spleen diameters can also be used for predicting esophageal variceal bleeding [7].

This study aimed to evaluate the use of non-invasive fibrosis markers and ultrasonographic parameters in predicting oesophageal variceal bleeding.

PATIENTS AND METHODS

This prospective cohort study was conducted at Internal Medicine Department, Ain Shams hospitals and lasted for 3 months. This study included 86 patients diagnosed with EV attending to Internal Medicine clinics.

Inclusion criteria: Patients over eighteen. Patients identified with EV using UGI endoscopy. Both male and female. Liver cirrhosis.

Exclusion criteria: Previous GI surgery. Active gastro-intestinal tract bleeding. Malignancy. Portal, hepatic, and splenic vein thrombosis. Refusal to participate.

METHOD

All patients were subjected to:

1) ***Complete history taking:*** Personal history (Name, age, parity, residence, occupation, special habits of medical importance specially smoking, age, gender, BMI and complaint & its duration), present history (Analysis of the current patient complaint, history of sensitivity to drugs, past surgical history (History of previous operations) and medical history.
2) ***Physical examinations:*** General examination to exclude systemic diseases, vital signs (BP, Temperature, HR, RR) and other signs (Pallor, Cyanosis, Jaundice, and Lymph node enlargement).
3) ***Investigational Studies:*** Routine laboratory investigations **(**All patients had a thorough laboratory evaluation, which included hematological and biochemical tests for Hb, PC, TLC, PT, serum levels of bilirubin, ALT, AST, t. protein, albumin, and blood urea.

Enrolled patients were classed based on the Child-Turcotte-Pugh (CTP) class. Non-invasive parameters such as MELD, AST/ALT ratio, APRI, PC/SD, and FIB-4 were determined for each patient based on their laboratory results. The MELD score was determined using the United Network for Organ Sharing (UNOS) Website's MELD calculator.

Outcomes measurements and follow up: Every patient was monitored in-person or over the phone for six months, and any UGI bleeding was recorded and compared to the results of the AAR, APRI, FIB-4, PVD, and PC/SD ratio with EGD.

Ethical approval: The Ethics Committee of Ain Shams Faculty of Medicine authorized this study. After receiving all of the information, each participant signed his permission. The Helsinki Declaration was followed throughout the course of the investigation.

Statistical analysis:

The SPSS version 22.0 for Windows® was used to analyze the gathered data. Both percentages and numbers were used to display the qualitative data. The mean ± SD, median, and range were used to display the quantitative data. We used the Kolmogorov-Smirnov test to check for normalcy in quantitative data. The X^2-test was used to look at the link between two or more qualitative factors. ROC curve analysis was used to assess each test's overall diagnostic performance. A perfect test is said to be a curve that runs from the lower left corner to the upper left corner and then to the upper right corner. To determine the statistical significance, P values ≤ 0.05 are regarded as significant.

RESULTS

According to table (1), the mean age was 44.01 ± 8.19, there was 44 patients (51.2%) were males, and 42 patients (48.8%) were females.

Table (1): Distribution of demographic data among the studied group

	Studied group (N=86)	
	mean	**±SD**
Age (years)	44.01	8.19
	N	**%**
Sex		
Male	44	51.2%
Female	42	48.8%

According to table (2), there was no statistically significant difference between two groups regarding MELD score and AST/ALT. There was significant increase in EV with bleeding group than EV without bleeding regarding APRI, FIB-4, and spleen diameter, while there was significant decrease in EV with bleeding group than EV without bleeding regarding PC/SD, and PLT.

Table (2): Comparison of non-invasive markers between EV with bleeding group and EV without bleeding group

	EV with bleeding group (N=11)	EV without bleeding group (N=75)	P value
MELD score	18.09± 7.88	15.36± 8.12	0.28
AST/ALT	2.6± 0.5	4.52 ± 3.3	0.058
PLT	125.45 ± 14.27	155.42 ± 34.32	**0.006***
PC/SD	782.7 ± 88.31	1059.9 ± 287.09	**0.002***
APRI	9.33 ± 2.47	0.77 ± .013	**<0.001***
FIB-4	4.24 ± 1.11	2.68 ± 0.62	**<0.001***
Spleen diameter	160.27 ± 1.67	145.7 ± 6.74	**<0.001***

At cutoff value of 65.3, platelets had sensitivity of 63% and specificity of 71.5% with significance for prediction of oesophageal variceal bleeding. At cutoff value of 6.6, fib.4 had sensitivity of 66% and specificity of 58% with significance for prediction of oesophageal variceal bleeding. At cutoff value of 2, APRI had sensitivity of 61% and specificity of 52% with significance for prediction of EV bleeding. At cutoff value of 1.49, AST.ALT had sensitivity of 57% and specificity of 49.1% with no significance for prediction of EV bleeding. At cutoff value of 1.49, MELD had sensitivity of 58% and specificity of 49.5% with no significance for prediction of EV bleeding.

Table (3): ROC analysis for prediction of EV bleeding.

	Area	Cutoff value	sensitivity	specificity	Std. Error[a]	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval	
							Lower Bound	Upper Bound
Platelets	0.714	65.3	63%	71.5%	0.062	**0.002**	0.591	0.836
Fib.4	0.668	6.6	66%	58%	0.064	**0.01**	0.543	0.794
APRI	0.599	2	61%	52%	0.065	**0.03**	0.472	0.726
AST.ALT	0.537	1.49	57%	49.1%	0.067	0.602	0.406	0.668
MELD	0.518	14.2	58%	49.5%	0.068	0.8	0.385	0.65

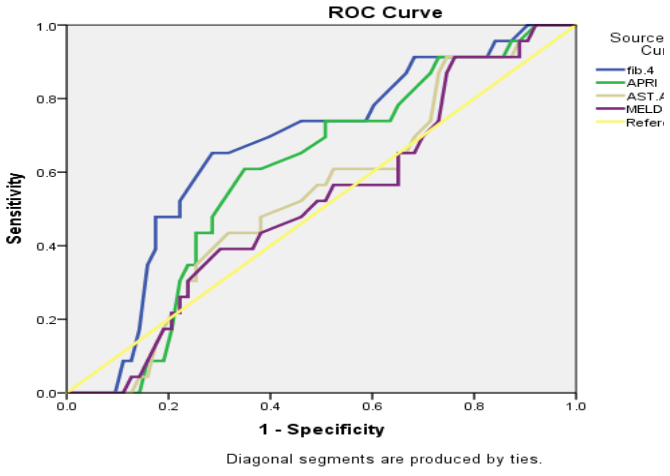

Figure (1): ROC curve of MELD, AST.ALT, APRI and fib.4 for prediction of EV bleeding.

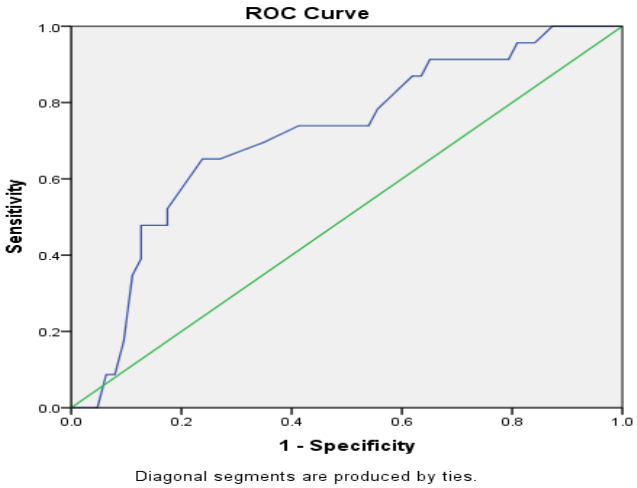

Figure (2): ROC curve of platelets for prediction of EV bleeding.

DISCUSSION

With a rising death rate worldwide, liver cirrhosis ranks as the thirteenth most common cause of death. Portal hypertension is a common side effect of liver cirrhosis development and is important for the disease's clinical presentation [8]. The development of EV brought on by elevated hepatic vascular resistance along with hepatic fibrosis and regenerative nodules is one of the most dangerous side effects of portal hypertension. Furthermore, the most frequent fatal consequence of cirrhosis is still variceal hemorrhage brought on by varices rupturing [9].

Thus, it is clinically crucial to determine whether EV is present in cirrhotic individuals in order to stop their bleeding. UGI endoscopy is still the gold standard for diagnosing EV, and the most recent Baveno VI Meeting Consensus suggests that all cirrhotic patients have endoscopic screening at the time of diagnosis and that patients with EV get periodic endoscopy examinations [10]. However, since EV is present in fewer than 50% of cirrhosis patients, regular endoscopic screening could not be cost-effective. Moreover, primary prevention is necessary due to the low frequency of varices [11]. Additionally, individuals may find the invasive and painful upper endoscopy operation intolerable. In order to determine whether patients benefit from routine endoscopy screening and potentially significantly lower the number of unnecessary endoscopies, it is crucial to forecast the presence of EV using non-endoscopic and non-invasive indicators [12].

It has recently been shown that a number of non-invasive indicators, including MELD, AST to ALT ratio (AST/ALT), APRI, PC/SD, FIB-4, FI, and King's score, are a straightforward, non-invasive, and more practical way to determine if EV is present in cirrhotic patients. The results of these earlier investigations, however, are debatable, and it is unclear if they will be useful in therapeutic settings. The findings of these investigations varied for various liver cirrhosis etiologies and demographics [13, 14].

The current study aimed to assess the predictive value of ultrasonographic measures and non-invasive fibrosis markers for EV bleeding. The study included 86 participants who had been diagnosed with EV who attended Internal Medicine clinics, Ain Shams Hospitals. Regarding demographic data, the current study revealed that the mean age of patients was 44.01 ± 8.19 years, 44 (51.2%) patients were males, and 42 patients (48.8%) were females. Our findings are in line with **Kraja *et al.*** [15] who used non-invasive markers to evaluate "predictors" of EV and variceal hemorrhage in Albanian patients with liver cirrhosis. They said that their patients were 51.5 ± 13.1 years old on average, with 30 (21.6%) being women and 109 (78.4%) being men. Similarly, our results agree with **Galal *et al.*** [16] who determined APRI, AAR, FIB-4, FI, and king scores that were assessed for their predictive usefulness in predicting the existence of varices and their grade, as well as the frequency and grading of EV in a sample of cirrhotic patients. They found that the patients' mean age was 53.6 ± 11 years, with 38 (37.6%) being female and 63 (62.4%) being male.

As regards laboratory investigations, our results showed that the mean WBCs was 6.53 ± 1.53, mean RBCs was 4.78 ± 0.77, mean Hb was 11.85 ±1.6, mean PLT was 151.59 ± 33.93, mean serum creatinine was 0.81 ± 0.29, mean serum urea was 31.1 ± 6.73, mean ALT was 48.5 ± 5.48, mean AST was 66.33 ± 9.75, mean PT was 30.47 ± 2.13, mean PTT was 39.03 ± 3.43, mean INR was 1.53 ± 0.28, mean bilirubin was 1.81 ± 0.59, mean total protein was 5.3 ± 0.57, and mean albumin was 3.17 ± 0.51. Our findings demonstrated that 8 (9.3%) patients had ascites, the mean child Turcotte Pugh score was 6.83 ± 1.71, 45 patients (52.3%) had class A, and 41 patients (47.7%) had class B. Our results agree with **Mostafa *et al.*** [17] who assessed the noninvasive tests' prognostic values for EV detection in Egyptian cirrhotic patients. As regards Child-Pugh (CP) Score, 129 (53.75%) patients had class A and 72 (30%) had class B.

Regarding non-invasive markers, this study revealed that the mean MELD score was 13.48 ± 2.5, mean AST/ALT was 1.36 ± 0.12, mean PC/SD was 1024.47 ± 285.2, mean APRI was 1.14 ± 0.31, and the mean FIB-4 was 2.88 ± 0.93. Our results supported those of **Kraja *et al.*** [15] who stated that the mean MELD score was 15.7 ± 5.2, mean AST/ALT was 2.18 ± 1.62, mean PC/SD was 1146 ± 780, mean APRI was 2.63 ± 3.79 and the mean FIB-4 was 5.83 ± 5.33.

As regards distribution of varices, our results revealed that 54 (62.8%) patients had small varices, 32 patients (37.2%) had large varices, 54 patients (62.8%) had grade 1, 20 patients (23.3%) had grade 2, 12 patients (14%) had grade 3, and 11 patients (12.8%) had hemorrhage. Our findings were in line with **Kothari *et al.*** [1] who reported that EV and/or EV bleeding might be predicted using non-invasive PH indicators. On EGD, they found that 133 patients (65.84%) had a big EV, 55 patients (27.23%) had a small EV, and 14 patients (6.93%) had no EV.

According to our findings, the two groups did not vary statistically significantly regarding WBCs, RBCs, Hb, serum creatinine, serum urea, ALT, AST, PT, PTT, INR, bilirubin, total protein, and albumin. In agreement with our findings, **Cifci & Ekmen's** [18] goal was to use non-invasive fibrosis markers to forecast the likelihood of EV hemorrhage in order to decrease the number of problems related to endoscopic scans, boost cost-effectiveness, and to identify the optimal timing for invasive operations. In terms of ALT, AST, and serum albumin, they showed no statistically significant difference between the two groups. In contrast, our results disagree with **Kothari *et al.*** [1] who revealed that hemoglobin, s. albumin and total protein were much lower in the EV bleeding group.

The results of this study showed that the two groups did not differ statistically significantly regarding

MELD score and AST/ALT. On the other hand, there was a significant increase in EV with bleeding group than EV without bleeding regarding APRI, FIB-4, and spleen diameter, while there was significant decrease in EV with bleeding group than EV without bleeding regarding PC/SD, and PLT. Our findings are in line with **Kothari *et al.*** [1] who reported that The MELD scores of the two groups did not differ in a way that was statistically significant. However, the EVB group had considerably higher averages for both the FIB-4 and APRI values (FIB-4, 7.98 vs. 3.9; APRI, 2.75 vs. 1.19 respectively). The EVB group's platelet count and PC/SD ratio were considerably lower than those of the no EVB group ($p<0.001$). Also, our results are consistent with **Cifci & Ekmen** [18] who reported that in terms of MELD, there was no discernible difference between the groups. However, there were much fewer platelets in the bleeding group. They discovered that the EVB group had considerably higher FIB-4 and APRI indices than the non-EVB group ($p=0.002$, <0.001).

Our findings reported that platelets had sensitivity of 63% and specificity of 71.5% with significance for prediction of EV bleeding at cutoff value of 65.3. At cutoff value of 6.6, FIB-4 had sensitivity of 66% and specificity of 58% with significance for prediction of EV bleeding. At cutoff value of 2, APRI had sensitivity of 61% and specificity of 52% with significance for prediction of EV bleeding. At cutoff value of 1.49, AST/ALT exhibited a sensitivity of 57%, specificity of 49.1%, and no significance for predicting EV bleeding. MELD demonstrated a sensitivity of 58% and specificity of 49.5% at a cutoff value of 1.49, with no significant difference in predicting EV bleeding.

Regarding ROC curve analysis, our results agree with **Kothari *et al.*** [1] who revealed that APRI and FIB-4 were significant for variceal bleeding. The ROC curve for FIB-4 indicated that 3.91 was the optimal cut-off value. This cut-off yielded 72.13% sensitivity, 60.28% specificity, and 63.86% diagnostic accuracy. An APRI >1.05 cut-off yielded an AUC of 0.72, sensitivity of 68.85%, specificity of 58.16%, and diagnostic accuracy of 61.39% in predicting variceal bleeding. They concluded that FIB-4 and APRI appear to be promising indicators of EV bleeding. Also, our findings are in line with **Cifci & Ekmen** [18] who reported that MELD was not a significant predictor of variceal bleeding. Although substantial, the AUC values for FIB-4 (AUC =0.63) and APRI (AUC =0.59) had little correlation with the EVB prediction. At a cut-off value of 66.5×10^9/L, the number of platelets, which was shown to be the greatest predictor of EVB (AUC, 0,70; OR, 3,74), had a 62% sensitivity and 70% specificity. They came to the conclusion that EVB might be predicted using non-invasive fibrosis markers like FIB-4 and APRI. Furthermore, the PLT cut-off value of 66.5 10^9/L is significant for EVB.

For cirrhosis, two traditional non-invasive scores with strong diagnostic effectiveness are the APRI and FIB-4 index [19]. According to **Zhang *et al.*'s** [20] study, the APRI's AUC value (0.729) was higher than that of the AAR, FIB-4, and S-index when it came to identifying the presence and severity of EV. Additionally, an APRI score of 1.4 or higher can serve as a reference indicator for the early intervention of severe EV. Additionally, they demonstrated that the FIB-4 index was a predictor of EV on its own, with an AUROC value of 0.64. Furthermore, **Vanbiervliet *et al.*'s** [21] investigation demonstrated that the APRI score was an independent predictor of recurrent EVB.

According to a major research by **Deng *et al.*** [22] the AUC value of FIB-4 in predicting the presence of EV was 0.77. According to a research by **Kraja *et al.*** [15], the FIB-4 score is a highly significant predictor of the existence of EVs. With a cut-off value of 3.23 (AUC, 0.66), the FIB-4 score was deemed an important predictor for EV in the same research, and a weak predictor for EVB with a cut-off value of 5.02 (AUC, 0.51). They concluded that the best liver NFM to employ as an initial screening method for individuals with cirrhosis is FIB-4. As well, the study conducted by **Galal *et al.*** [16] demonstrated that with a cutoff value of 3.52, the fibrosis index prediction score was a noninvasive, moderately sensitive method that could reasonably predict whether EV will be present in cirrhotic individuals.

CONCLUSION

The present study concluded that platelets counts, FIB-4 index and APRI score appeared to be promising markers in the prediction of EV bleeding. They can be used as screening method to predict EVB and appropriate referral to higher centers. Measuring platelets counts, FIB-4 index and APRI score is simple, reliable, objective, and cost effective. Nevertheless, before these indicators are routinely used in clinical practice, more extensive research is required.

- **Funding: No fund**
- **Availability of data and material: Available**
- **Conflicts of interest: No conflicts of interest.**
- **Competing interests: None**

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