Research Article

Fib٤ index versus MELD score as a non-invasive predictor of vaiceal rebleeding in HCV-related cirrhotic patients.

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Abstract

Background:- MELD score has a significant relationship with the occurrence of variceal rebleeding during hospitalization. The calculations of FIB-٤ index are simple, quick, and do not require standardization. It is inexpensive because the constitutive of FIB-٤ parameters are included in the standard investigation of any liver disease (age, AST, ALT, platelet count) a fact that may be of particular importance in emerging countries. **Aim:-**This study aimed to evaluate the diagnostic accuracy of Fib ٤ index in comparison to MELD score in prediction of variceal rebleeding in HCV-related cirrhotic patients. **Methods:** This prospective study included one hundred fifty patients with HCV-related liver cirrhosis and bleeding esophageal varices who were subjected to therapeutic band ligation and followed up for four weeks. The included patients were classified according to the occurrence of rebleeding during the follow up period into: ٤٢ patients with variceal rebleeding (group A) and ١٠٨ patients without variceal rebleeding (group B). All patients underwent detailed history taking, thorough clinical examination, routine laboratory testsand calculation of Fib ٤ index, and MELD score were done for all patients at the time of presentation. **Results:** FIB-٤ index and MELD score demonstrated statistically significant correlation with the grade of esophageal varices. The sensitivity, specificity, and the accuracy of FIB-٤ index, MELD score in the prediction of variceal rebleeding were (٤١.٦٪, ٩٤٪, and ٨٠.٤٤٪), and (٤١.٦٪, ٩٧٪, and ٨٢.٦٪) respectively. **Conclusion:** Calculation of Fib٤ index for patients with first variceal bleeding could decrease the need for emergency therapeutic endoscopy.

Key words: Fib٤ index, MELD score, variceal rebleeding.

Introduction

Variceal bleeding is one of the most serious complications in patients with chronic liver disease and carries a high mortality rate of ٢٠-٣٥٪[١]. Mortality per bleeding episode is around ١٠-٢٠٪[٢], and one year survival is only ٦٣٪[٣].

The most accepted endoscopic method for treating bleeding varices is endoscopic band ligation, which is effective in approximately ٩٠٪ of patients.

Even though the initial bleed may be controlled effectively by endoscopic therapy, the risk of subsequent rebleeding is substantil[٤].

A previous report showed that early rebleeding rate ranges from ٣٠٪ to ٤٠٪ within the first ٦ week, and is significantly associated with the risk of death within ٦ week[٥].

Different scoring systems have been used in order to predict morbidity and mortality in cirrhotic patients. Two samples of the most commonly used systems are Child-Pugh (CP) score and MELD (Models for the End-Stage Liver Disease) score[٦]. MELD score is a useful tool to assess prognosis in critically ill cirrhotic patients[٧].

FIB-٤ index is a simple, inexpensive, noninvasive test, quick and need no standardization which combines standard biochemical values (platelets, ALT, AST) and age to determine the degree of hepatic fibrosis[٨]. This study was designed mainly to evaluate the diagnostic accuracy of Fib ٤ index in comparison to MELD score in the prediction of variceal rebleeding in HCV-related cirrhotic patients.

Patients and methods

This prospective cross-sectional study included a hundred fifty patients with HCV-related liver cirrhosis who were admitted to the Endemic-Medicine Department-Minia University Hospital or referred to our endoscopy unit at Minia University Hospital-Egypt in the period from January ٢٠١٥ to September ٢٠١٥ with haematemsis, they were subjected to therapeutic band ligation or injection sclera therapy and grading of esophageal varices by using Grade I-IV classification[٩].All patients werefollowed up for four weeks to detect the occurrence of variceal rebleeding.

Informed consents were obtained from all patients before participating in this study according to the ١٩٧٥ Helsinki Declaration. Diagnosis of Liver cirrhosis was based on physical findings, laboratory investigations, and ultrasonographic findings. The included patients were classified according to the occurrence of rebleeding during the follow up period into: ٤٢ patients with variceal rebleeding (group A) and ١٠٨ patients without variceal rebleeding (group B). Exclusion criteria included patients with liver cirrhosis due to causes other than HCV and patients receiving beta blockers.

All patients were subjected to detailed history taking, clinical examination, and biochemical workup.Calculation of Fib-٤ index (Age x AST)/ (Platelts x (sqr (ALT)). Calculation of MELD score was done according to original formula proposed by the Mayo Clinic Group = {٩.٥٧xloge creatinine (mg/dl) +٣.٧٨ xloge bilirubin (mg/dl) +١١.٢ xlog eINR+٦.٤. We used on-line available worksheet to compute MELD scores (rst/mayomode١٥.html). Ultrasono-graphic examination (studying the hepatic right lobe and left lobe diameter, the presence of periportal thickening, the splenic longest axis and the presence of ascites and Portal vein diameter) were done to all patients . The study was approved from Clinical Research Ethics Committee of Minia University Hospital.

Statistical analysis

Statistical analysis of the data was performed by using SPSS_٢٢ software package. Categorical data parameters were presented in the form of frequency and percent. Quantitative data were expressed in the form of mean, SD. Comparison was performed by chi-square test for categorical data and student t-test for quantitative data. Probability level (P-value) was assumed significant if less than ٠.٠٥ and highly significant if P-value was less than ٠.٠٠١. P-value was considered non-significant if greater than or equal to ٠.٠٥. Receiver operating characteristic (ROC) curve analysis was performed to identify the discriminative capacity of Child-Pugh, MELD scores and FIB-٤ in predicting rebleeding. A cut off value of Child-Pugh score or MELD score was chosen as both sensitivity and specificity were optimal.

Results

A hundred fifty patients with HCV related liver cirrhosis were included in this study, they were ٩٦ (٦٤٪) males and ٥٤ (٣٦٪) females, with a mean age ٥٦.٦±٧.٠٢ years. Patients were classified according to the occurrence of variceal rebleeding during the follow up periodinto: ٤٢ patients with variceal rebleeding (group A) and ١٠٨ patients without variceal rebleeding (group B). The demographic data, clinical findings, laboratory results, and endoscopic grades of esophageal varices of the studied groups are summarized in table (١). The percentage of patients with grade III-IV esophageal varices was statistically significant higher in group A٣٨(٩٠.٥٪) patientsversus ٥٩ (٥٤.٦٪) patients in group B (p=٠.٠١٤) Table (١). There were statistically signi-ficant differences between the two groups regarding Fib٤ index (١١.٧٩ ± ٩.٩٠ Versus ٥.٠٠ ± ٣.٣٩ p<٠.٠٠١), MELD score (١٨.١٦ ± ٥.٢٣ versus١٣.٨٣ ± ٣.٨٧p<٠.٠٠١) and Child-Pugh score (٩.١٤ ± ٢.٥٣ versus ٨.٣٦ ± ١.٩١ p=٠.٠٤٣) Table (١). Significant correlations were noted between grade I-II esophageal varices and Fib ٤ index in the two groups (٩.٦٥±٤.٦١versus ٤.٨٢ ± ٢.٠٨ p<٠.٠٠١), also there were statistically significant correlation between grade III-IV esophageal varices and both Fib ٤ index (١٢.١٥ ± ١٢.١٦Versus ٥.١٦ ± ٢.٦٤ p<٠.٠٠١) and MELd scores (١٩.٢١ ± ٤.٨٤ versus ١٤.١٢ ± ٣.٩٥p<٠.٠٠١) in the two groups Table (٢). MELD score had the

highest area under the curve (AUC=٠.٧٧) at cut-off value > ٢٠ in the prediction of variceal rebleeding with a sensitivity of ٤١.٦٪, a specificity of ٩٧٪, a PPV of ٨٣٪ and an NPV of ٨٢.٥٪, followed by FIB-٤ index with (AUC=٠.٧) at cut-off value >١٠.٩ with a sensitivity of ٤١.٦٪, a specificity of ٩٤٪, a PPV of ٧١٪ and a NPV of ٨٢٪.The accuracy of Fib٤ index and MELD score in the prediction of variceal rebleeding were (٨٢.٦٪, and ٨٠.٤٤٪ respectively) Table(٣) and Figure (١).

Table (١): The demographic data, clinical findings, laboratory results, and endoscopic grades of esophageal varices of the studied groups.

Variables	Group A N=٤٢	Group B N=١٠٨	P. value (sig.)
Age:	٥٦.٥ ± ٦.٦	٥٦.٧ ± ٧.١	٠.٨٧٩ NS
Sex (males)	٣٣ (٧٨.٦٪)	٦٣ (٥٨.٣٪)	٠.٠٢٠*
General examination:			
Jaundice	٢١ (٥٠.٠٪)	٣٣ (٣٠.٦٪)	٠.٠٢٥*
LL edema	٢٤ (٥٧.١٪)	٥٤ (٥٠.٠٪)	٠.٤٣١ NS
Pallor	١٥ (٣٥.٧٪)	٦٠ (٥٥.٦٪)	٠.٠٢٩*
Hepatic encephalopathy	٦ (١٤.٣٪)	١٢ (١١.١٪)	٠.٥٩٠ NS
Laboratory findings			
AST (U/L)	١٧٢.٥ ± ١١٣.٥	٧٠.٩ ± ٤٤.٩	<٠.٠٠١**
ALT (U/L)	٨٤.٨ ± ٧٩.٣	٥٥.١ ± ٢٨.٥	<٠.٠٠١**
Albumin (g/dL)	٢.٤٦ ± ٠.٦٠	٢.٨٣ ± ٠.٤١	<٠.٠٠١**
Createnine (mg/dL)	١.٣٦ ± ٠.٩٧	١.٠٨ ± ٠.٤٢	٠.٠١٥*
Urea (mg/dL)	٨١.٨ ± ٦٠.٦	٥٧.٢ ± ٢٧.٦	<٠.٠٠١**
TLC (x١٠٣)	١١.١٦ ± ٤.٨٧	٧.٩٢ ± ٢.٤١	<٠.٠٠١**
Platelet count	١١٦.٨ ± ٦٤.٢	١١٨.٧ ± ٣٧.٦	٠.٨٢٦ NS
T. Billirubin (U/L)	٣.٠٢ ± ٢.١٤	١.٨٩ ± ٠.٩٤	<٠.٠٠١**
Prothrombin time (INR)	١.٨٦ ± ٠.٥٢	١.٤٣ ± ٠.٢٦	<٠.٠٠١**
Grade of Esophageal varices			
Grade I-II	٤ (٩.٥٪)	٤٩ (٤٥.٤٪)	
Grade III-IV	٣٨(٩٠.٥٪)	٥٩(٥٤.٦٪)	٠.٠١٤*
FIB-٤ index	١١.٧٩ ± ٩.٩٠	٥.٠٠ ± ٣.٣٩	<٠.٠٠١**
MELD score	١٨.١٦ ± ٥.٢٣	١٣.٨٣ ± ٣.٨٧	<٠.٠٠١**
Child-Pughscore	٩.١٤ ± ٢.٥٣	٨.٢٦ ± ١.٩١	٠.٠٤٣*

Data was presented in the form of frequency and percent. Quantitative data was presented in the form of mean ± SD

T-test and chi-square test were used to test the significant groups. ** Significant (p<٠.٠١),*Significant (p<٠.٠٥),NS Not significant.

Table (٢): The relation between grades of esophageal varices and (Fib٤ index and MELD score).

Variables	FIB-٤	MELD
GradeI- II		
Group A	٩.٦٥ ± ٤.٦١	١٣.٥٠ ± ٣.٧٩
Group B	٤.٨٢ ± ٢.٠٨	١١.٨٣ ± ٢.٠٤
P. value (sig.)	<٠.٠٠١**	٠.٢٩٥ NS
GradeIII- IV		
Group A	١٢.١٥ ± ١٢.١٦	١٩.٢١ ± ٤.٨٤
Group B	٥.١٦ ± ٢.٦٤	١٤.١٢ ± ٣.٩٥
P. value (sig.)	<٠.٠٠١**	<٠.٠٠١**

Quantitative data was presented in the form of mean ± SD. ** Significant (p<٠.٠١).* Significant (p<٠.٠٥).NS Not significant.

Table (٣): The best cut off, sensitivity, specificity and accuracy of FIB-٤ index, MELD score in the prediction of variceal rebleeding.

Variable	Cutoff	AUC	P value	Sensitivity	Specificity	PPV	NPV	Accuracy
FIB٤	>١٠.٩	٠.٧	٠.٠٣٦*	٤١.٦٧	٩٤.١٢	٧١.٤	٨٢.١	٨٠.٤٤٪
MELD	>٢٠	٠.٧٧	٠.٠٠١*	٤١.٦٧	٩٧.٠٦	٨٣.٣	٨٢.٥	٨٢.٦٪

AUC(area under curve),PPV(positive predictive value),NPV(negative predictive value)

Figure (١): ROC analysis of FIB-٤, and MELD score in the prediction of variceal rebleeding.
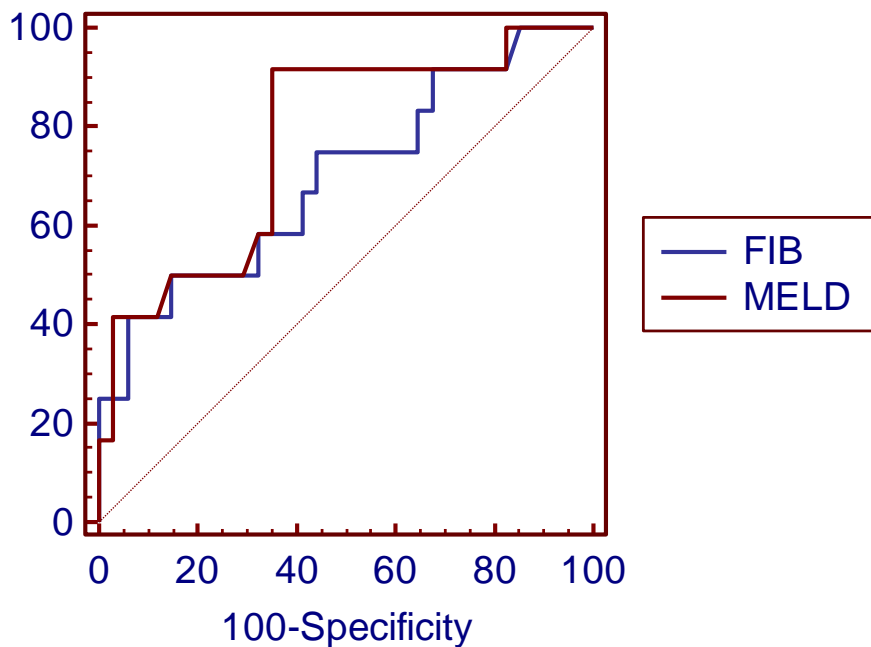
Discussion

Variceal hemorrhage carries high rebleeding and mortality rates. In patients with esophageal varices (EV), the combi-nation of endoscopic variceal ligation (EVL) and pharmacologictreatment is recommended as the standard treatment for prevention of rebleeding[٥]. Rebleeding and recurrence of varices after endoscopic treatment remain the main problems after controlling the acute variceal bleeding episode[١٠].MELD is the score of choice for stratification of liver transplant candidates for allocation of donor liver[١١]. The MELD score is a good predictor of short term esophageal varices rebleeding rate[١٢]. It is now possible to use MELD score as a predictor of survival and variceal rebleeding[١٣]. The FIB-٤ index could be used to accurately identify patients with significant fibrosis who might benefit from anti-HCV therapy and just as importantly patients with mild disease in whom therapy could be deferred[١٤].

Our results showed that There were statistically significant differences between the two groups regarding the grades of esophageal varices; grade I-II were found in ٤(٩.٥٪) patients in group A versus ٤٩(٤٥.٤٪) patients in group B while grade III-IV were found in ٣٨(٩٠.٥٪) patients in group A versus ٥٩(٥٤.٦٪) patients in group B (p=٠.٠١٤), this finding is in agree-ment with Xu et al., ٢٠١١[١٥] who found that early rebleeding prevalence after esopha-geal band ligation is related to the size and number of varices. In our results there were statistically significant differ-ence between the two groups regarding Fib٤ index (١١.٧٩ ± ٩.٩٠ Versus ٥.٠٠ ± ٣.٣٩ p<٠.٠٠١), MELD score (١٨.١٦±٥.٢٣ versus ١٣.٨٣± ٣.٨٧ p<٠.٠٠١) and Child-Pugh (٩.١٤±٢.٥٣ versus ٨.٣٦±١.٩١ p=٠.٠٤٣), this is in agreement with Hassan et al., ٢٠١٤[١٦] who found that the value of Fib٤ index was statistically significant differentin patients with esophageal varices versus those without esophageal varices (٤.٣٨±٢.٧٥ versus ٢.٧٤±١.٤٠ p=٠.٠٠٦ respectively). On contrary, our finding is not in agreement with Ebrahimi et al., ٢٠١٤[١٧] Who found that there were no statistically significant differences between rebleeding group and non rebleeding group regarding MELD score and Child score

(١٣.٢± ٤.٤ versus ١٦.٨ ± ٩.٢ p=٠.١٤) and (٩.٣±١.٦ versus ٩.٥±٢.٦ p= ٠.١٣) respectively.

On the other hand, in this study significant correlations were noted between grade I-II esophageal varices and Fib ٤ index in the two groups (٩.٦٥ ± ٤.٦١versus ٤.٨٢ ± ٢.٠٨ p<٠.٠٠١), also there were statistically significant correlation between grade III-IV esophageal varices and both Fib ٤ index (١٢.١٥ ± ١٢.١٦ versus٥.١٦ ± ٢.٦٤ p<٠.٠٠١) and MELd scores (١٩.٢١ ± ٤.٨٤versus١٤.١٢ ± ٣.٩٥ p<٠.٠٠١) in the two groups, a finding that goes in accord to Hassan et al., ٢٠١٤[١٦] who found that there were statistically significant difference between Fib٤ index and grades of esophageal varices (grade ١, ٢, and ٣) (٢.٨٦±١.٣٩, ٤.٦٥±٢.٦٨ ٦.١٠, and ±٣.٢٥ p= ٠.٠٠٣ respectively).

Our results showed that MELD score had the highest area under the curve (AUC= ٠.٧٧) at cut-off value > ٢٠ in prediction of variceal rebleeding with a sensitivity of ٤١.٦٪, a specificity of ٩٧٪, a PPV of ٨٣٪, an NPV of ٨٢.٥٪, and accuracy ٨٢.٦٪. This is in agreement toKamath et al., ٢٠٠١[١٨], who found that MELD score ≥ ١٧ were associated with a higher mortality rate (accuracy ٩٨٪ and AUC ٠.٧٦٨). In a study done byHunter and Hamdy, ٢٠١٣[١٩], patients with high MELD scores values (above ١٨) had significantly more re-bleeding risks in comparison with those with values lower than ١٨ . Another study done by Bambha et al., ٢٠٠٨[٢٠], showed that MELD score had a significant correlation with the occurrence of variceal rebleeding during hospitalization.

Finally, the current study revealed that the area under curve (AUC), sensitivity, specificity, PPV, NPV, and accuracy of the Fib٤ index in prediction of variceal rebleeding were (٠.٧, ٤١.٦٪, ٩٤٪, ٧١٪, ٨٢٪, and ٨٠.٤٤٪ respectively). This is in agreement with a meta-analysis done by Deng et al., ٢٠١٥[٢١], they found that the summary of area under curve of FIB-٤ score for the prediction of varices was ٠.٧٧٥٥, and that for the prediction of large varices was ٠.٧٠٩٥.

Hassan et al., ٢٠١٤[١٦] used a cut-off value of fib٤ of ٣.٣ for which the area under the curve was ٠.٧٦٢ for the diagnosis of lower esophageal varices with ٧٢.٩٪ sensitivity, ٦٦.٧٪ specificity, ٧٩٪ PPV, ٥٧٪ NPV and ٧٠٪ overall accuracy. AlsoIwata et al., ٢٠١٢[٢٢] demonstrated that there was a statistically significant difference regarding FIB-٤ values between risky esophageal varices group and non-risky esophageal varices group (p >٠.٠٥).

A limitation of our study was that relatively few rebleeding cases occurred, which might affect the statistical analysis because of the unbalanced sample size ratio of case to control. It is expected that more samples will be collected from multiple centers in the future.

Conclusion and recommendations

The diagnostic accuracy of Fib ٤in prediction of variceal rebleeding is comparable to MELD score. Also calculations of FIB-٤ index are simple, quick, do not require standardization and inexpensive.So calculation of Fib٤ index for patients with first variceal bleeding could decrease the need for emergency therapeutic endoscopy and facilitate the preparation for elective therapeutic endoscopic sessions.

Acknowledgements

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