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Simple Predictors of Gastro Esophageal Varices Bleeding in Cirrhotic Patients

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ABSTRACT

Background: Liver stiffness (LS), measured by transient elastography (TE), was correlated with portal hypertension as well as the presence of esophageal varices (EV).

Objective: The aim of the current study was to examine non-invasive markers that serve as "predictors" of esophageal varices (EV) and variceal hemorrhage in individuals with liver cirrhosis.

Patients and methods: A total of 250 Egyptian HCV associated cirrhotic persons, age more than 18, body mass index (BMI) under 35 with no history of ascites, GIT bleeding, HCC, abdominal collaterals, Portal, or splenic vein thrombosis by ultrasonography were recruited in our study. They were divided into Group I (no varices), Group II (small varices) and Group III (large varices).

Results: All groups were age and BMI matched, in group III platelet count was lower and MELD score was higher significantly than groups I and II (115.4±41.6 vs 149.6±60.6 and 132.1±44.9) and (12.1±2.9 vs 9.1+2.5 and 10.1+2.2) respectively. Hemoglobin, platelet count and serum albumin were significantly decreased in group III in comparison with groups I and II (P-value <0.001), while serum bilirubin and INR levels were significantly more in group III than in groups I and II (P-value <0.001). AFP was significantly increased in group II than groups I and III (P-value 0.008).

Conclusion: Our findings demonstrate the potential for using predictors to stratify cirrhotic individuals for the likelihood of developing extensive EV, hence enhancing the cost-effectiveness of screening endoscopy.

Keywords: Fibroscan, liver stiffness, esophageal varices, splenic stiffness, Comparative study, Cairo University.

INTRODUCTION

Liver cirrhosis, characterized by severe fibrosis as well as regenerating nodules, represents the terminal stage of the hepatic fibrosis process [(1)]. Poor prognostic indications include the major consequences of cirrhosis, such as portal hypertension (PHT), liver failure, hepatorenal syndrome in addition to esophageal varices (EV) [(2)].

Over ninety percent of those with cirrhotic conditions have EV, which can lead to bleeding. Individuals with small EV (SEV) have a five percent probability of bleeding EV, whereas those with large EV (LEV) have a 15% chance [(3)].

About 10 to 20% individuals will die from their bleeding episodes [(4)]. As a result, EV screening is strongly recommended in guidelines and consensus statements to those with cirrhosis [(5)].

Therefore, it is commonly advised that individuals with cirrhotic conditions undertake active surveillance, which is a bothersome process for both the persons and their doctors. Around 50% of cirrhotic cases will not acquire EV within the first decade following diagnosis [(6)]. Currently, several non-invasive markers, for instance model for end-stage liver disease, platelet count to spleen diameter (PC/SD), aspartate aminotransferase (AST) to alanine aminotransferase (ALT) ratio (AST/ALT), fibrosis-4-index (FIB-4), aspartate aminotransferase to platelet ratio index (APRI), fibrosis index (FI) and King's score, have been established as a simple, non-invasive and simpler practical different to forecast the existence of EVs in cirrhotic persons [(7)]. Nevertheless, the outcomes of these prior investigations have been debated also their practical value in clinical exercises remains unclear. The findings of these research differ according to the investigation's population and the cause of liver cirrhosis [(8)].

Therefore, the aim of our prospective research was to evaluate the non-invasive markers, based on routine laboratory variables, that could expect the possibility of EVs in liver cirrhosis cases in Albania, a hepatitis B virus infection hotspot in Southeastern Europe also a Mediterranean country with an increased utilization of domestic alcoholic drinks [(9)].

The purpose of this trial was to evaluate non-invasive indicators as "predictors" of EV along with variceal hemorrhage among people with liver cirrhosis.

PATIENTS AND METHODS

A total of 250 individuals with hepatitis C virus - caused liver cirrhosis were recruited in our study. There were 3 distinct categories of participants: 50 individuals who had hepatic cirrhosis but no EVs made up Group I, 100 individuals with hepatic cirrhosis and minor EVs made up Group II, and other 100 individuals with hepatic cirrhosis and significant EVs made up Group III. Participants attended the Hepatology and Gastroenterology outpatient clinic at Ahmed Maher Teaching Hospital from March 2013 to September 2015. Liver cirrhosis was first diagnosed through medical records. All participants fulfilled the following criteria:

Inclusion criteria: Mature patient's ≥18 years old. Infection with the hepatitis C virus. Mild pelvic ascites, but not severe or massive ascites, may be acceptable for individuals with liver cirrhosis. There was no previous

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history of hepatocellular cancer or upper GIT hemorrhage, and BMI <35.

Exclusion criteria for the recruited patients:
The individuals were under 18 years old. Other liver cirrhosis causes besides HCV. BMI ≥35, Cirrhosis of the liver with moderate to massive ascites. Histories of upper digestive tract hemorrhage. History of hepatocellular carcinoma. Portal vein thrombosis or splenic vein thrombosis. Abdominal ultrasonography persons with collaterals. Schistosomiasis sufferers.

Methods: All participants were subjected to full history taking, liver stiffness measurement (LSM), laboratory investigations, full clinical examination, abdominal ultrasonography, upper gastrointestinal endoscopy and splenic stiffness measurement.

Ethical Approval:
This study was ethically approved by Cairo University's Research Ethics Committee. Written informed consent was obtained from all participants. This study was executed according to the code of ethics of the World Medical Association (Declaration of Helsinki) for studies on humans.

Statistical analysis
The collected data were introduced and statistically analyzed by utilizing the Statistical Package for Social Sciences (SPSS) version 20 for windows. Qualitative data were defined as numbers and percentages. Chi-Square test and Fisher's exact test were used for comparison between categorical variables as appropriate. Quantitative data were tested for normality by Kolmogorov-Smirnov test. Normal distribution of variables was described as mean and standard deviation (SD), and independent sample t-test/ANOVA test was used for comparison between groups. P value ≤0.05 was considered to be statistically significant.

RESULTS
Consistent with the modified Child-Pugh score: most of group I cases were child A (96%), only 4% were child B with no cases with child C. MELD score was statistically significantly higher in group III than in group I and II (**Table 1**).

Table (1): Demographic characteristics of the studied patients.

	Group I N=50		Group II N=100		Group III N=100		* P-value
	Mean ± SD	Range	Mean ± SD	Range	Mean ± SD	Range	
Age (years)	49.7±7.38	60-32	50.3±6.04	63-37	51.35±4.98	62-36	0.249
BMI (kg/m²)	28.31+3.18	34.4-17.3	28.65+2.35	34.7-23.8	27.8+2.67	34.7-23	0.084
	N	%	N	%	N	%	
Sex Female/ Male	28/22	56/44	33/67	33/67	23/77	23/77	<0.001
Child classification							
Child A	48	96%	89	89%	79	79%	0.044
Child B	2	4%	11	11%	20	20%	
Child C	0	0.0%	0	0.0%	1	1%	
MELD score (mean + SD)	9.14±2.474		10.06±2.169		12.11±2.899		<0.001

The clinical findings of the studied cases were expressed in **table 2**, splenomegaly was statistically significantly greater in group III than group I and II, while there were no statistically significant variances as regard hepatomegaly, jaundice, ascites and lower limb edema.

Table (2): Clinical features of the studied patients.

Clinical Features	Group I		Group II		Group III		*P-value
	N	%	N	%	N	%	
Hepatomegaly	3	6%	9	9%	7	7%	0.744
Splenomegaly	7	14 %	10	10%	27	27%	0.005
Jaundice	0	0.0%	4	4%	6	6%	0.210
Ascites	0	0.0%	1	1%	1	1%	0.777
Lower limb Oedema	0	0.0%	0	0.0%	0	0.0%	

Table 3 showed that hemoglobin, serum albumin as well as platelet count were significantly reduced in group III in evaluation with groups I as well as II, while serum bilirubin also INR levels were significantly more in group III than in groups I and II. AFP was significantly decreased in group II than groups I and III.

Table (3): Laboratory parameters of the studied patients.

Variable	Group I N=50	Group II N=100	Group III N=100	*P-value
	Mean±SD	Mean±SD	Mean±SD	
Hb(g/dl)	12.62±1.53	12.95±1.58	11.9±1.75	<0.001
TLC(x10^3/mm3)	5.7±1.87	5.2±1.67	5.09±1.15	0.676
Platelets (x10^3/mm3)	149.6±20.6	132.08±14.94	115.4±4.59	<0.001
ALT(U/L)	66.46±5.56	66.06±4.71	58.10±3.78	0.235
AST(U/L)	65.44±4.09	67.34±7.90	66.27±8.09	0.953
Total bilirubin(mg/dL)	0.92±0.25	1.12±0.25	1.45±0.25	<0.001
Serum albumin(g/dL)	3.83±0.51	3.56±0.45	3.42±0.33	<0.001
INR	1.246±0.216	1.28±0.157	1.37±0.175	<0.001
Alphafetoprotein (ng/ml)	14.84±3.82	29.85±3.7	28.58±2.95	0.008

As regard impact on some noninvasive parameters in prediction the incidence of EV, in groups II and III total bilirubin, spleen size and platelet count/ spleen size ratio were significantly more than in group I (P-value <0.001) (**Table 4**) with cutoff values 0.82 (sensitivity 85% and specificity 48%), 13.5 (sensitivity 85% and specificity 54%) and 992 (sensitivity 70% and specificity 76%) respectively. While platelet count also serum albumin were significantly decreased in groups II and III than in group I (P-value 0.001), with cutoff values 149 (sensitivity 70.5% and specificity 48%), 3.65 (sensitivity 75.5% and Specificity 70%) respectively (**Table 5**).

Table (4): Correlation between mean values of some non-invasive parameters and the existence of EV.

EV	N	%	T.Bil	Spleen size	Platelet	Albumin	Plt/Splenic size ratio
Group I	50	20%	0.926	13.74	149.61	3.836	115
Group II, III	200	80%	1.288	15.19	123.78	3.49	837
P-value			<0.001	<0.001	0.001	<0.001	<0.001

Table (5): Cutoff values of some non-invasive parameters in estimations of the presence of EV.

Variable	Cut off	Sensitivity	Specificity
T.Bilirubuin	0.82	85%	48%
Splenic size	13.5	85%	54%
Platelet count	149.000	70.5%%	48%
Albumin	3.65	75.5%	70%
Platelet/splenic size ratio	992	70%	76%

As regard differentiating small and large EVs, total bilirubin and spleen size were significantly increased in group III than in group II (**Table 6**) with cutoff values 1.025 (sensitivity 71.7% and specificity 53%), 14.05 (sensitivity 78% and specificity 38%) respectively. While, platelet count, serum albumin and platelet count/splenic size ratio was significantly reduced in group III than in group II with cutoff values 128.5 (sensitivity 67% and specificity 50%), 3.55 (sensitivity 71% and Specificity 49%) and 926 (sensitivity 75% and specificity 47%) respectively (**Table 7**).

Table (6): Correlation between mean values of some non-invasive parameters and the size of EVs.

EVs	N	%	T.Bil	Spleen size	Platelet	Albumin	Plt/Splenic size ratio
Group II	100	40%	1.124	14.67	132.08	3.56	918
Group III	100	40%	1.45	15.72	115.49	3.42	756
P-value			<0.001	<0.001	0.007	0.011	0.001

Table (7): Cutoff values of some non-invasive parameters for differentiating small and large EVs.

	Cut off	Sensitivity	Specificity
T.Bilirubuin	1.025	71.7%	53%
Splenic size	14.05	78%	38%
Platelet count	128.500	67%	50%
Albumin	3.55	71%	49%
Platelet/splenic size ratio	926	75%	47%

DISCUSSION

Disparities amongst the sexes exist in the prevalence, appearance, natural history and prognosis of many liver illnesses. While there were not any statistically significant variations in age or BMI among the 3 groups, our investigation found that EVs were more common in males than females regardless of size. This is consistent with previous research showing that men generally have more severe liver diseases besides a greater risk of difficulties as well as death. MELD score was statistically significantly larger in group III than in group I and II. Recent research, however, have failed to find any link among sexuality as well as EVs [(10)]. In addition, there was a link among the size of EVs as well as the age of the individual, with larger EVs being linked to older patients and smaller EV being linked to younger cases. This could be because portal hypertension and the development of large EV require more time to manifest in older patients [(11)].

Many alternative prognostic models for hepatic encephalopathy have been presented. For close to 3 decades, the Child-Pugh score has been the gold standard for assessing cirrhosis prognosis in cases with advanced liver disease. Child-Pugh score also its consequences (albumin, bilirubin and prothrombin time) were the best indicators of mortality risk in a recent large systematic analysis despite significant limitations [(12)].

The existence of EV was substantially connected with higher Child score and MELD score, both of which are indicators of liver disease severity, in the present research. These outcomes were matched with numerous authors who displayed the strong correlation amongst severity of liver disease and expanding of EVs [(13,14,15)].

Laboratory parameters in the present study showed significantly increased bilirubin and decreased albumin in patients with varices especially large varices, this was like to a trial executed by **Hossain *et al.*** [(16)] who determined that the occurrence of EVs is higher in hypoalbuminic patients.

In our study platelet count is significantly more in participants without EVs than persons with EVs with cutoff value 149 (sensitivity 70.5%, specificity 48%), in addition, platelet count is significantly increased in cases with small EVs than others with large EVs with cutoff value 128.5 (sensitivity 67%, specificity 50%). These is accepted with international guidelines and we not need do screening for paralysis (<150).

In literature platelet count was considered predictor of EVs. **Wang *et al.*** [(1)] stated that platelet count is statistically connected with the grade of EVs. Moreover, **Nada *et al.*** [(17)] noticed that platelet count is significantly correlated with the occurrence of EVs.

Our previous pilot trial revealed threshold values of platelets for diagnosis of EVs 80 (sensitivity 85%, specificity 75%) and for differentiating small and large EVs 69.5 (sensitivity 80%, specificity 90%) [(18)]. The variance of outcomes amongst the 2 trials may be because of the greater number of persons in the recent one.

On combining two non-invasive parameters, we found that Platelet count/ Spleen size ratio is significantly higher in individuals with EVs than those without EVs with cutoff value 992 (sensitivity 70%, specificity 76%), in addition, Platelet count/ Spleen size ratio is significantly higher in cases with small EVs than those with large EVs with cutoff value 926 (sensitivity 75%, specificity 47%).

Similar studies were performed on a reduced number of participants and revealed nearly the same results as **González-Ojed *et al.*** [(19)] who determined that the Platelet count/ Spleen size ratio in a study of 91 patients, may be an effective method for identifying EV in people with cirrhosis of the liver, at cutoff value ≤884.3 had 84% sensitivity and 70% specificity.

Moreover, in another study in which 100 patients were recruited and concluded that platelet count/ Spleen diameter ratio is a strong variable which is independently connected with the incidence of EVs in chronic liver disease and irrespective of the etiology, at best cutoff ≥909 (sensitivity 98.6% and specificity 96%) [(20)].

Our previous pilot study revealed cutoff values of Platelet count/ Spleen size ratio for diagnosis of EVs 545 (sensitivity 85%, specificity 84%) and for differentiating little and big EVs 472 (sensitivity 90%, specificity 80%) [(18)]. The alteration of outcomes among the two investigations may be because of the greater overall patient population in the most recent.

On the other hand, **Chawla S *et al.*** [(21)] said that the ratio of platelets to spleen size may not be appropriate as a noninvasive screening method for EVs; esophagogastroduodenoscopy remains the gold standard.

Sharma and Aggarwal [(22)] reported in a prospective trial that splenomegaly and platelet count were both significant predictors of the existence of big varices.

CONCLUSION

Our results demonstrate that predictors can be applied to stratify people with cirrhotic conditions according to the probability of developing large EVs as well as this stratification can be utilized to enhance the cost-effectiveness of screening endoscopy.

DECLARATIONS

- **Consent for publication:** I attest that all authors have agreed to submit the work.
- **Availability of data and material:** Available
- **Competing interests:** None
- **Funding:** No fund
- **Conflicts of interest:** no conflicts of interest.

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