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Serum Biomarkers for Early Detection of Portal Hypertension

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Abstract: ***Portal hypertension is in charge of a large portion of the aggravated conditions, namely variceal hemorrhage, ascites and hepatic encephalopathy that denote the transition from compensated to decompensated cirrhosis. Due to the invasiveness, requirement for advanced technical expertise and high costs associated with HVPG measurements, the introduction of simple, noninvasive screening and diagnostic methods would represent a great clinical advancement. The aim of the study was to evaluate the diagnostic efficacy of noninvasive liver fibrosis indexes in the diagnosis of portal hypertension (PH) This is a prospective study conducted in the period 2012-2016 including 87 cirrhotic patients. These patients are partly admitted at the Department of Gastrohepatology at University Hospital "Mother Teresa" in Tirana and partly also followed at the policlinic of specialities in Tirana. Noninvasive liver fibrosis indexes could be used not only as a first-line screening method for CSPH but also for predicting esophageal varices (EV) in cirrhotic patients as well as proxy for fluxmetric measurement.***

Keywords: portal hypertension, serum biomarker, cirrhosis

1. Introduction

Portal hypertension (PH) and associated complications, such as esophageal varices (EV) and ascit and decompensation are mostly consequences of liver cirrhosis (1,2). HP and its complications account for most of the morbidity and mortality in patients with chronic liver disease. PH is in charge of a large portion of the aggravated conditions, namely variceal hemorrhage, ascites and hepatic encephalopathy that denote the transition from compensated to decompensated cirrhosis. Studies have shown that PH's early diagnosis is necessary to start treatment at the right time (3). Currently, the measurement of hepatic venous pressure gradient (HVPG) is considered as the gold standard for PH assessment and is the most important predictor of complications derived from PH in patients with cirrhosis (4). However, HVPG measurement is an invasive procedure requiring technical expertise, which is available only in some centers. Therefore, the need for simple and appropriate non-invasive alternatives has become urgent.

Recently, many laboratory, clinical and echographic variables have been evaluated as non-invasive HVPG measurement alternatives (5). However, none of them can be recommended in daily clinical practice due to inadequate accuracy or poor validity. Among non-invasive alternative methods, the determination of serum markers is a simple and easily evaluable method in the clinic. Recently, various seric markers of fibrosis have been identified as EV predictors (6). However, the diagnostic efficacy of these liver fibrosis indices in PH's prediction of patients with cirrhosis is poorly estimated so far. It is generally accepted that PH's pathophysiology involves increasing the intrahepatic vascular resistance that represents the primary factor and portal blood entry (7). Subsequently, in view of the idea that PH is for the most part ascribed to expanded vascular obstruction caused by hepatic fibrosis, it is conjectured that serum liver fibrosis records can likewise be utilized as PH surrogate marker. In this study, serum markers that can easily be measured in clinical practice were evaluated and compared to the diagnostic performance of some recently proposed non-invasive fibrosis indices as new PH predictors in cirrhosis patients and as an alternative to HVPG measurement. It was also considered whether the combination of markers could increase PH's predictive diagnostic accuracy and help stratify the PH scale in patients with cirrhosis as a non-invasive first-line screening method.

2. Material and Methods

This is a prospective study conducted in the period 2012-2016 involving 96 patients with hepatic cirrhosis, despite the etiology of cirrhosis, hospitalized at the Department of Gastro-Hepathology, University Hospital "Mother Theresa", Tirana, as well as diagnosed and followed in the outpatient service at the polyclinic of specialities of Tirana. Diagnosis of hepatic cirrhosis was based on clinical, laboratory, imaging (abdominal and / or elastography) findings, as well as examination of the upper digestive endoscopy and at least one of the following criteria: (1) heparin hepatic decompensation, including ascites, varicose hemorrhages, and hepatic encephalopathy, (2) imaging and / or endoscopic signs indicating data on hepatic cirrhosis, and (3) phase 4 fibrosis confirmed by elastography; Examination of ultrasound and ECHO Doppler measurement of the blood flow to the portal vein, elastography, upper digestive endoscopy were performed in patients. Recent studies in the literature show the correlation of the HVPG gradient with the endoscopic grade of esophageal varices (9). Numerous recent studies show a significant inverse correlation between the mean velocity (cm/s) of the blood flow to the portal vein and HVPG (<0.001 and r = -0.69 and - 0.58 respectively) and conclude that Echo Doppler can be used as a HVPG measurement substitute (10,11).

In this study, the following serum markers were evaluated in all patients: aminotransferase aspartate (AST) -at-alanine aminotransferase (ALT), platelet count, albuminemia, INR,

GGT, cholesterol, etc. as seric laboratory tests to analyze some of the variables, non-invasive liver fibrosis assessment, such as AAR (AST / ALT ratio), APRI (AST report on PLT), FI fibrous index and their connection to PH. ROC curves for significant fibrosis, advanced fibrosis and cirrhosis were constructed and optimal cut-off values for each non-invasive fibrosis index were determined from the area under the curve (AUC) and the predictive values of each index were compared with ROC curves of Echo Doppler.

3. Results and Discussion

Characteristics of patients: The study included a total of 96 patients, 76 (79.2%) males and 20 (20.8%) females.30 (31.2%) of patients had compensated cirrhosis whereas 66 (68.8%)a decompenSated cirrhosis. Clinical characteristics according toChild index are shown in table 1. Factors related to fluximetry from univariate analysis: To evaluate the variables associated with PH's presence, markers were easily evaluated in clinical practice were assessed. PH-grade variables were analyzed using univariate analysis. Factors related to PH's presence were: ascites, AST values, ALT, ALB values, and especially PLT numbers. Prothrombin time and INR were significantly associated with the presence of severe HP. The multivariate logic model of seric markers showed that the index of AST-to-platelet ratio (APRI) and Fib-4 correlated with PH The AAR values ($p = 0.6$ and and FI ($p = 0.1$) did not reach statistical significance to predict PH. The 14cm / s average blood flow velocity at the portal vein measured with echo Dopper was considered the criterion for determination of severe hypertension with 91% sensitivity and 96% specificity. From the comparison of the ROC curves between the fluximetry (echo Doppler) and the seric markers APRI and Fib-4, no significant difference was found between them (pairwise comparison of ROC APRI-Echo_Doppler curves $p=0.8$, Echo_Doppler ~ Fib_4 $p = 0.5$) suggesting that these serial markers can be successfully used in clinical practice for PH grade assessment (figure 1). Portal hypertension is a common complication of cirrhosis and contributes to the development of a variety of other complications. Recent studies have shown that fluximetry measured by echo Doppler perform well in assessing fibrosis or cirrhosis irrespective of etiology and in prediction of variceal bleeding (12). This is a real-time, free and recurrent examination and is considered as the first-choice imaging technique in patients with cirrhosis that provided important prognostic data on portal vein diameter, portal blood flow rate, congestion index, spleen size, flow mode in hepatic veins, and the presence porto-systemic abdominal collaterals. In addition, recent guidelines show that flux measurements also provide prognostic information, such as its changes relate to a corresponding consequent result (13,14). In contemporary literature, other non-invasive methods along with fluximetry have been reported as a first-line screening tool for the identification of patients at risk for PH who may benefit from the measurement of serum markers, which was also the purpose of this study. In patients with cirrhosis, PH is associated with increased intrahepatic vascular resistance and increased portal flow (15,17). Hepatobiliary fibrosis results in vascular compression due to collagen deposition around the sinusoids and the formation of regenerative nodules, which play a major role in increasing intrahepatic vascular resistance. In this study, it was found that the seric indexes APRI and Fib-4 yield same results with fluximetry and can be widely and easily used in clinical practice, which as results from literature studies, correlate with the degree of esophageal varices (10,11). As noted in the Baveno IV consensus, serum markers can predict so patients with no clinically significant hypertension as well as those with severe portal hypertension (18). Findings similar to this study are also reported in other studies in literature. In a prospective study, was reported that an APRI score ≥ 1.09 showed acceptable accuracy for severe PH prediction with an AUC of 0.716. In another study, Eun Ju Cho et al investigated the diagnostic value of non-invasive markers, such as APRI, Forns index, FIB-4, and Lok index in prediction of PH in alcoholic cirrhosis patients (19). The results of this study showed that PH was more precisely predicted in patients with compensated alcoholic cirrhosis. However, the study was limited to alcoholic cirrhosis. Currently, the inclusion of non-invasive methods, including seric markers and image-based methods, is increasingly used to evaluate hepatic fibrosis or cirrhosis. These methods offer a new PH assessment tool (20-22). However, their diagnostic accuracy was not very different from most comparable analytical parameters. Interesting is the finding that all serum hepatic fibrous indices that were considered in the current study included at least one of the variables independently associated with PH grade, such as AST, PLT and ALB. Since clinically significant PH is a precursor of severe PH, the PH screening model can be used to set an early diagnosis and timely treatment. Combinations of single non-invasive indexes provide a tool for selecting patients at high risk for severe PH for whom HVPG measurement may be more urgent, with a relatively small number of cases not correctly diagnosed. Such non-invasive first screening methods are particularly necessary since measurement of HVPG is not widely available for economic cost reasons.

4. Conclusion

Due to invasiveness and high costs associated with hepatic vein pressure gradient measurements, the introduction of simple, non-invasive screening and diagnostic methods represent major clinical progression. Non-invasive hepatic fibrosis indices can also be used for predicting esophageal varices in patients with cirrhosis.

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Table 1: Clinical characteristics of patients according to Child index

Variablat	Child A (n=16)	Child B (n=37)	Child C (n=43)	P
Age, M (SD)				
Gender				
Female	5 (25.0)	7 (35.0)	8 (40.0)	0.5
Male	11 (14.5)	30 (39.5))	35 (46.1)	
Etiology				
Alcoholic	8 (16.3)	22 (44.9)	19 (38.8)	0.7
Viral	8 (19.0)	13 (31.0)	21 (50.0)	
Autoimmune	1 (20.0)	2 (40.0)	2 (40.0)	
Type of cirrhosis				
Compensated	15 (50.0)	12 (40.0)	3 (10.0)	<0.01
Decompensated	1 (1.5)	25 (37.9)	40 (60.6)	
Portal hypertension				
Yes	7 (9.2)	30 (39.5)	39 (51.3)	<0.01
No	9 (45.0)	7 (35.0)	4 (20.0)	
Esophageal varices				
Yes	8 (11.0)	29 (39.7)	36 (49.3)	0.3
No	8 (34.8)	8 (34.8)	7 (30.4)	
Ascites				
Yes	0	15 (32.6)	31 (67.4)	<0.01
No	16 (32.0)	22 (44.0)	12 (24.0)	
Encephalopathy				
Yes	0	4 (16.7)	20 (83.3)	<0.01
No	16 (22.2)	33 (45.8)	23 (31.9)	

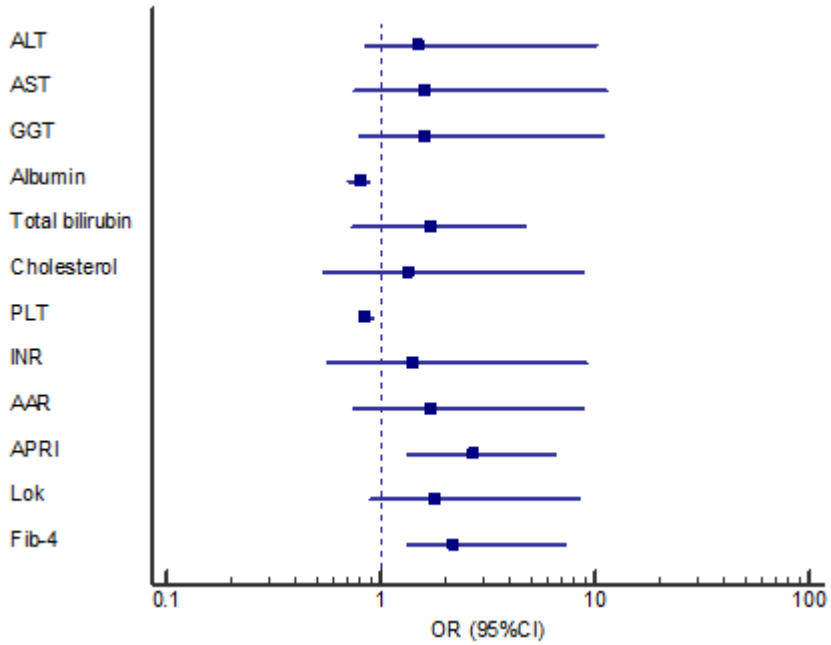

Figure 1: Prediction of PH-Forest plot