Non-invasive prediction of Liver fibrosis and cirrhosis

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ABSTRACT

Liver biopsy has traditionally been considered the gold standard for the evaluation of hepatic fibrosis and is used as a benchmark for initiating treatment. Liver biopsy is an invasive procedure, with a risk of rare but potentially life-threatening complications and it is prone to sampling errors. These limitations have led to the development of non-invasive methods. There are various serum based biomarkers in an algorithm model for estimation of liver fibrosis stage and to determine cirrhosis such as Bonacini score, Lok index, AP index, APRI, AAR index, Fibro Q, FIB4, GUCI index, and King score. The Bonacini score is one of the newest non-invasive marker which can be used to determine liver cirrhosis. **Aim**: To evaluate prognostic significance of non-invasive markers determining the liver fibrosis and cirrhosis.Objectives: 1. To evaluate the Bonacini score, AP index, APRI, AAR index, Fibro Q, FIB4, Lok index, GUCI index, King score prognostic significance determining the liver cirrhosis. 2. To evaluate the correlation between non-invasive markers and stages of liver fibrosis and cirrhosis. 3. To evaluate which non-invasive marker has the highest prognostic significance determining the liver cirrhosis. **Methodology**: A retrospective study was held at the Lithuanian University of Health Sciences Gastroenterology Clinic. The total number of patients was 203. Patients who had liver fibrosis or cirrhosis were 103 and other patients were as control group. Liver biopsy was performed for these patients and determined stages of liver fibrosis (F1-F4) according to METAVIR. Analyzed data: age, platelets count, AST, ALT, INR, prothrombin. Non-invasive scores: Bonacini score, AP (Age-Platelet) index, APRI (AST to Platelet Ratio Index), AAR index, Fibro Q, FIB4, Lok index, GUCI (Göteborg University Cirrhosis index), King score were calculated by this data. Statistical analysis was performed using IBM SPSS Statistics 22 software package. **Results**: A total of 203 patients were enrolled in research. 103 (50,7%) patients had severe fibrosis (F3) or cirrhosis (F4) and the 100 (49,3%) patients were as control group of research. Cut off level of Bonacini score for cirrhosis was 6,5 (sens–78%, specif–84%, AUROC 0,961), of Lok score – 0,33 (sens–81,6%, specif–89%, AUROC 0,932), of FibroQ – 4,25 (sens–82,9%, specif–87,4%, AUROC 0,916), of FIB4 – 0,808 (sens–82,7%, specif–87,4%, AUROC 0,922). Bonacini, Lok, FibroQ, FIB4 scores had significantly high predictive value for liver cirrhosis (p<0,001). Bonacini, Lok, FibroQ, FIB4 parameters significantly (p<0,001) correlated with other scores as AP, APRI, King, GUCI index. AP index (r=0,702), APRI (r=0,266), King score (r=0,293), GUCI index (r=0,41) significantly (p<0,001) correlated with stages by METAVIR.**Conclusions**: 1. Non-invasive scores - Bonacini, Lok, FibroQ, FIB4 - had statistically significant predictive value for liver cirrhosis. 2. Bonacini, Lok, FibroQ, FIB4 parameters significantly correlated with other scores: AP index, APRI, King score, GUCI index, also correlated with stages of METAVIR. 3. According to area under the ROC curve the strongest predictive predictive value for liver cirrhosis had Bonacini score. Keywords: liver, fibrosis, cirrhosis.

Introduction

Liver biopsy has traditionally been considered the gold standard for the evaluation of hepatic fibrosis and is used as a benchmark for initiating treatment [1,2]. Various factors such as toxins, heavy metals, drugs and infection with hepatitis viruses are able to influence on the function of hepatis. One of the most important effects of these factors on liver is gradual necrosis of active liver cells and if this disturbance remained untreated, can lead to liver fibrosis, cirrhosis and finally death. Therefore, it is necessary to diagnose the liver fibrosis [3].

Liver biopsy has been used in clinical trials for the confirmation of chronic hepatitis and to rule out other causes such as alcohol or fatty liver, as well as to identify cirrhosis. In addition, liver biopsy can differentiate different types of liver diseases such as steatosis, steatohepatitis or iron overload, which provides useful information for patient management and prognosis [4]. But liver biopsy is an invasive procedure, with a risk of rare but potentially life-threatening complications and it is prone to sampling errors. Liver biopsy is also associated with significant costs and requires expertise of a specialist. These limitations have led to the development of non-invasive methods [5,6].

There are various serum based biomarkers in an algorithm model for estimation of liver fibrosis stage and to determine cirrhosis such as Bonacini score, Lok index, AP index, APRI, AAR index, Fibro Q, FIB4, GUCI index, and King score [7].

The Bonacini score is one of the newest non-invasive marker which can be used to determine liver cirrhosis. Bonacini score constituents are AST/ALT, PT-INR and platelet count in a simple manner as described in table 1. According to this score, different points are given to ingredients of this index and ultimately they added together.

Parametes/Score	0	1	2	3	4	5	6
INR	<1.1	1.1-1.4	>1.4				
ALT/ AST ratio	>1.7	1.7-1.2	1.19-0.6	<0.6			
PLT ×1 000 /mm³	>340	340-280	279-220	219-160	159-100	99-40	<40

Table 1. Determinants of Bonacini score.

For example in a study by Colli on 176 patients with chronic HCV infection, they observed that this score was able to identify 67% of patients with a high (>75%) or low (<10%) probability of cirrhosis, and ultimately 33% of the HCV patients need liver biopsy for assessing their liver fibrosis score [1,8].

Another simple scoring system for estimation of liver fibrosis stage is Lok index. This index is based on serum AST and ALT levels, platelet count and PTINR. For this scoring system two cut points introduced: 0.2 to rule out cirrhosis and 0.5 to confirm cirrhosis. All

values that are between these cut points are considered indeterminate. There are various studies that used this score for estimation of liver fibrosis stage, because is a reasonable performance [9].

Fibro Q is a index that is more complicated than previous indices and is dependent to age (years), AST level, platelet count and also PT International Normalized Ratio (INR). PT INR measures the extrinsic pathway of coagulation. In 2012, Hsieh et al showed that FibroQ is a simple and useful test for predicting significant fibrosis in patients with chronic hepatitis C [10,11].

Other simple index that related to age (years), AST and ALT levels (U/L) and platelet count, is FIB-4. Yang et al reported that FIB-4 index had a significant power for differentiation between patients with mild and significant fibrosis in nonalcoholic fatty liver disease [12].

The Metavir score (F0F4) is widely used for grading the severity of hepatic fibrosis. F0 indicates no scarring; F1 indicates minimal scarring; F2 indicates that scarring has extended to outside the areas in the liver that contain blood vessels; F3 indicates bridging fibrosis is spreading and connecting to other areas that contain fibrosis; and F4 indicates cirrhosis or advanced scarring of the liver [2,5].

Aim

To evaluate prognostic significance of non-invasive markers determining the liver fibrosis and cirrhosis.

Excercises

1. To evaluate the Bonacini score, AP index, APRI, AAR index, Fibro Q, FIB4, Lok index, GUCI index, King score prognostic significance determining the liver cirrhosis.
2. To evaluate the correlation between non-invasive markers and stages of liver fibrosis and cirrhosis.
3. To evaluate which non-invasive marker has the highest prognostic significance determining the liver cirrhosis.

Methods

A retrospective study was held at the Lithuanian University of Health Sciences Gastroenterology Clinic. The total number of patients was 203. Patients who had liver fibrosis or cirrhosis were 103 and other patients were as control group. Patients with chronic hepatitis C, alcoholic liver disease, non-alcoholic steatohepatitis, cholestatic liver disease, haemochromatosis were included in the study. Liver biopsy was performed for these patients and determined stages of liver fibrosis (F1-F4) according to METAVIR (Figure 1).
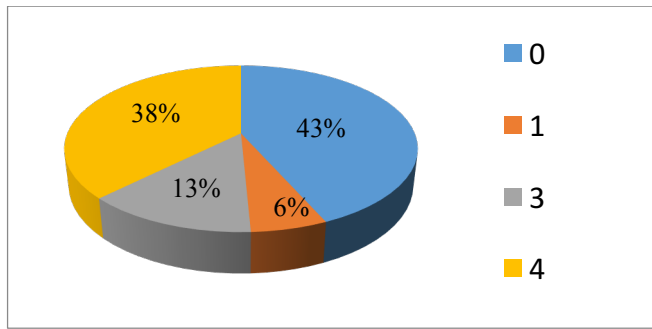
Figure 1. Stages by METAVIR

Analyzed data: age, platelets count, AST, ALT, INR, prothrombin. Non-invasive scores: Bonacini score, AP (Age-Platelet) index, APRI (AST to Platelet Ratio Index), AAR index, Fibro Q, FIB4, Lok index, GUCI (Göteborg University Cirrhosis index), King score were calculated by this data.

Statistical analysis was performed using IBM SPSS Statistics 22 software package. The Kruskal-Wallis analysis of variance was used to compare non-invasive parameters among the different fibrosis stages. The Bonacini and other scores as cirrhosis diagnostic indicators were assessed using ROC curves. Associated with any cut off value was the probability of a true positive (sensitivity) and the probability of a true negative (specificity). The most commonly used index of accuracy is area under the ROC curve (AUROC), values close to 1.0 indicating high diagnostic accuracy. Spearman coefficients of correlation was used to evaluate the relationship between parameters. Differences were considered as statistically significant when the p value was less than 0,05.

Results

A total of 203 patients were enrolled in research. 103 (50,7%) patients had severe fibrosis (F3) or cirrhosis (F4) and the 100 (49,3%) patients were as control group of research. Aetiologies of severe fibrosis/cirrhosis were: chronic hepatitis C (HCV)(n=77), alcoholic liver disease (n=3), non-alcoholic steatohepatitis (n=9), haemochromatosis (n=6), cholestatic liver disease (n=8), unknown aetiology (n=8).

The Kruskal-Wallis analysis results were evaluated and found significantly high difference between Bonacini score in patients with liver cirrhosis and without (p<0,001). The diagnostic value of Bonacini and other scores for cirrhosis and different degrees of fibrosis were evaluated by ROC curves and logistic regression. Based on the Banacini, Lok, FibroQ, FIB4 scores distribution according to fibrosis stage, cirrhosis and ROC curves, the best discriminant cut off levels were determined (positive predictive value of at least 90%) (Figure 2).
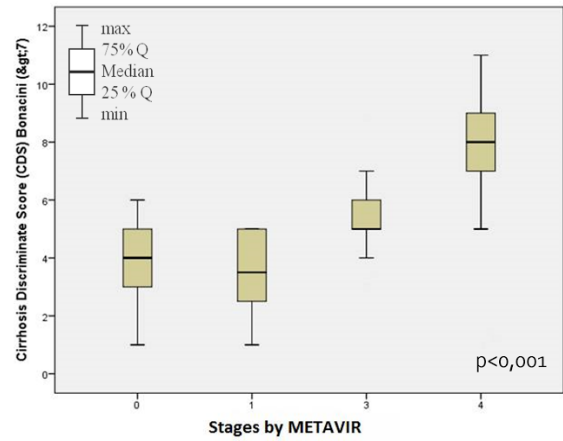

Figure 2. Bonacini score difference among the stages by METAVIR (*p value – criteria of Kruskal-Wallis)

Cut off level of Bonacini score for cirrhosis was 6,5 (sens–78%, specif–84%, AUROC 0,961), of Lok score – 0,33 (sens–81,6%, specif–89%, AUROC 0,932), of FibroQ – 4,25 (sens–82,9%, specif–87,4%, AUROC 0,916), of FIB4 – 0,808 (sens–82,7%, specif–87,4%, AUROC 0,922). Bonacini, Lok, FibroQ, FIB4 scores had significantly high predictive value for liver cirrhosis (p<0,001) (Figure 3).
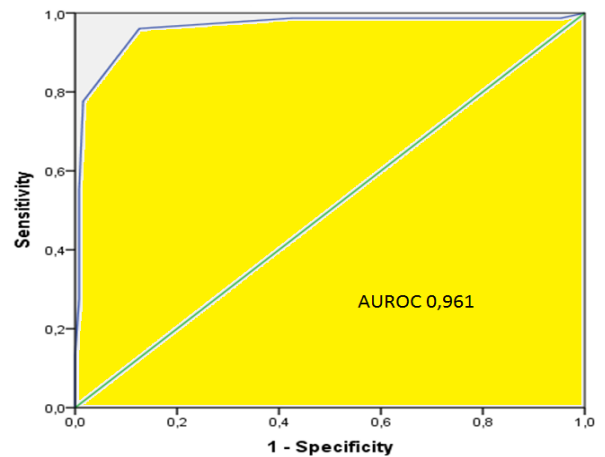

Figure 3. Diagnostic accurancy of Bonacini score for liver cirrhosis (Cut off level – 6,5, sensitivity – 78%, specificity – 84%, AUROC – 0,961)

Bonacini, Lok, FibroQ, FIB4 parameters significantly (p<0,001) correlated with other scores as AP, APRI, King, GUCI index. AP index (r=0,702), APRI (r=0,266), King score (r=0,293), GUCI index (r=0,41) significantly (p<0,001) correlated with stages by METAVIR

Conclusions

1. Non-invasive scores - Bonacini, Lok, FibroQ, FIB4 - had statistically significant predictive value for liver cirrhosis.
2. Bonacini, Lok, FibroQ, FIB4 parameters significantly correlated with other scores: AP index, APRI, King score, GUCI index, also correlated with stages of METAVIR.
3. According to area under the ROC curve the strongest predictive predictive value for liver cirrhosis had Bonacini score.

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