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The value of indirect serum markers in predicting severity of fibrosis in treatment naive patients with non-cirrhotic hepatitis C virus infection

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Abstract
We conducted this study for determining the value of indirect serum markers such as aspartate aminotransferase (AST), alanine aminotransferase (ALT), INR (International Normalized Ratio) and platelet counts and the roles of the scores such as AST-to-ALT ratio (AAR), AST-to-platelet ratio index (APRI), FIB-4 index, King's score, Goteborg University Cirrhosis Index (GUCI) and FibroQ in predicting severity of fibrosis in treatment naive patients with non-cirrhotic hepatitis C virus (HCV) infection. Treatment naive non-cirrhotic chronic HCV patients who underwent percutaneous liver biopsy between 01 January 2012 and 01 June 2015 were included in the study. For evaluating the difference in variables, patients were divided into 2 groups such as no or minimal fibrosis group (fibrosis score<2) and significiant fibrosis group (fibrosis score≥2). Statistical analyses were performed by SSPS 15.0. Overall, 78 (98.7%) male and only 1 (1.3%) female patients with a mean age of 24.27±6.08 years were included in the study. Mean age was 24.27±6.08 years. There was no difference in age variable (p=0.054), platelet counts (p=0.798), INR values (p=0.672), AAR (p=0.522) and FibroQ (p=0.535) between significiant fibrosis group and no or minimal fibrosis group. We found that as a predictor of significiant fibrosis, area under ROC curve (AUROC) for APRI was 0.727 (p=0.001), for FIB-4 index was 0.722 (p=0.001), for King's score was 0.753 (p<0.001) and for GUCI was 0.720 (p=0.001). Consequently, although they do not substitute liver biopsy, APRI, FIB-4 index, GUCI or King's score can be used as screening tests to predict significiant fibrosis in treatment naive patients with HCV infection.

Keywords: Hepatitis C virus, fibrosis, indirect serum markers, AAR, APRI, FIB-4 index, King's score, GUCI, FibroQ

Introduction

Chronic hepatitis C virus (HCV) is a global health problem with 80-185 million infected individuals worldwide and a leading cause of cirrhosis and hepatocellular carcinoma, although the treatment of HCV has shown significant progress with the development of direct-acting antivirals [1].

Accurate evaluation and staging of liver fibrosis is substantial for predicting prognosis and selecting treatment options in patients with viral hepatitis. Percutaneous liver biopsy is still the gold standard for detection of liver fibrosis [2]. However, liver biopsy is an invasive method and may cause severe complications such as bleeding, biliary perforation and peritonitis, pneumothorax or death, and also, even if rarely, it has some other drawbacks including inaccurate staging due to the sampling mistakes, lack of standardization of staining, observer-dependent diagnostic variations, need for hospitalization and for repeated biopsies for defining the therapy response or predicting prognosis in the posttreatment follow-up and financial burden [3-7].

Non-invasive modalities including direct or indirect serum markers and imaging tools evaluating liver stiffness are available for determining fibrosis degree in patients with viral hepatitis [4-25]. Whereas direct serum markers and imaging tools are not routinely available in clinical practice, indirect serum markers are cheaper and allow a more widespread use [4-7]. Furthermore, indirect serum markers, particularly such as aspartate aminotransferase (AST), alanine aminotransferase (ALT), INR (International Normalized Ratio) and platelet count have been evaluated in different scores or indices including AST-to-ALT ratio (AAR), AST-to-platelet ratio index (APRI), Forns' index, FIB-4 index (fibrosis index based on four factors), Lok index, King's score, Goteborg University Cirrhosis Index (GUCI) and FibroQ (fibrosis quotient) in some studies with questionable results [4-25].

In this regard, for determining the value of indirect serum markers and the roles of the scores such as AAR, APRI, FIB-4 index, King's score, GUCI and FibroQ in predicting severity of fibrosis and so, in avoiding unnecessary

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biopsies in treatment naive patients with non-cirrhotic HCV infection, we conducted this study.

Materials and Methods

Patients and data: Chronic HCV patients who underwent percutaneous liver biopsy in two centers, namely Kasımpasa Military Hospital Infectious Diseases Clinic and Gulhane Military Medical Academy Training and Research Hospital Department of Infectious Diseases, between 01 January 2012 and 01 June 2015 were evaluated retrospectively. Treatment naive chronic HCV patients were included in the study. Patients with hepatitis B (HBV) or human immunodefincy virus (HIV) coinfection, inadequate liver histopathology and laboratory data, cirrhosis or with comorbidities such as autoimmune hepatitis, metabolic disorders, hepatosteatosis, alcohol abuse, chronic inflamatory diseases, malignancies, corticostreoid or warfarine use, myeloproliferative disorders and other any infectious diseases were excluded.

The data including patients' age and gender, platelet counts, serum AST and ALT levels, INR values, serum HCV ribonucleic acid (RNA) levels, fibrosis scores were recorded. These laboratory findings were performed with blood samples which had been taken about one week before liver biopsy. Fibrosis scores were evaluated via means of modified histological activity index.

According to fibrosis scores, patients were divided into 2 groups such as no or minimal fibrosis group (fibrosis score<2) and significiant fibrosis group (fibrosis score≥2), for evaluating the difference in scores and variables.

For this study, ethics commitee approval was obtained from Gulhane Military Medical Academy General Ethics Committee and Publication Ethics Board. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration.

Scores: AAR, APRI, FIB-4 index, King's score, GUCI and FibroQ were calculated for all patients using laboratory data based on the following formulas:

AAR= AST (U/l) / ALT (U/l)

APRI= [(AST(U/l)/Upper limit of normal) / Platelet count (10^3/mm^3)] × 100 (Note: Upper limit of normal of males 40 U/l).

FIB-4 index= [(AST (U/l)×Age (years)] / [Platelet count (10^3/mm^3) × √ALT (U/l)]

King's score= [AST (U/l)×Age (years)×INR] / [Platelet count (10^3/mm^3)].

GUCI= [(AST(U/l)/Upper limit of normal)]×INR×100 / [Platelet count (10^3/mm^3)].

FibroQ= AST (U/l)×Age (years)×INR×10] / [Platelet count (10^3/mm^3) × ALT (U/l)].

Statistical analyses: Statistical analyses were performed by SSPS 15.0 (SSPS Inc., Chicago, ILL., USA). The variables were investigated using visual (histograms, probability plots) and analytic methods (Kolmogorov-Simirnov/Shapiro-Wilk's test) to determine whether or not they are normally distributed. All continuous variables were summarised as mean±standart deviation or median [interquartile range (Iq)]. The Mann-Whitney U test or Student's *t*-test were applied to compare continuous variables, depending on the normality of the data distribution. *p* values <0.05 were considered to be statisticaly significant for all analysis.

The capacity of scores in predicting significiant fibrosis were analyzed using ROC (Receiver Operating Characteristics) curve analysis. When a significiant cut-off value was observed, the sensivity, specificity, positive predictive values (PPV) and negative predictive values (NPV) were presented.

Results

Overall, 78 (98.7%) male and only 1 (1.3%) female treatment naive patients with non-cirrhotic HCV infection were included in the study. Mean age was 24.27±6.08 years and median age (interquartile range) was 21 (3) with an age range of 20-49 years. Baseline characteristics of patients are described in Table 1.

Table 1. Baseline characteristics of patients.

Variables	Mean±Standart Deviation (Minimum-Maximum)	Median (Interquartile Range)
Age (years)	24.27±6.08 (20-49)	21 (3)
AST (U/l)	55.58±30.25 (14-173)	46 (48)
ALT (U/l)	92.16±66.83 (7-308)	74 (98)
PLT (10^3/mm^3)	260.65±58.95 (150-428)	248 (74)
INR (International Normalized Ratio)	1.04 ±0.13 (0.77-1.80)	1.01 (0.11)
HCV RNA (log^{10} IU/ml)	5.75±1.07 (2.76-8.58)	5.90 (1.56)
Fibrosis Score	1.38±0.86 (0-3)	1 (1)

AST: Aspartate aminotransferase ALT: Alanine aminotransferase PLT: Platelet counts HCV RNA: Hepatitis C virus ribonucleic acid

There were 13 patients (16.5%) with fibrosis score 0, 30 patients (38%) with fibrosis score 1, 29 patients (36.7%) with fibrosis score 2 and lastly 7 patients (8.9%) with fibrosis score 3. According to fibrosis scores, patients were divided into 2 groups such as no or minimal fibrosis group (fibrosis score<2) and significiant fibrosis group (fibrosis score≥2). There were 43 patients (54.4%) with no or minimal fibrosis and 36 patients (45.6%) with significiant fibrosis.

Results of age, laboratory and histological variables and scores according to the fibrosis groups were described in Table 2. While there was no difference in age variable (p=0.054), platelet counts (p=0.798), INR values (p=0.672), AAR (p=0.522) and FibroQ (p=0.535) between significiant fibrosis group and no or minimal fibrosis group, serum AST levels, serum ALT levels, HCV RNA levels, APRI, FIB-4 index, King's score and GUCI were significiantly higher in patients with significiant fibrosis compared with no or minimal fibrosis group (respectively; p=0.001, p=0.005, p=0.025, p=0.001, p=0.001, p<0.001 and p=0.001) (Table 2.).

Table 2. Results of variables and scores according to the fibrosis groups.

Variables	No or Minimal fibrosis (Fibrosis score < 2)	Significiant fibrosis (Fibrosis score ≥ 2)	p Value
	n=43 (54.4%)	n=36 (45.6%)	
	M±SD (Min.-Max.)		
Age (years)	22.77±4.30 (20-39)	26.06±7.36 (20-49)	0.054
AST (U/l)	44.88±24.14 (14-101)	67.92±32.30 (16-173)	**0.001**
ALT (U/l)	72.63±54.24 (17-203)	115.50±73.43 (7-308)	**0.005**
PLT (10^3/mm^3)	263.26±63.87 (150-428)	257.53±53.20 (173-377)	0.798
INR	1.03±0.10 (0.84-1.30)	1.05±0.16 (0.77-1.80)	0.672
HCV RNA (log_{10} IU/ml)	5.51±1.10 (2.76-8.58)	6.05±0.98 (3.62-7.30)	**0.025**
AAR	0.72±0.21 (0.20-1.29)	0.75±0.41 (0.27-2.29)	0.522
APRI	0.43±0.23 (0.14-1.02)	0.68±0.35 (0.19-1.97)	**0.001**
FIB-4 index	0.48±0.15 (0.20-0.88)	0.69±0.31 (0.31-1.90)	**0.001**
King's score	4.05±2.14 (1.15-9.75)	7.43±4.36 (1.85-19.91)	**<0.001**
GUCI	0.44±0.23 (0.14-1.02)	0.72±0.43 (0.19-2.37)	**0.001**
FibroQ	0.70±0.38 (0.16-2.47)	0.82±0.56 (0.27-2.93)	0.535

M±SD (Min.-Max.): Mean±Standart Deviation (Minimum-Maximum)
AST: Aspartate aminotransferase
ALT: Alanine aminotransferase
PLT: Platelet counts
INR: International Normalized Ratio
HCV RNA: Hepatitis C virus ribonucleic acid
AAR= AST (U/l) / ALT (U/l)
APRI= [(AST(U/l)/Upper limit of normal) / Platelet count (10^3/mm^3)] × 100
FIB-4 index= [(AST (U/l)×Age (years)] / [Platelet count (10^3/mm^3) × √ALT (U/l)]
King's score= [AST (U/l)×Age (years)×INR] / [Platelet count (10^3/mm^3)]
GUCI= [(AST(U/l)/Upper limit of normal)]×INR×100 / [Platelet count (10^3/mm^3)]
FibroQ= AST (U/l)×Age (years)×INR×10] / [Platelet count (10^3/mm^3) × ALT (U/l)]

In parallel with these results, we also performed ROC curve analysis to evaluate whether significiant fibrosis (fibrosis score≥2) could be detected efficiently with APRI, FIB-4 index, King's score, and GUCI in treatment naive patients with non-cirrhotic HCV infection (Figure 1.). We found that as a predictor of significiant fibrosis in treatment naive non-cirrhotic HCV patients, area under ROC curve (AUROC) for APRI was 0.727 (p=0.001), for FIB-4 index was 0.722 (p=0.001), for King's score was 0.753 (p<0.001) and for GUCI was 0.720 (p=0.001) (Figure 1.).

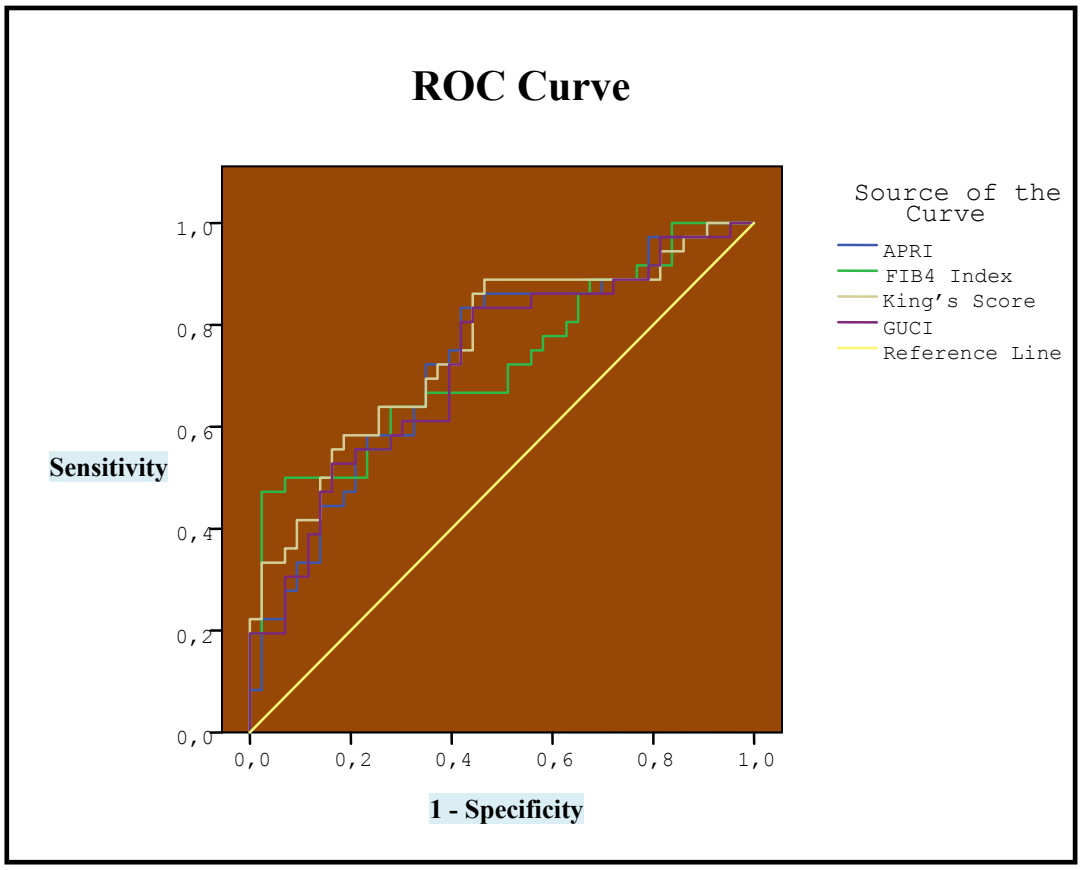

Figure 1. ROC curve analysis for APRI, FIB-4 index, King's score, and GUCI to predict significiant fibrosis.

As a result of our findings, to predict significiant fibrosis in treatment naive non-cirrhotic HCV patients, we considered that optimal cut-off value (with highest sensivity + specificity rates) defining significant fibrosis for APRI was 0.46 (sensivity: 75%, specificity: 58.1%, PPV:60% and NPV:73.5%), for FIB-4 index was 0.53 (sensivity: 66.7%, specificity: 62.8%, PPV:60% and NPV:69.2%), for King's score was 4.4 (sensivity: 72.2%, specificity: 60.5%, PPV:60.5% and NPV:72.2%), and for GUCI was 0.46 (sensivity: 75%, specificity: 58.1%, PPV:60% and NPV:73.5%).

We also defined cut-off values as a screening test (with high sensivity rates) for APRI was 0.38 (sensivity: 86.1%, specificity: 51.2%, PPV:59.6% and NPV:81.5%), for FIB-4 index was 0.38 (sensivity: 88.9%, specificity: 27.9%, PPV:50.8% and NPV:75%), for King's score was 3.3 (sensivity: 88.9%, specificity: 51.2%, PPV:60.4% and NPV:84.6%), and for GUCI was 0.46 (sensivity: 88.9%, specificity: 25.6%, PPV:50% and NPV:73.3%).

Discussion

Accurate evaluation and staging of liver fibrosis is substantial for predicting prognosis and selecting treatment options in patients with viral hepatitis. Due to the drawbacks of percutaneous liver biopsy, there are several attempts about non-invasive modalities such as direct or indirect serum markers and imaging tools to subsitute liver biopsy [4-25]. AST, ALT, INR, γ-glutamyl-transpeptidase, total bilirubin, α2-macroglobulin, apolipoprotein A1, haptoglobin, cholesterol and platelet count or indices, singly or especially in a combination including age-platelet index, AAR, APRI, Forns' index, FIB-4 index, Fibrotest, Fibroindex, Lok index, King's score, GUCI and FibroQ, are defined as indirect serum markers of liver fibrosis [4-25]. However, these scoring systems have been also reported to have better accuracy in diagnosis of cirrhosis than significiant fibrosis in some studies [10, 18, 22, 23]. So, we aimed to investigate the value of the scores such as AAR, APRI, FIB-4 index, King's score, GUCI and FibroQ which consist of easily accesible, cheap and routinely followed laboratory findings in patients with primary viral hepatitis.

In our cohort, the patients included in the study were particularly young adults (mean age was 24.27±6.08 years) and there was only one female patient, since study centers are military hospitals and so our patients are usually young adult males. In addition, there was only 7 patients (8.9%) with fibrosis score 3 and no patient with fibrosis score 4.

This condition may have resulted from short exposure duration to HCV in our young adult patients.

As expected, serum AST levels, serum ALT levels and HCV RNA levels were significiantly higher in patients with significiant fibrosis, even if these laboratory findings may ondulate in patients with HCV, however, there was no difference in age variable and INR levels between non-significiant fibrosis and significiant fibrosis group. While mean age in patients with non-significiant fibrosis was lower (22.77±4.30 years) than that in patients with significiant fibrosis (26.06±7.36 years), there was no statistical difference (p=0.054) between the two groups. There was also no difference (p=0.798) in platelet counts between the groups ($263.26\pm63.87\times10^3/mm^3$ vs. $257.53\pm53.20\times10^3/mm^3$). Immune mechanisms, HCV-mediated bone marrow suppression, hypersplenism, inadequate production of trombopoietin, endothelial dysfunction, drugs used in therapy or lastly fibrosis may cause thrombocytopenia and lower platelet numbers may be seen with 24% prevalence in patients with HCV infection [20, 26]. However, platelet counts may be lower in patients with advanced liver fibrosis or cirrhosis. Hence, the small number of patients with advanced fibrosis (fibrosis score≥3) in significiant fibrosis group and/or limited number of study patients may have caused no difference in age variable and platelet counts between two groups.

APRI, FIB-4 index, King's score and GUCI were significiantly higher in patients with significiant fibrosis, however, there was no difference in AAR and FibroQ between significiant fibrosis group and non-significiant fibrosis group, Both AST levels and ALT levels were higher in significiant fibrosis group compared with non-significiant fibrosis group, so as a theory, if the rates of these increases in AST levels and ALT levels are close, the ratio of these indirect serum markers (AST/ALT) may stay the same in significiant fibrosis group and in non-significiant fibrosis group. Therefore, we think that non-invasive tests consisting of AST/ALT ratio (AAR, FibroQ e.g.) may not be useful for predicting significiant fibrosis (not cirrhosis) in patients with chronic viral hepatitis. There are also studies suggesting our findings and showing the scoring systems to have better accuracy in diagnosis of cirrhosis than significiant fibrosis [10, 18, 22, 23]. Hence, AST/ALT ratio may show increase significiantly and may be more useful particularly in predicting cirrhosis. All the same, FIB-4 index, another non-invasive test contain AST and ALT levels in its formula, can described as more useful than the others in predicting significiant fibrosis, maybe since the square root of ALT levels is used.

We defined optimal cut-off values (with highest sensivity + specificity rates) and cut-off values as screening tests (with high sensivity rates) for APRI (0.46 and 0.38), FIB-4 index (0.53 and 0.38), King's score (4.4 and 3.3) and GUCI (0.46 and 0.30) with similiar sensivity and NPV rates. In the literature, the cut-off values of the scores for defining severity of fibrosis are still questionable with a wide range and varied sensivity and specificity rates [5-10, 12-18, 21-25]. The difference between the defined cut-off values may result from patients included the study (infected with HCV, HBV and HIV, or liver transplant recipients etc.), the methods used to evaluate fibrosis degree (Ishak, Knodell, etc.), predicted fibrosis degree (significiant, advanced or cirrhosis), the definition of significiant or severe fibrosis in the study, the inclusion of cirrhotic patients in the study, the authors' choice of high sensivity or high specificity, the time of the calculation (pre or posttreatment) [5-10, 12-18, 21-25].

As other drawbacks of the scoring systems, platelet counts may be altered by infections, chronic inflamatory diseases, and some haematological disorders or some drugs such as warfarin may affect INR values or AST and ALT levels may increase in the presence of hepatosteatosis or hepatotoxic drug use and also may show undulation in patients with viral hepatitis [4, 9, 11, 20]. Accordingly, the scoring systems used to predict the severity of fibrosis may deviate in such cases. In this regard, when using or evaluating these scoring systems, especially comorbidities or drug use which may affect the components of the scoring systems should be taken into consideration [4].

In addition to the shortcomings of non-invasive tests mentioned above and the fact that percutaneous liver biopsy is still the gold standard, as a result of our study, it can be said that non-invasive tests consisting of AST/ALT ratio (AAR, FibroQ e.g.) may not be useful in patients without cirrhosis but with significiant fibrosis, while APRI, FIB-4 index, King's score and GUCI may be more beneficial in those to predict significiant fibrosis in treatment naive patients with non-cirrhotic HCV infection with acceptable sensivity (86.1%-88.9%) and NPV (73.3%-84.6%) rates.

There are several limitations of the present study. First of all, the retrospective design is the most important one of these limitations. Then, although it was a two-center study, small number of study patients is another crurical drawback. Most of our patients were young adults and male, and accordingly, the limited number of patients with advanced fibrosis (fibrosis score≥3) in significiant fibrosis group and the inclusion of only one female patient into the study are the other limitations. Lastly, fibrosis scores were evaluated by different observers, not the same observer, since the retrospective design. This is another important drawback.

Conclusion

Consequently, we think that there is a need for a basic, useful and cost-effective scoring system, at least as a screening test, in determining severity of liver fibrosis. Although they do not substitute liver biopsy, APRI, FIB-4

index, GUCI or King's score can be used as screening tests to predict significiant fibrosis in treatment naive patients with HCV infection, but comorbidities or drug use affecting the components of the scoring systems should be taken into consideration. However, in order to highlight the role and importance of non-invasive scoring systems to predict fibrosis degree in patients with HCV infection, randomized large-scale studies are required.

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