Validation of three noninvasive laboratory variables to predict significant fibrosis and cirrhosis in patients with chronic hepatitis C in Saudi Arabia

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BACKGROUND: We tested the clinical utility of the platelet count, the aspartate aminotransferase/alanine aminotransferase (AST/ALT) ratio, and the AST to platelet ratio index (APRI) score in predicting the presence or absence of advanced fibrosis and cirrhosis in patients with chronic hepatitis C in Saudi Arabia.

METHODS: Liver biopsy procedures performed on chronic hepatitis C patients in our gastroenterology unit at King Khalid University Hospital were traced from records between the years 1998 to 2003. The hospital computer database was then accessed and detailed laboratory parameters obtained. By plotting receiver operating characteristic curves (ROC), three selected models (platelet count, AST/ALT ratio, and the APRI score) were compared in terms of the best variable to predict significant fibrosis.

RESULTS: Two hundred and forty-six patients with hepatitis C were included in this analysis. Overall, 26% of patients had advanced fibrosis. When comparing the three above-mentioned prediction models, the APRI score was the one associated with the highest area under the curve (AUC) = 0.812 (95% CI, 0.756-0.868) on the ROC curves, compared to the platelet count and AST/ALT ratio, which yielded an AUC of 0.783 (0.711-0.855) and 0.716 (0.642-0.789), respectively.

CONCLUSION: The APRI score seemed to be the best predictive variable for the presence or absence of advanced fibrosis in Saudi hepatitis C patients.

Liver biopsy continues to be an integral part in the diagnosis and management of many liver diseases.¹ In the case of hepatitis C, liver biopsy is very useful in determining prognosis, which reflects significantly on the decision to prescribe effective current antiviral therapy. Because liver biopsy is costly² and not without risk, many studies have been performed to evaluate the use of readily available laboratory test results to predict significant fibrosis or cirrhosis in patients with chronic hepatitis C.³ These tests have either been simple, readily available laboratory tests such as transaminases and the platelet count⁴⁻⁶ or more advanced, not widely available serum markers of fibrosis, like the Fibrotest⁷ and other liver matrix constituents and mediators of matrix remodeling.^{8,9}

In this study we reviewed all liver biopsies performed for patients with chronic hepatitis C in our unit at a large university hospital in Saudi Arabia in

an attempt to validate the clinical utility of the platelet count, AST/ALT ratio, and the AST to APRI score in predicting the presence or absence of advanced fibrosis and cirrhosis in patients with chronic hepatitis C.

METHODS

Liver biopsy procedures performed in our gastroenterology unit at King Khalid University Hospital, Riyadh, Saudi Arabia were traced from records between the years 1998 to 2003. Histopathology reports were obtained on all patients. In our unit, liver biopsy is performed in patients with chronic viral hepatitis if they have (1) elevated liver enzymes, (2) a detectable virus in the blood by a sensitive polymerase chain reaction (PCR) test, and (3) when there are no contraindications for antiviral therapy. The liver biopsies in these cases were performed routinely before initiation of antiviral therapy. Only a minority of the patients in this

cohort underwent liver biopsy despite normal liver enzymes because of other reasons, mainly suspicion of early cirrhosis. Patients were excluded from the study if the biopsy specimen was considered inadequate by the pathologist, if the clinical data on the patient was missing, if the patient was on antiviral therapy, if the patients had hepatitis B and C co-infection, if the patient had hepatitis D co-infection, or if the patient was on hemodialysis.

Histological assessment was performed by three experienced liver pathologists who were not blinded to the basic clinical data of the patients. The following histological parameters were collected: overall liver architecture, portal tract inflammation, interface hepatitis, cholestasis, bile duct injury, liver cell abnormalities, presence of steatosis, grade of inflammation, and stage of fibrosis according to the METAVIR liver histology classification system.¹⁰ Advanced fibrosis was defined as a fibrosis stage of 3 or 4. We were unable to collect data regarding the size of the biopsy and the number of fragments obtained because of the retrospective nature of the study, but all reported biopsies were considered adequate by the reporting pathologist and all contained more than 4 portal tracts.

The hospital computer database was then accessed and the following laboratory data were collected on each patient: WBC count, hemoglobin, mean corpuscular volume (MCV), platelet count, total bilirubin, albumin, alkaline phosphatase (ALP), ALT, AST, gamma-glutamyl-transferase (GGT) and viral hepatitis serology. Forty-five U/L was considered the upper limit of normal for ALT and AST. The APRI score was calculated by dividing the AST level by 45 (upper limit of normal) and then multiplying it by 100, and then dividing the total in the platelet count, as described by the original article by Wai.¹⁹

The data was entered in MS Excel software. SPSS PC+ statistical software was used for the statistical analysis. The association between the categorical variables was assessed by using the chi-square test or Fisher exact test. The sensitivity, specificity, positive and negative predictive values were calculated to assess the valuables (platelet count, AST/ALT ratio, and the APRI score) in the prediction of the presence or absence of advanced fibrosis and cirrhosis in patients with hepatitis C. The receiver operating characteristic curves (ROC) were drawn to find the optimum cut-off points that have high sensitivity and specificity. The area under the curve (AUC) was calculated with its 95% confidence intervals.

RESULTS

Two hundred and seventy-nine liver biopsies were identified. Of these, 13 were excluded from the analysis (9 because of inadequate biopsy size and 4 because of missing laboratory data). Twenty patients were further excluded because they were on antiviral therapy, had hepatitis B and C co-infection, or were on hemodialysis.

The baseline characteristics of the 246 included patients are shown in Tables 1 and 2. The mean age of the patients was 45 years and about 60% were males. The mean ALT was 112. Most patients had either grade 2 or 3 inflammation (78%), while only a minority had grades 1 or 4. On the other hand, biopsies from the majority of patients had stage 1 (28%) and stage 2 (40%) fibrosis, while only about 26% had advanced fibrosis (Table 2).

For predicting advanced fibrosis, the platelet count was applied as a predictive variable and it was found from the ROC curve that the AUC was 0.783, while with the AST/ALT ratio the AUC was 0.716 (Figure 1). For platelet count we tried using 120 and 100 as cut-offs to predict the presence or absence of advanced fibrosis, while we used >0.65 and 0.70 as cut-offs for the AST/ALT ratio (Table 3).

The APRI score yielded the highest AUC (0.812). We were not able to find a single APRI score cut-off value to predict the presence or absence of advanced fibrosis, but rather we found that two cut-off points were best used (Table 3). A cut-off point of more than 1.5 would correctly predict the presence of advanced fibrosis with 90% specificity and 32% sensitivity. On the other hand, a cut-off value of less than 0.50 would predict the absence of advanced fibrosis with a sensitivity of 87% and a specificity of 59%.

Table 1. Laboratory features of patients.

Parameter	
Age	45(16-76)
% males	59
Platelet count (X10 ⁹ /L)	200 (60-636)
Total bilirubin (μmol/L)	13.9 (6-37)
Albumin (g/L)	36.59 (30-42)
Alkaline phosphatase (U/L)	131 (13-275)
Alanine aminotransferase (U/L)	112 (16-628)
Aspartate aminotransferase (U/L)	74 (22-132)
Gamma-glutamyl-transferase (IU/L)	141 (8-378)

DISCUSSION

When the physician is evaluating a patient with chronic hepatitis C, the most important question that will influence the clinical decision to treat with antiviral therapy is whether this patient is at risk for developing significant liver fibrosis. This question is very important because only about 10% to 20% of patients with chronic hepatitis C¹¹ will actually develop cirrhosis. So far, liver biopsy has been the only widely accepted method to answer this important question. Because liver biopsy is costly and is associated with rare but significant risk, and is not accepted by some patients, many research groups have been searching for alternatives.¹² These fibrosis-predicting parameters may be clinical (history and physical examination), laboratory, or radiological. Of these, much attention has been put on laboratory markers of advanced fibrosis.³ According to Fontana and Lok, an ideal noninvasive test should satisfy as many of the following criteria as possible: it should be simple, readily available, inexpensive, accurate, reproducible, sensitive to the effect of treatment, and useful in tracking disease progression.³ Unfortunately, no single marker or predictive variable has satisfied all these criteria. Reviewing the literature, we found that the three simple laboratory tests that have been well investigated and found to be useful in patients with chronic hepatitis C: are the platelet count,¹³⁻¹⁵ the AST/ALT ratio,¹⁶⁻¹⁸ and the APRI score.¹⁹

In our study, we attempted to validate these scores in our patients in Saudi Arabia. This was based on the fact that there are potential differences between our patients in Saudi Arabia and the patients on which these tests were initially developed and subsequently validated. These factors include the difference in age and mode

Table 2. Histological features of biopsies.

Parameter	
Grade 1	47 (19.1%)
Grade 2	121 (49.2%)
Grade 3	69 (28%)
Grade 4	9 (3.7%)
Stage 0	12(4.8%)
Stage 1	69 (28%)
Stage 2	100 (40.7%)
Stage 3	53 (21.5%)
Stage 4	12 (4.8%)

of virus acquisition, a lower frequency of alcohol consumption in the Saudi population, and the prevalence of other non-cirrhotic causes of portal hypertension in Saudi Arabia, especially schistosomiasis, which may affect the fibrosis progression.

In patients with hepatitis C, when the three above-mentioned predictors were compared, the APRI score was the one associated with the highest AUC, 0.812 (95% CI, 0.756-0.868), on the ROC curves, compared with the platelet count and AST/ALT ratio, which yielded an AUC of 0.783 (0.711-0.855) and 0.716 (0.642-0.789) respectively (Figure 1). Two cutoff values were identified for the APRI score, which we feel are helpful in clinical practice; these are >1.5 and <0.5. If the APRI score is <0.50, this is associated with a sensitivity of about 90% and a specificity of about 60% in predicting the absence of advanced fibrosis, while if a

Figure 1. Receiver operating curves (ROC) for platelet count, AST/ALT ratio, and APRI score as predictors for advanced fibrosis (Diagonal segments are produced by ties).

Table 3. Accuracy of platelet count, AST/ALT ratio, and APRI score in predicting advanced fibrosis.

Negative predictive value	Positive predictive value	Specificity	Sensitivity	Presence of advanced fibrosis		Model
				No	Yes	
Platelets						
76	80	35	96	174	42	>120
				7	23	<120
90	76	15	99	180	55	>100
				1	10	<100
AST/ALT ratio						
83	44	74	58	47	38	>0.70
				134	27	<0.7
86	45	70	67	54	44	>0.65
				127	21	<0.65
APRI score						
78	53	90	32	18	21	>1.50
				163	44	<1.50
93	43	59	87	73	57	>0.50
				108	8	<0.50

cutoff value of the APRI score was >1.50, this is associated with a high specificity of >90% and sensitivity of 30% in predicting advanced fibrosis (Table 3). These results are quite comparable to the results reported by Wai in which the AUC of APRI for predicting significant fibrosis and cirrhosis were 0.80 and 0.89, respectively,¹⁹ and to the more recently reported prospective validation by Castera.⁷

Our study suffers from some of the inherent weaknesses of any retrospective analyses. We were unable to collect information on the size of the biopsy and number of fragments. Recently, Bedossa and others have shown

that there is a wide sampling variability in assessment of fibrosis in liver biopsy most of which is related to the size of the biopsy.²⁰

In Saudi Arabian patients with chronic hepatitis C, while a low platelet count and a high AST/ALT ratio were good predictors of advanced fibrosis, the APRI score seems to be more precise in predicting the presence or absence of advanced fibrosis. The validation of the utility of these simple laboratory predictive factors of advanced fibrosis and cirrhosis in a population different in many ways from the population on which it was initially developed proves the universal utility of these factors.

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