Noninvasive assessment of hepatic fibrosis in Egyptian patients with chronic hepatitis C virus infection

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Abstract

AIM: To evaluate the accuracy of specific biochemical markers for the assessment of hepatic fibrosis in patients with chronic hepatitis C virus (HCV) infection.

METHODS: One hundred and fifty-four patients with chronic HCV infection were included in this study; 124 patients were non-cirrhotic, and 30 were cirrhotic. The following measurements were obtained in all patients: serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), albumin, total bilirubin, prothrombin time and concentration, complete blood count, hepatitis B surface antigen (HBsAg), HCVAb, HCV-RNA by quantitative polymerase chain reaction, abdominal ultrasound and ultrasonic-guided liver biopsy. The following ratios, scores and indices were calculated and compared with the results of the histopathological examination: AST/ALT ratio (AAR), age platelet index (API), AST to platelet ratio index (APRI), cirrhosis discriminating score (CDS), Pohl score, Göteborg University Cirrhosis Index (GUCI).

RESULTS: AAR, APRI, API and GUCI demonstrated good diagnostic accuracy of liver cirrhosis (80.5%, 79.2%, 76.6% and 80.5%, respectively); P values were: < 0.01, < 0.05, < 0.001 and < 0.001, respectively. Among the studied parameters, AAR and GUCI gave the highest diagnostic accuracy (80.5%) with cutoff values of 1.2 and 1.5, respectively. APRI, API and GUCI were significantly correlated with the stage of fibrosis (P < 0.001) and the grade of activity (P < 0.001, < 0.001 and < 0.005, respectively), while CDS only correlated significantly with the stage of fibrosis (P < 0.001) and not with the degree of activity (P > 0.05). In addition, we found significant correlations for the AAR, APRI, API, GUCI and Pohl score between the non-cirrhotic (F0, F1, F2, F3) and cirrhotic (F4) groups (P values: < 0.001, < 0.05, < 0.001, < 0.001 and < 0.005, respectively; CDS did not demonstrate significant correlation (P > 0.05).

CONCLUSION: The use of AAR, APRI, API, GUCI and Pohl score measurements may decrease the need for liver biopsies in diagnosing cirrhosis, especially in Egypt, where resources are limited.

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Key words: Age platelet index; Aspartate aminotransferase platelet ratio index; Aspartate aminotransferase-to-alanine aminotransferase ratio; Cirrhosis discriminating score; Fibrosis evaluation; Göteborg University Cirrhosis Index; Hepatitis C virus infection; Liver fibrosis; Pohl score

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INTRODUCTION

Egypt has the highest prevalence of adult hepatitis C virus (HCV) infection in the world, affecting an average of 15%-25% of the population in rural communities[2]. Worldwide, HCV is one of the major causes of chronic liver diseases, which include inflammation, fibrosis and cirrhosis. Furthermore, HCV has been associated with increased morbidity and mortality in hepatocellular carcinoma[3-5]. Although liver biopsy is an invasive procedure and includes a risk of complications, such as pain, pneumothorax, puncture of other viscera and hemorrhage, it is still the gold standard for grading the severity of necro-inflammation and staging the extent of liver fibrosis in patients with chronic HCV infection[6-8].

In addition to the added cost, liver biopsy cannot be performed universally in all patients with impaired hemostasis of any origin[9]. The procedure is known to underestimate liver fibrosis when small tissue samples are collected, and it is prone to intra- and inter-observer variation[10-13]. Moreover, several studies have suggested that liver biopsy is far from being a perfect diagnostic tool because its accuracy in detecting pathology is dependent on the size of the biopsy[14-17]. Previous reports have proposed that a liver biopsy sample should contain a minimum of 5 portal tracts and be at least 15 mm in length to be considered adequate[18-20]. Other authors have recommended even larger samples[21]. In 2003, a French survey reported that liver biopsy may be refused by up to 59% of patients[22]. In 2005, an Italian survey reported major discrepancies among hepatologists regarding when and how to take a liver biopsy from the same subgroup of chronic hepatitis C patients[23].

Considering these limitations, many studies have recently focused on the development of non-invasive markers as surrogates of liver biopsy[24-34]. An accurate assessment of hepatic fibrosis can be achieved with various markers and indices. In this study, we aimed to assess the assessment of hepatic fibrosis can be achieved with various markers as surrogates of liver biopsy in patients with chronic HCV infection in a country known to have a high prevalence of the disease[1,2].

MATERIALS AND METHODS

Patients

This study included 154 patients with chronic HCV infection. They were selected from the gastroenterology and hepatology clinics of the Faculty of Medicine, Cairo University, Egypt, over the period from March 2009 to November 2010. All selected patients were potential candidates for interferon therapy.

Exclusion criteria

Patients with chronic hepatitis B infection, autoimmune hepatitis, decompensated liver disease, hepatocellular carcinoma, history of previous antiviral therapy and presence of absolute contraindication for liver biopsy were excluded from this study.

Methods

All patients were subjected to full history intake, thorough physical examination and the following laboratory test measurements: serum ALT, AST, albumin, total bilirubin, prothrombin time and concentration, complete blood count, HCV antibody (anti-HCV), hepatitis B surface antigen (HBsAg), HCV-RNA by quantitative polymerase chain reaction (PCR), circulating autoantibodies (ANA, ASMA), abdominal ultrasonography and ultrasonographic guided liver biopsy.

Liver biopsies were performed using 18-20 gauge Trucut needles (GMSN.N, GHATWARY MEDICAL). To assess necroinflammation, the grade of activity was evaluated using a modified hepatic activity index: mild (0-6), moderate (7-12) and severe (13-18). Fibrosis was staged according to the METAVIR scoring system from F0 to F4. Based on the results obtained from histopathological assessment of their liver biopsies, patients were divided into two groups: the non-cirrhotic group (F0, F1, F2 and F3) and the cirrhotic group (F4).

Definition of the noninvasive indices

The following ratios, scores and indices[24-34] were calculated and compared with the results of histopathological examination: (1) AAR; (2) APRI, calculated using the following equation: (AST/upper limit of normal)/platelet count × 10; (3) API, calculated by summing the scores awarded for the following patient laboratory results (a possible value of 0-10): age (in years) < 30 = 0; 30-39 = 1; 40-49 = 2; 50-59 = 3; 60-69 = 4; 70 = 5; (4) CDS, calculated by summing the scores awarded for the following patient laboratory results (a possible value of 0-11): platelet count (× 10^9/L) < 100 = 0; 100-119 = 1; 120-139 = 2; 140-159 = 3; 160-179 = 4; > 180 = 5; (5) GUCI, calculated using the following equation: normalized AST × INR × 100/platelet count (× 10^9/L); and (6) Pohl score, which was considered positive if the AAR was ≥ 1 and the platelet...
Demographic and baseline laboratory data of non-cirrhotic and cirrhotic patients are shown in Table 1. Our findings demonstrated a statistically significant correlation for AAR, APRI, API, GUCI and Pohl score between the cirrhotic and non-cirrhotic patients; CDS was not found to be significant. Pohl score was positive (indicating cirrhosis) in 40% of cirrhotic patients, whereas it was positive in only 9.67% of non-cirrhotic patients, with a P value of 0.004 (Figure 1 and Table 2).

Patient age, AST and platelet count correlated significantly with both the grade of activity and the stage of fibrosis. However, neither ALT nor HCV RNA load demonstrated statistically significant correlations with the grade of activity or the stage of fibrosis. With regard to other laboratory parameters, INR, albumin and alkaline phosphatase levels were significantly correlated with stage of fibrosis but not with grade of activity, whereas serum bilirubin was significantly correlated with grade of activity but not with stage of fibrosis (Table 3).

The results of our study revealed a significant correla-
tion between APRI, API and GUCI, and both the grade of activity and the stage of fibrosis. CDS correlated significantly with the stage of liver fibrosis but not with the grade of necroinflammatory activity. In contrast, the AST/ALT ratio had no significant correlation with either the stage of fibrosis or the grade of activity (Table 4).

For non-invasive diagnosis of liver cirrhosis (F4), using AAR, APRI, API and GUCI, Table 5 and Figure 2 show the cutoff values, sensitivity, specificity, positive predictive values (PPV), negative predictive values (NPV), and area under the receiver operating characteristics curve of these parameters.

### DISCUSSION

Although it is costly, requires hospitalization for at least 6-18 h, is invasive and carries a risk of complications with an associated morbidity rate of 0.3% and 0.6% and mortality rate of 0.05%, liver biopsy remains the gold standard for assessing liver histology. However, limitations of liver biopsy include the underestimation of fibrosis stage, given that only 1/50 000 of the organ is removed, and the reported inter- and intra-observer discrepancies rates of 10%-20%.

In this study, we found that the optimal cutoff AAR-value for diagnosing cirrhosis was ≥ 1.2, with a sensitivity of 46%, specificity of 88.7% and PPV and NPV of 50% and 87.3%, respectively. These results support previous findings by Giannini et al, who recommended an AAR value of ≥ 1 as a cutoff value for diagnosing cirrhosis. However, Ehsan et al reported a higher cutoff value (≥ 1.5) for diagnosing cirrhosis, with a sensitivity of 44% and a specificity of 91%.

Elevation of the AST/ALT ratio in cirrhotic patients may be explained by the reduction in AST clearance, which leads to an increase in serum AST levels. In addition, advanced liver disease may be associated with mitochondrial injury, resulting in increased release of AST present in the mitochondria and cytoplasm.

Thrombocytopenia in patients with advanced fibrosis may be due to reduced hepatic production of thrombopoietin, increased splenic sequestration of platelets secondary to portal hypertension or the myelosuppressive action of HCV.

Results from the current study revealed a significant correlation between APRI and both the stage of liver fibrosis and the grade of activity. The optimal cutoff APRI value for the diagnosis of cirrhosis was ≥ 1.36, which was consistent with findings by Ichino et al and Ehsan et al, who reported cutoff values of 1.3 and 1.5, respectively.

In the present study, we found a significant correlation between API and both the stage of fibrosis and the grade of activity (P < 0.001 for both). Our results revealed that the optimal AP index cutoff value for the diagnosis of cirrhosis was ≥ 5.5, with 60% and 80.6% sensitivity and specificity, respectively, and 42.86% and 89.29% PPV and NPV, respectively. The results of the current study are in agreement with the results of previous studies by Lackner et al and Poynard et al.

Results from this study showed that there was a significant correlation between GUCI and both the stage of liver fibrosis and the grade of activity. We recommend a GUCI value of ≥ 1.56 as an optimal cutoff value for
the diagnosis of cirrhosis, with 60% sensitivity, 88.7% specificity, and a PPV and NPV of 89.83% and 80.52%, respectively. These results supported those reported by Islam et al. who found a significant correlation between GUCI and both stage of fibrosis and grade of activity. Similar results were reported by Ehsan et al. who recommended a GUCI cutoff value of $\geq 1.5$ for the diagnosis of cirrhosis, with 89% specificity and 74% sensitivity.

In the present study, we found a statistically significant correlation ($P = 0.004$) between positive Pohl score (AAR $\geq 1$, and platelet count $< 150 \times 10^3/\text{L}$) and the presence of cirrhosis (F4). These findings supported the results of Pohl et al. and Lackner et al. who confirmed the diagnostic accuracy of the Pohl score in significant fibrosis and cirrhosis.

In our study, there was a significant correlation between CDS and stage of liver fibrosis ($P < 0.001$), but the relationship was not significant with regard to the grade of activity ($P = 0.056$). The CDS values were not significant between the cirrhotic and non-cirrhotic patients ($P = 0.17$), which disagreed with results reported by Ichino et al. who recommended a CDS value of $\geq 8$ as a cutoff value for the diagnosis of cirrhosis.

Some studies showed no correlation between the histological outcome and HCV-RNA levels, while other reports suggested that the viral titer may influence the severity of liver damage and that high titer viremia correlates with the most severe liver damage. The current study revealed no significant correlation between HCV RNA load as measured by quantitative PCR and both the grade of activity and fibrosis stage.

Our results agreed with the studies conducted by Lee et al. and Saleem et al. In contrast, Kato et al. found significantly higher HCV RNA loads in patients with chronic active hepatitis and cirrhosis compared to those with chronic persistent hepatitis. These discrepancies could be attributed to the fact that serum HCV RNA load is not a stable parameter because it fluctuates. In addition, a high amount of circulating HCV does not always imply a more active state of viral replication in the liver nor does it indicate a more severe degree of liver disease. HCV is known to replicate both within the liver as well as in extra-hepatic sites.

In conclusion, the API index, APRI, AST/ALT ratio and GUCI showed good accuracy, moderate sensitivity, and high specificity for the diagnosis of early cirrhosis. These measures also demonstrated significant correlation with both the stage of liver fibrosis and the grade of activity. The combination of these non-invasive biochemical markers may replace the requirement for liver biopsy, particularly for cases with cirrhosis or early cirrhotic changes in which the procedure has known limitations and complications.

**COMMENTS**

**Background**

Hepatitis C virus (HCV) is one of the major causes of chronic liver diseases worldwide. It has been associated with increased morbidity and mortality in hepatocellular carcinoma. In patients with chronic HCV infection, liver biopsy is essential to the assessment of hepatic fibrosis. Evaluating the degree of fibrosis is an important step in determining the need and priority for treatment with antiviral drugs. However, liver biopsy is a costly and invasive procedure with a risk of complications and a tendency to underestimate liver fibrosis. Hence, alternative non-invasive diagnostic tools are needed.

**Research frontiers**

In the area of liver cirrhosis assessment, the focus of research is on how to use biochemical markers and indices [aspartate aminotransferase (AST) / alanine aminotransferase (ALT) ratio (AAR), AST to platelet ratio index (APRI), age platelet index (API), cirrhosis discriminating score (CDS), Göteborg University Cirrhosis Index (GUCI) and Pohl score] calculated from simple routine laboratory tests, such as serum levels of bilirubin, ALT, AST, albumin and platelet count, to determine the severity of liver fibrosis and to evaluate their accuracy in comparison to liver biopsy.

**Innovations and breakthroughs**

The results showed that APRI, API, GUCI and CDS were significantly correlated with the degree of liver fibrosis. AAR, APRI, API, GUCI and Pohl score can accurately diagnose early liver cirrhosis. AAR and GUCI gave the highest accuracy for the diagnosis of liver cirrhosis (80.5%). These simple biochemical markers, especially when used in combination, may decrease the use of liver biopsy in the assessment of fibrosis and diagnosis of cirrhosis in patients with chronic HCV infection.

**Applications**

The study results suggest that these biochemical markers can identify significant fibrosis and cirrhosis in patients with chronic HCV; their combined application may decrease the need for liver biopsy, thereby reducing its associated costs and complications. Important fields for further study include the use and evaluation of these markers for repeated assessment in monitoring the progression of liver fibrosis and its regression following interferon treatment in patients with chronic hepatitis C.

**Terminology**

CDS, GUCI and Pohl score are indices calculated to develop noninvasive diagnostic markers of liver fibrosis depending on simple biochemical tests such as platelet count, AST and ALT.

**Peer review**

In this paper, the authors focused on the noninvasive assessment of liver fibrosis in Egyptian patients with chronic HCV infection using different indexes. It is potentially interesting and well-written and provides useful information in a selected population with a high prevalence of chronic HCV infection.

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**Table 5 The accuracy of different ratios and indices in the diagnosis of early liver cirrhosis**

| Item       | Cutoff value | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) | Accuracy (%) | AUROC | $P$ value |
|------------|--------------|----------------|----------------|---------|---------|--------------|-------|-----------|
| AAR        | 1.2          | 46             | 88.7           | 50      | 87.3    | 80.5         | 0.761 | 0.002     |
| APRI       | 1.36         | 46.7           | 87.1           | 46.7    | 87.1    | 79.2         | 0.697 | 0.018     |
| API        | 5.5          | 60             | 80.6           | 42.9    | 89.3    | 76.6         | 0.826 | 0.000     |
| GUCI       | 1.56         | 60             | 85.5           | 50      | 89.8    | 80.5         | 0.783 | 0.001     |
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