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Systematic review

APRI test and hyaluronic acid as non-invasive diagnostic tools for post HCV liver fibrosis: Systematic review and meta-analysis

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ABSTRACT

Background and study aims: Hepatitis C virus (HCV) accounts for a sizable proportion of chronic liver disease cases and represents the most common indication for liver transplantation. Precise diagnosis of hepatic fibrosis stage is considered a funnel-neck in proper management and follow-up of HCV-infected patients. Given the possible complications of liver biopsy, a non-invasive method for assessing hepatic fibrosis is needed. This study aimed to evaluate the diagnostic accuracy of APRI and hyaluronic acid as non-invasive diagnostic assessment tools for post HCV liver fibrosis.

Patients and methods: Systematic literature searching identified studies performed on Egyptian territory to evaluate APRI and hyaluronic acid as non-invasive tests of fibrosis and using liver biopsy as the reference standard. Meta-analysis was performed for areas with an adequate number of publications. Validation of meta- analysis on APRI was done on a subset of 150 treatment-naïve post-hepatitis C patients.

Results: Both APRI and hyaluronic acid have superior predictive power for hepatic cirrhosis (F4) than for significant fibrosis (F2-F3). The pooled estimate for sensitivities and specificities of APRI and hyaluronic acid to diagnose F4 were (84% and 82%) and (83% and 89%) respectively. In the subgroup of treatment naïve post-hepatitis C patients, APRI had higher diagnostic performance to diagnose liver cirrhosis with 93.8% sensitivity and 72.4% specificity (AUC; 0.908, 95%CI; 0.851–0.965, p-value; <0.001) compared to its accuracy to diagnose significant hepatic fibrosis with 65.1% sensitivity and 77.8% (AUC; 0.685, 95% CI; 0.59–0.78, p-value; 0.001).

Conclusion: APRI score and hyaluronic acid levels are simple and reliable non-invasive markers to detect advanced fibrosis among post-hepatitis C patients.

Introduction

Chronic hepatitis C (CHC) infection is a major health problem worldwide with nearly 180 million people around the world (~3% of the population) currently infected with hepatitis C virus (HCV). Prevalence of infection differs significantly by region, ranging from 0.1% to 20%, however, solid epidemiological data are subtle on account of the asymptomatic nature of HCV and the absence of screening projects in many countries [1–3].

The World Health Organization (WHO) indicated that Egypt has the highest prevalence of HCV, where the results of blood screening and testing for the Egyptian blood donors showed 20% positive for HCV (GAR-WHO, n.d.). The most prevalent genotype in Egypt is genotype 4 at a rate of 86% followed by genotype 1 at 6%, genotype 3 at 3% and genotype 2 at 1% respectively [4]. Recent national survey elucidated that there has been about 30% reduction in HCV prevalence among Egyptian population during the period between 2008 and 2015 [5].

Accurate diagnosis of hepatic fibrosis stage is a funnel-neck in managing HCV patients as with the treatment of CHC patients at early to moderate fibrosis stage fibrosis can regress and possibly even resolve after eradication of the causative agent [6]. As well as, early diagnosis of liver cirrhosis is highly important to prevent life-threatening complications by enrolment of patients with liver cirrhosis into oesophageal varices and hepatocellular carcinoma (HCC) surveillance programs, which are associated with improved overall survival [7].

In light of limitations of liver biopsy as "gold standard" tool for assessment of hepatic fibrosis stage, several non-invasive markers

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of liver fibrosis have been developed [8–10]. The aspartate aminotransferase-to-platelet ratio index (APRI) is calculated in the following way: APRI = [AST level (/ULN)/Platelet counts (109/L)] × 100 and is one of the simplest marker panels that can diagnose significant fibrosis and cirrhosis with acceptable accuracy [9]. The WHO guidelines on the evaluation of the degree of liver fibrosis and cirrhosis in hepatitis C patients recommended that "In resource-limited settings, APRI test could be used for the assessment of hepatic fibrosis rather than other noninvasive tools that require more resources such as elastography or Fibrotest" [11]. Similarly, several studies have proven the usefulness of serum hyaluronic acid level as a non-invasive marker of liver fibrosis or cirrhosis in HCV-infected patients [12,13].

Considering the high incidence rates of HCV infection in Egypt as well as, limited country resources for expensive diagnostic modalities which need highly experienced operators to measure hepatic fibrosis stage (such as elastography), the need for non-invasive, affordable, and credible diagnostic markers for hepatic fibrosis assessment deemed important.

The aim of current work is to evaluate the diagnostic value of the APRI test and hyaluronic acid as non-invasive predictors of post-hepatitis C liver fibrosis in Egyptian patients by performing a systematic review and *meta*-analysis on relevant research material. The results of *meta*-analysis then validated on a subset of treatment naïve chronic hepatitis C patients.

Methodology

Search strategy

A systematic web-based literature search of all publications in Midline (PubMed) and Google Scholar, as well as the Egyptian National S&T Information Network (ENSTINET) was conducted on February 2013 using several combinations of the keywords (hepatic fibrosis, chronic hepatitis C and Egyptian patients). Libraries of (Kasr EL-Aini, Ain Shams, El Mansoura, and National Hepatology Institute) and a reference list of reviews were searched manually for additional relevant studies. Consultation with experts in the field also was performed to identify additional published and unpublished primary studies, the search was conducted by two independent researchers with disagreements resolved by mutual discussion. All the studies from electronic and hand aided search was revised to prevent duplication of the studies.

Inclusion and exclusion criteria

All candidate articles from our primary search had their abstract or full text scrutinised to determine whether they were primary studies. Then, the full text was additionally assessed to check for the fulfilment of the inclusion/exclusion criteria. Disagreements were resolved through consensus. Inclusion/exclusion criteria for primary studies required the following features:

(i) A detailed description of an adult with chronic hepatitis C under study.
(ii) A minimum number of chronic hepatitis C subjects ≥30
(iii) Description of liver biopsy as the reference standard. Fibrosis staging based on Metavir test: F0 = no fibrosis; F1 = portal fibrosis with no septa; F2 = few septa; F3 = numerous septa without cirrhosis; and F4 = cirrhosis [14].
(iv) Description of APRI test and hyaluronic acid as an index test.
(v) Patients subjected to liver biopsy as well as APRI test and/or hyaluronic acid level assessment.
(vi) Biomarkers assessed blind to the biopsy result.
(vii) Both prospective and retrospective studies were acceptable.

Exclusion criteria were limited to duplicate publications of a primary study that contained all or some of the original data, in this situation, the updated manuscript was to be chosen, assuming the relevant data for *meta*-analysis were available.

A final number of 8 articles for APRI test and 6 studies for Hyaluronic acid were found to fulfil our inclusion criteria with a relevant methodology.

Outcome measures

The primary outcome of our analysis was to determine the diagnostic performance of APRI test and hyaluronic acid for detection of significant fibrosis (F2-3) or cirrhosis (F4) compared with the reference standard of liver biopsy. Sensitivity and specificity with 95% confidence interval (CI) values were reported for individual studies.

Data extraction

The required information from primary studies was extracted by 2 independent researchers. Data included patients' age, gender, details of test and reference ranges, histologic fibrosis stage, diagnostic threshold (or cut-offs) values used for detecting different hepatic fibrosis stages, test performance characteristics, reasons for participant exclusion, and methods for handling indeterminate or missing data. A 2 × 2 table was constructed for APRI test as well as for Hyaluronic acid with reported cut-off for diagnosing significant fibrosis and frank liver cirrhosis.

Methodological quality assessment

Each of the studies meeting inclusion criteria was analysed by two independent reviewers, data was presented following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines [15]. The PRISMA checklist can be found in S1. The consensus was reached in disagreements by referral to a third reviewer.

Data analysis

For the meta-analysis, from the 2 × 2 tables, the sensitivity and specificity were calculated. The estimates of sensitivity and specificity with their 95% confidence interval (CI) were plotted in paired forest plots. The heterogeneity of diagnostic test was evaluated using a chi- square test of homogeneity and the inconsistency index (I_2). The I_2 statistic is defined as the percentage of variability as a result of heterogeneity beyond that from chance, with values >50% representing the possibility for substantial heterogeneity. Given that we had moderate to high heterogeneity based on I_2 index, we used the random effects modelling to the average effect size accounting for between study variation as well as, we performed subgroup analysis.

Pooled estimates of sensitivity and specificity along with their 95% CI were determined using random effect modelling approach to account for study size and between-study heterogeneity.

Subgroup analysis

Validation of results from the meta-analysis on APRI test was done by performing a prospective case series study on 150 treatment naïve chronic hepatitis C patients (93 males and 57 females) with overall mean age of (43 ± 11) attended the outpatient clinic of Ahmed Maher hospital during the period from January 2014 to September 2014. An ultrasound-guided liver biopsy was performed to all patients after taking their informed consent and when platelets count and coagulation profile within acceptable

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