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# Do serum markers of liver fibrosis vary by HCV infection in patients with alcohol use disorder?

Arantza Sanvisens[a], Alvaro Muñoz[b], Ferran Bolao[c], Paola Zuluaga[a], Magí Farré[d], Inmaculada Jarrin[e], Jordi Tor[a], Roberto Muga[a,*]

[a] Department of Internal Medicine, Hospital Universitari Germans Trias i Pujol, IGTP, Universitat Autònoma de Barcelona, Badalona, Spain
[b] Department of Epidemiology, Johns Hopkins University, Bloomberg School of Public Health, Baltimore, MD, USA
[c] Department of Internal Medicine, Hospital Universitari de Bellvitge, IDIBELL, Universitat de Barcelona, L'Hospitalet de Llobregat, Spain
[d] Department of Clinical Pharmacology, Hospital Universitari Germans Trias i Pujol, IGTP, Universitat Autònoma de Barcelona, Badalona, Spain
[e] Centro Nacional de Epidemiología, Instituto de Salud Carlos III, Madrid, Spain

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ABSTRACT

*Introduction:* HCV infection is frequent in patients with alcohol use disorder (AUD). Ethanol and hepatitis C have a synergistic effect that increases the risk of end-stage liver disease. We aimed to assess fibrosis of the liver in patients admitted to treatment of AUD.

*Methods:* Data were collected in two hospital units between 2000 and 2014. Liver fibrosis was assessed by serum biomarkers APRI, FIB-4 and Forns, and Advanced Liver Fibrosis (ALF) was defined if APRI > 1.5, FIB-4 > 3.25 or Forns > 6.9. Correlations were analyzed by Pearson's coefficients and logistic regression models were used.

*Results:* 1313 patients (80% M) had complete data; age at admission was 45 years (IQR: 39–52 yrs), age of initial regular alcohol consumption was 20 years (IQR: 17–26 yrs) and the amount of alcohol consumed preceding admission was 200 g/day (IQR: 120–270 g/day). Prevalence of HCV infection was 18%. Prevalence of ALF in HCV positive patients was 40.6% by APRI, 30.6% by FIB-4, and 43.3% by Forns. Correlations were high for APRI vs. FIB-4 r = 0.906, APRI vs. Forns r = 0.710, and, FIB-4 vs. Forns r = 0.825. There was no significant difference in the APRI/FIB-4 correlation by HCV status (z = 1.35, p = 0.177). However, the APRI/Forns correlation was significantly higher in HCV positive patients (p < 0.001). Patients with HCV infection were two times more likely to present with ALF at admission (OR = 2.1, 95%CI:1.5–3.1).

*Conclusions:* HCV infection is associated with severity of fibrosis in patients with excessive alcohol consumption. In this context, APRI and FIB-4 are highly correlated which facilitates the assessment of liver damage.

## 1. Introduction

Excessive alcohol consumption is the third leading cause of premature death in western countries, and cirrhosis of the liver accounts for approximately 1%–2% of all deaths in Europe. Alcohol use disorder (AUD) and hepatitis C virus (HCV) infection frequently co-occur (Shoreibah et al., 2014; Singal et al., 2011). In fact, alcohol and HCV infection are the leading causes of end-stage liver disease and the most common indication for liver transplant in the US and Europe (Zakhari, 2013).

AUD has been associated with a greater exposure to HCV infection, with an increased risk of viral persistence, and with more extensive damage of the liver. A recent systematic review of 24 studies found that the average prevalence of HCV infection among patients with AUD was 16.3% (Novo-Veleiro et al., 2013). The combined effect of HCV infection and ethanol consumption in humans affects various host cells and has been associated with alterations in the modulation of Reactive Oxygen Species production, in the lipopolysaccharide signaling pathway, and in cytokine production; these molecular alterations eventually generate an environment of hepatocellular injury that will impair the normal antiviral immune responses and activation of cell proliferation (Szabo et al., 2010).

Besides HCV infection, alcoholic liver disease (ALD) represents a spectrum of liver damage that begins with fatty liver changes in the majority of individuals who participate in excessive alcohol consumption. In this context, up to 20–40% of heavy drinkers will develop

*Abbreviations:* AUD, alcohol use disorder; HCV, hepatitis C virus; ALD, alcoholic liver disease; APRI, Aspartate aminotransferase/Platelet Ratio Index; AST, aspartate aminostransferase; ALT, alanine aminotransferase; GGT, gamma glutamil transferase; ALF, advanced liver fibrosis; IQR, Inter Quartile Range; OR, odds ratio

* Corresponding author at: Department of Internal Medicine, Hospital Universitari Germans Trias i Pujol, Universitat Autònoma de Barcelona, 08916 Badalona, Spain.
*E-mail address:* rmuga.germanstrias@gencat.cat (R. Muga).

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fibrosis of the liver and, in 8-20% of cases, the disease will progress to end-stage liver disease (Bataller and Gao, 2015). A challenge to establishing early diagnosis of ALD is that patients will remain asymptomatic at the beginning of excessive alcohol consumption.

Evaluating the severity of liver damage is of paramount importance in individuals linked to the treatment of AUD in order to prevent advanced disease. In fact, liver disease is the main cause of death in individuals with AUD (Rivas et al., 2013; Timko et al., 2006), and a recent study concluded that liver disease was the leading cause of death among those with and without HCV infection (Fuster et al., 2015).

In both HCV-related liver disease and ALD, fibrosis of the liver is the main prognostic factor for developing cirrhosis (Lingala and Ghany, 2015; Szabo et al., 2010; Westbrook and Dusheiko, 2014). Liver biopsy has been the standard diagnostic method for the assessment of inflammation and fibrosis for decades, but individuals with substance use disorder have not been regularly subjected to invasive procedures. In addition, several non-invasive methods for the direct and indirect measurement of fibrosis, including serum biomarkers, have been found to be reasonably accurate at the extremes of histological fibrosis (Fontana et al., 2008; Forns et al., 2002; Sanvisens et al., 2009; Sterling et al., 2006; Vallet-Pichard et al., 2007; Wai et al., 2003).

Over the past years, both FIB-4 and the Aspartate aminotransferase/Platelet Ratio Index (APRI) have been validated against liver biopsy in detecting either the absence or the presence of advanced liver fibrosis in HCV-infected patients and as prognostic markers in longitudinal studies (Kassaye et al., 2015; Sterling et al., 2006; Vergniol et al., 2011; Wai et al., 2003). However, clinical outcomes of AUD patients being analyzed with serum markers of fibrosis are scarce.

Transient elastography is widely used to assess fibrosis in ALD, but the presence of steatosis may also distort results, leading to overestimation of fibrosis (Mueller et al., 2010). Existing information on the benefit of serum biomarkers has been summarized in the European Association for the Study of the Liver Guidelines for ALD and in several reviews (Chrostek and Panasiuk, 2014; European Association for the Study of Liver, 2012; Parkes et al., 2012). Of note, the majority of studies analyzing the impact of chronic HCV infection and ALD are conducted in liver units, which may favor the selection of patients towards those with more advanced, clinically symptomatic liver disease.

In this study, we aimed to assess fibrosis of the liver with laboratory-derived serum biomarkers in well characterized patients linked to the treatment of AUD. In doing so, we also explored the potential for correlations between biomarkers and their clinical utility in patients with and without HCV infection.

## 2. Material and methods

### 2.1. Study design

A cross-sectional study of patients admitted for the treatment of AUD was performed in two hospital-based units located in metropolitan Barcelona, Spain: Hospital Universitari de Bellvitge in L'Hospitalet de Llobregat, and Hospital Universitari Germans Trias i Pujol in Badalona. All patients were consecutively admitted between January 2000 and December 2014.

Participants gave written informed consent and the study was approved by the Ethics Committees of the participant hospitals. The methods used in this study complied with the ethical standards for medical research and principles of good clinical practice defined by the World Medical Association's Declaration of Helsinki. Fig. 1 depicts the flow chart of the subgroup comprising the study population. After application of exclusion criteria, the study population included 1313 patients of whom 236 (18%) were HCV-RNA positive.

#### 2.1.1. Clinical assessment and treatment

Patients were referred to the hospital facility (addiction unit) by primary care physicians and specialists in addiction medicine at community-based outpatient clinics. All patients received a diagnosis of alcohol dependence according to the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV; American Psychiatric Association, 2000).

On the day of admission, patients underwent an interview including questions on the evolution of alcohol consumption and other substance use (i.e., cocaine, opiates). The history of alcohol consumption included quantity, frequency and duration of the AUD. Alcohol consumption was quantified in grams of ethanol per day. Current use of other substances was ascertained by urine detection at admission. Anthropometric data (height and weight) were obtained as well.

In all cases, blood samples were drawn for biochemical and hematological parameters including liver function tests [aspartate aminostransferase (AST), alanine aminotransferase (ALT), gamma glutamil transferase (GGT) and total bilirubin].

HCV diagnosis was based on enzyme immunoassay (EIA) analysis and positive tests were confirmed using HCV RNA (real time Polymerase Chain Reaction). Patients with positive HCV-RNA results were considered to have ongoing infection.

Pharmacologic treatment during admission included benzodiazepines, vitamin B complex and other pharmacotherapy, depending on medical co-morbidities and severity of alcohol withdrawal syndrome.

On average, the length of stay was six days and, at discharge, patients were encouraged to follow up at their outpatient clinic. Other details regarding admission for the treatment of AUD can be found elsewhere (Fuster et al., 2015; Zuluaga et al., 2016).

Serum markers of liver fibrosis:

The indexes of fibrosis were calculated as follows

APRI index:

$$APRI = \frac{AST\,[U/L]/UpperLimitAST\ \ [U/L]}{Platelet\,[10^9/L]} \times 100$$

For the purposes of this study, the upper limit of AST was 35 U/L. APRI values between 0.5 and 1.5 were considered mild/moderate fibrosis; values greater than 1.5 were considered Advanced Liver Fibrosis (ALF) (Wai et al., 2003).

FIB-4 index:

$$FIB4 = \frac{Age\ [years] \times AST\,[\mathrm{U/L}]}{Platelet\ [10^9/\mathrm{L}] \times \sqrt{ALT\,[\mathrm{U/L}]}}$$

FIB-4 values between 1.45 and 3.25 were considered mild/moderate fibrosis; values above 3.25 were considered to be ALF (Sterling et al., 2006).

Forns index:

$$Forns = 7.811 - 3.131 \times \ln\,(Platelet\,[10^9/\mathrm{L}]) + 0.781 \times \ln\,(GGT\,[\mathrm{U/L}]) + 3.467 \times ln(Age\,[years]) - 0.014 \times Cholesterol\,[\mathrm{mg/100\,mL}]$$

Forns values between 4.2 and 6.9 were considered mild/moderate fibrosis; values greater than 6.9 were considered to be ALF (Forns et al., 2002).

### 2.2. Statistical analysis

Descriptive statistics were expressed in median values (Inter Quartile Range [IQR]) for quantitative variables and as absolute frequencies and percentages for qualitative variables. We used the chi-square test to detect significant differences in qualitative variables and *t*-test was used for mean differences in quantitative variables.

Relationships between indexes of fibrosis were explored using Pearson's correlation coefficient. In order to make comparisons, we normalized them using a logarithmic transformation. To assess the differences between correlation coefficients, Fisher r-to-z transformation (i.e., $z = 0.5*\ln[(1 + r)/(1 - r)]$) was used.

Logistic regression models were used to assess the role of HCV infection as a predictor of ALF according to APRI, FIB-4 and Forns