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Serum tests, liver stiffness and artificial neural networks for diagnosing cirrhosis and portal hypertension

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ABSTRACT

Background: The diagnostic performance of biochemical scores and artificial neural network models for portal hypertension and cirrhosis is not well established.
Aims: To assess diagnostic accuracy of six serum scores, artificial neural networks and liver stiffness measured by transient elastography, for diagnosing cirrhosis, clinically significant portal hypertension and oesophageal varices.
Methods: 202 consecutive compensated patients requiring liver biopsy and hepatic venous pressure gradient measurement were included. Several serum tests (alone and combined into scores) and liver stiffness were measured. Artificial neural networks containing or not liver stiffness as input variable were also created.
Results: The best non-invasive method for diagnosing cirrhosis, portal hypertension and oesophageal varices was liver stiffness (*C*-statistics = 0.93, 0.94, and 0.90, respectively). Among serum tests/scores the best for diagnosing cirrhosis and portal hypertension and oesophageal varices were, respectively, Fibrosis-4, and Lok score. Artificial neural networks including liver stiffness had high diagnostic performance for cirrhosis, portal hypertension and oesophageal varices (accuracy > 80%), but were not statistically superior to liver stiffness alone.
Conclusions: Liver stiffness was the best non-invasive method to assess the presence of cirrhosis, portal hypertension and oesophageal varices. The use of artificial neural networks integrating different non-invasive tests did not increase the diagnostic accuracy of liver stiffness alone.

1. Introduction

In the natural history of any chronic liver disease the diagnosis of cirrhosis and portal hypertension is essential for management and prognosis. The occurrence of complications is mainly related to portal hypertension, which is best evaluated by hepatic venous pressure gradient (HVPG) [1]. Historically, liver biopsy was considered the "gold standard" in the diagnosis of different stages of chronic liver diseases, but its value is currently questioned due to sampling error, lack of standards or intra and interobserver agreement [2]. The diagnosis of cirrhosis is now based on histological, clinical, and haemodynamic findings [3].

Usually, the complications of cirrhosis occur when HVPG is higher than 10 mmHg – the threshold defining clinically significant portal hypertension (PH) [4] – therefore, HVPG is an excellent prognostic indicator of decompensation [5]. However, the HVPG measurement is invasive and not widely available [6]. As stated in the last Baveno consensus conferences, non-invasive markers of portal hypertension are required [7,8].

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In recent years, several serum tests and liver stiffness measurement by transient elastography have been able to evaluate the amount of fibrosis in chronic hepatitis, as an alternative to liver biopsy, and more recently some of them have been validated as markers of clinically significant PH and oesophageal varices (EV) [6,9–11].

Due to the complex processes in liver diseases and to frequent non-linear correlations between different markers and clinical outcomes, artificial neural networks (ANNs) were proposed in the diagnosis and prognostic of chronic liver diseases [12–14]. ANNs are computer models based on non-linear statistical analysis intended to identify relationships between input and output variables [12]. The performance of ANNs is comparable with the Cox proportional hazards models, but this model can be used even when the conditions for the Cox model are not met [13–16].

The aim of this study was to investigate whether ANNs might represent a new effective non-invasive strategy for the diagnosing cirrhosis and clinically significant PH from easily available non-invasive tests. To test this hypothesis, we investigated and compared the diagnostic performance of six different serum tests, of liver stiffness measured by transient elastography, and of ANNs in the diagnosis of cirrhosis, clinically significant PH and the presence of EV.

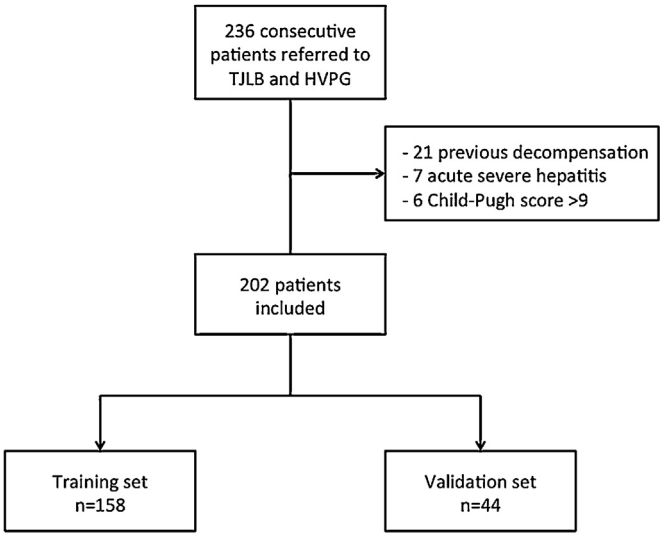

Fig. 1. Inclusion flowchart. TJLB, transjugular liver biopsy; HVPG, hepatic venous pressure gradient.

2. Materials and methods

2.1. Patients

Patients were included in this prospective diagnostic study if they had compensated long-lasting chronic liver diseases with suspicion of cirrhosis and portal hypertension based on clinical and laboratory data. Exclusion criteria were: previous decompensation of liver disease, hepatocellular carcinoma, Child–Pugh score over 9 points and presence of acute hepatitis (transaminases higher than 10-fold the upper limit of normal) since this is a well-known cause of increase liver stiffness independently of liver fibrosis.

All consecutive patients observed in a single tertiary reference centre in France for transjugular liver biopsy and HVPG measurement for the diagnosis of cirrhosis and portal hypertension over a period two years were screened. In order to build the ANNs and validate their performance, the included population was arbitrarily split using a random integer set generator into two groups: a training group including more than 75% of the population ($N = 158$) and a validation set ($N = 44$, Fig. 1).

Serological tests and liver stiffness measurement were performed on the day of HVPG measurement as detailed below. The diagnosis of cirrhosis was established by two senior hepatologists by using the following criteria: (1) histology: presence of F4 stage in Metavir classification [17] or (2) in case of F3 fibrosis with haemodynamic and/or clinical data suggesting cirrhosis. In case of disagreement, a third experienced hepatologist was asked to judge. All patients with cirrhosis have been screened for the presence of EV within 6 months of inclusion.

The study was designed according to the 2000 revision (Edinburgh) of the 1975 Declaration of Helsinki and was approved by the Ethical Committee. Written informed consent was obtained in all cases.

Haemodynamic measurements and liver biopsy were performed as previously described [4] and are details in Appendix A.

2.2. Serological scores of fibrosis

Fasting venous blood samples were collected from all patients in the same day as a HVPG measurement. The study included scores that are only based on usual biological parameters such as ALT, AST, platelets count, INR, albumin or bilirubin. The following blood tests were evaluated: aspartate aminotransferase/alanine aminotransferase index (AST/ALT index), aspartate aminotransferase-platelet ratio index (APRI), LOK score, Fibrosis 4 score (FIB-4), Goteborg University Cirrhosis Index (GUCI) and Risk Score. The scores were calculated according to the formulas published by the original authors [18–23]. The detailed formulas are available in Appendix A.

Liver stiffness was measured using transient elastography (Fibroscan®, Echosens, Paris, France) with the M probe according to the current guidelines and the methodology that was previously described (see also Appendix A) [24,25]. According to the available data [26] reliability criteria for liver stiffness were: IQR/median <0.30 and >60% success rate. According to a recent published meta-analysis, for the diagnosis of cirrhosis the 13.01 kPa cut-off was used [27]. For clinically significant PH and EV's presence two published cut-off values were used: 13.6 kPa [28], which favours sensitivity and 21.1 kPa [24], which has a greater specificity.

2.3. Artificial neural networks

The basic computing unit of the ANNs is the artificial neuron. Neurons of the ANNs are arranged in input, hidden and output layers [13]. Each neuron is interconnected with neurons of neighbouring layers. The input variables are fed to the input layer and their values are processed by the hidden layers up to the output layer that generates the outputs. Each neuron receives information from all neurons from the predecessor-neighbouring layer and, together with its own bias, computes its output and sends it to the neurons of the successor layer. The amplitude of the signal transmitted between neurons depends on the signal intensity emerging from the sending neuron and on the strength of their connection path, the latter being denoted as neural weight [13]. ANNs are capable of associating the input variables with the specific desired outcomes by finding the appropriate values of the neural weights and biases, a heuristic process called learning [29].

In this work, probabilistic ANNs were used for classifications. The ANNs training and performance evaluation have been performed using Statistica® 8 (StatSoft Inc., USA) software.

Only the variables correlated in univariate analysis with cirrhosis and HVPG were included in the ANNs. The input variables were: