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Screening for significant chronic liver disease by using three simple ultrasound parameters

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ABSTRACT

Objectives: Chronic liver diseases remain asymptomatic for many years. Consequently, patients are diagnosed belatedly, when cirrhosis is unmasked by lifethreatening complications. We aimed to identify simple ultrasound parameters for the screening of patients with unknown significant chronic liver disease.

Methods: Three hundred and twenty seven patients with chronic liver disease, liver biopsy, and ultrasound examination were included in the derivation set. 283 consecutive patients referred for ultrasound examination were included in the validation set; those selected according to the ultrasound parameters identified in the derivation set were then referred for specialized consultation including non-invasive fibrosis tests and ultimately liver biopsy if liver fibrosis was suspected.

Results: In the derivation set, three ultrasound parameters were independent predictors of severe fibrosis: liver surface irregularity, spleen length (>110 mm), and demodulation of hepatic veins. The association of ≥2 of the three above parameters provided 49.1% sensitivity and 86.9% specificity. In the validation set, at ≥2 of the three parameters were present in 23 (8%) of the patients. Among these patients, 8 had liver fibrosis ($F \geq 1$), 5 had significant fibrosis ($F \geq 2$) and two cirrhosis.

Conclusion: The generalized search of three simple ultrasound signs in patients referred for abdominal ultrasound examination may be an easy way to detect those with silent but significant chronic liver disease.

1. Introduction

The early detection of fibrosis is important for determining disease progression and postponing the evolution of chronic hepatitis into cirrhosis via the implementation of prompt and specific treatment [1]. However, as chronic liver disease can remain asymptomatic for a long time, numerous cirrhotic patients are diagnosed belatedly, when life-threatening complications start appearing.

Currently, histopathological examination of a liver biopsy remains the reference for liver fibrosis diagnosis and staging [2]. However, due to its limitations, liver biopsy cannot be widely performed in clinical practice [3–5].

Noninvasive methods for liver fibrosis diagnosis have been developed over the last decade. In this setting, blood fibrosis tests (FibroMeter®, Fibrotest®, Hepascore®) and transient elastography (Fibroscan®) have been shown to be accurate [6–10], and are now commonly used as first-intention tests for liver fibrosis diagnosis in chronic liver diseases. However, these tests are usually performed by a hepatologist to whom the patient has been referred following the appearance of symptoms suggestive of chronic liver disease. Thus the number of patient diagnosed early by these new tools, that is in the period before symptoms start appearing and during which preventative measures may be particularly beneficial, remains quite low in relation to the prevalence of the disease. This prevalence have been estimated to 2.8% in general population [11].

Many studies have identified the value of ultrasound (US) in providing information on liver fibrosis degree. Several US hemodynamic and morphological parameters have been associated with liver fibrosis, such as liver surface irregularity, different segmental ratios, the waveform of hepatic veins, a decrease in portal flow

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velocity, coarse echogenicity, and spleen length [12–17]. Moreover, abdominal US is widely used for various symptoms, and thus could be an excellent way to detect patients with signs evoking liver fibrosis or cirrhosis, who could then be referred to a liver specialists for confirmation of the diagnosis by blood fibrosis tests and/or transient elastography. To be feasible during a nonspecific US examination, these signs should be easy and quick to collect.

The aim of the present study was two-fold:

First to test simple signs, obtainable on every routine Ultrasound examination for their relevance in the detection of severe fibrosis, within a large cohort of patients with chronic liver disease and liver biopsy. Second, to evaluate if these signs were useful in order to detect liver fibrosis in a cohort of patient with no pre-test suspicion of liver disease.

2. Patients and methods

2.1. Patients

2.1.1. Derivation set

All patients with chronic liver disease hospitalized for a liver biopsy in the Hepato-Gastroenterology unit of our center between December 2001 and December 2009 were retrospectively included in the derivation set. Patients with complications of cirrhosis (ascites, variceal bleeding, systemic infection, hepatocellular carcinoma) were excluded as well as patients without any available US examination within 6 months of the liver biopsy.

2.1.2. Validation set

All consecutive patients referred to a US unit of our Radiology department between June 2012 and August 2012 for abdominal US examination, whatever the indication (abdominal pain, impaired general condition, urinary tract infections, etc.), were prospectively included in the validation set. Fig. 1 provides a flow chart of patient inclusion. 581 patients received an abdominal ultrasound examination for various symptoms during the three months of the inclusion period. Exclusion criteria were age <18 or >80 years, and any previously identified chronic liver or hematological disease.

The study was approved by the local ethics committee and informed consent was obtained from patients referred to hepatologist consultation.

2.2. Study design

2.2.1. Derivation set

All patients included in the derivation set had undergone liver biopsy and abdominal US study, including Doppler examination. The objective of the present work was to identify the US parameters associated with severe fibrosis as evaluated on liver biopsy.

2.2.2. Validation set

All patients included in the validation set had a US study, including Doppler examination. When the US signs identified in the derivation set suggested fibrosis, the patient was proposed noninvasive tests of liver fibrosis, i.e., blood test (FibroMeter®) and elastography (ARFI and Fibroscan®), and referred to a senior hepatologist. Ultimately, liver biopsy was proposed if the noninvasive fibrosis tests confirmed the suspicion of liver fibrosis.

2.3. Methods

2.3.1. Histological assessment

Histological evaluation of liver specimens was the reference for liver fibrosis in our study for all patients in the derivation set. In the validation set, it was performed only if judged as necessary by the hepatologist.

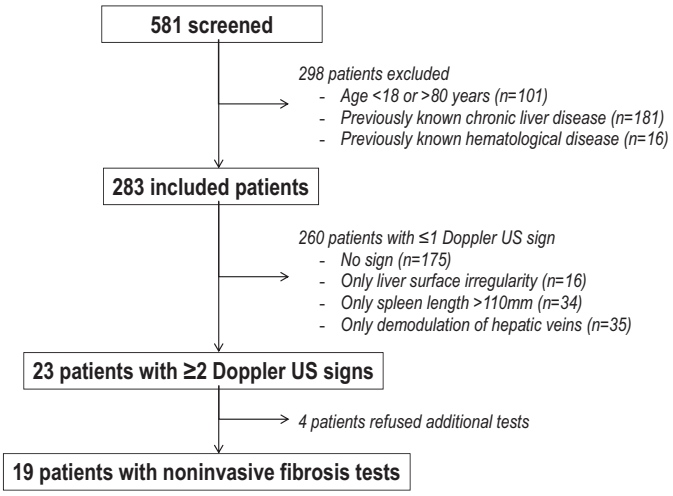

Fig. 1. Flow chart of the study.

Liver specimens were obtained by percutaneous liver biopsy using an 16-ga needle. A sample of at least 15 mm length was obtained. The histological reading was performed by an experienced senior pathologist, specialized in hepatology, and blinded for patient data and US findings. Fibrosis was evaluated according to Metavir *F* staging, i.e., *F*0: no fibrosis, *F*1: portal fibrosis without septa, *F*2: portal fibrosis with few septa, *F*3: portal fibrosis with numerous septa, *F*4: cirrhosis. Significant fibrosis was defined as Metavir $F \geq 2$, and severe fibrosis as Metavir $F \geq 3$.

However, as previously mentioned, liver biopsy is impaired by a false negative rate of 24% for the diagnosis of cirrhosis due to sampling errors, with most false-negative patients classified as *F*3. Consequently, to limit the possibility of misdiagnosis of at-risk patients, we chose severe fibrosis ($F \geq 3$) as the primary diagnostic target for the present study.

2.3.2. US Examination

Derivation set—Abdominal US examination was usually performed the day of liver biopsy using a Sequoia device (Siemens, Erlangen, Germany) with a 4–1 MHz curved probe for abdominal examination and a 8–15 MHz linear probe for liver surface examination. Operators were usually experienced radiologists (JL, CA) and were blinded for patient data, including histopathological findings.

The following seven parameters were recorded—*Liver surface irregularity* was detected on the anterior surface of the left lobe. *Maximal and mean portal flow velocity* measurement was realized with a sampling size approximately equal to the 2/3 diameter of the vessel with an angle kept at less than 60° between the Doppler beam and the axis of the vessel. *Hepatic vein Doppler* was performed on an intercostal scan plane, with a Doppler sample volume located within the middle or the right hepatic vein at least 3 cm from the outlet into the inferior vein cava to privilege the influence of hepatic changes on the hepatic vein waveform compared to that of the vena cava flow. During the measurement, patients had to maintain normal breathing, with no end-inspiratory or end-expiratory breath holding, which would result in a flattening of the hepatic vein waveform. According to the classification of Bolondi et al. we described three patterns of hepatic vein waveforms (HVW): normal triphasic waveform, biphasic oscillation with disappearance of the reversed flow phase, and flat monophasic waveform [13]. *Spleen length* was measured as the larger diameter through the hilum in a cranio-caudal axis. At this step raw values were kept, and secondarily a cut-off value was found for the validation set *Collateral circulation* was defined as any patent umbilical vein (i.e., diameter