Research Article

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Detection of early portal hypertension with routine data and liver stiffness in patients with asymptomatic liver disease: A prospective study

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Background & Aims: Detecting portal hypertension (PH) before the development of varices is important for prognosis and for designing interventional studies. None of the available strategies is used in practice. We evaluated a sequential screening-diagnostic strategy based on clinical data and transient elastography (TE) to detect PH in asymptomatic outpatients with liver disease.

Methods: Consecutive patients with chronic liver disease and no previous diagnosis of PH were screened by TE. Patients with liver stiffness (LS) $\geqslant$13.6 kPa were further evaluated by endoscopy and hepatic venous pressure gradient (HVPG). For analysis, patients were classified in 3 groups: group A, platelets $\geqslant$150,000/mm^3, normal abdominal ultrasound; group B, platelets <150,000/mm^3, normal ultrasound; group C, platelets <150,000/mm^3, abnormal ultrasound (splenomegaly, nodular liver surface).

Results: 250 patients were evaluated (69% group A, 20% group B, 11% group C). In 9% elastography was non-valid. LS $\geqslant$13.6 was found in 54 patients (8% A, 43% B, and 81% C, p <0.001). Endoscopy was performed in 49 of these: 20% had small varices, 0% high-risk varices. No patients from group A had varices, and 90% with varices belonged to group C. HVPG was obtained in 40 patients: 93% had PH (HVPG >5 mmHg) and 65% clinically significant PH (CSPH, HVPG $\geqslant$10). Only 3 patients, all from group A, had HVPG <5. All patients from groups B and C with LS $\geqslant$13.6 had PH. The LS 25 cut-off was excellent at ruling-in CSPH.

Conclusions: A simple strategy based on routine clinical data and TE could be useful to detect early PH among asymptomatic patients with chronic liver disease.

Keywords: Transient elastography; HVPG; Liver disease; Esophageal varices; Compensated cirrhosis; Non-invasive diagnosis.

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Abbreviations: HVPG, hepatic venous pressure gradient; CSPH, clinically significant portal hypertension; TE, transient elastography; US, ultrasonography; LS, liver stiffness; LSPS, liver stiffness*spleen diameter/platelet ratio; VRS, Variceal Risk Score; PHRS, Portal Hypertension Risk Score; INR, international normalized ratio; BMI, body mass index.

Introduction

The presence of a significant degree of portal hypertension is necessary for most of the clinical complications of liver cirrhosis to develop. It has been consistently shown [1] that the specific threshold for the development of such complications is a hepatic venous pressure gradient (HVPG) of 10 mmHg. Patients with an HVPG <10 mmHg are almost completely free of risk (as long as they stay below that value) and, conversely, all episodes of clinical decompensation occur in patients with values $\geqslant$10 mmHg (clinically significant portal hypertension, CSPH) [2–4]. Nonetheless, this knowledge, drawn from observational and diagnostic studies, has not been translated yet to the routine clinical management of patients with compensated cirrhosis. The reason is probably two-fold. First, the HVPG measurement is an invasive procedure, currently performed in specialized centers only. And second, the only therapeutic intervention accepted today in this population is the primary prophylaxis of variceal bleeding, for which the performance of an upper endoscopy is considered mandatory, and the assessment of portal pressure is deemed unnecessary [2,3].

In this regard, there is a rising interest on the design of new therapeutic approaches to prevent the transition from CSPH to the occurrence of complications [3–5]. These studies need to focus specifically in patients with different degrees of portal hypertension, but before the development of high-risk varices. Ideally, in order to make these approaches acceptable and widely available, the identification of these patients should be made non-invasively (i.e., avoiding the need to perform an HVPG to rule

in the presence of portal hypertension and an upper endoscopy to rule out high-risk varices). In this line, there had been significant efforts in the last years to assess the utility of non-invasive techniques and approaches for the evaluation of portal pressure and varices [6,7]. So far, the most promising technique is the measurement of liver or spleen stiffness by transient elastography (TE), either alone or combined with other parameters [6]. Indeed, several studies in the last few years have shown an excellent correlation of these parameters with HVPG, exploring the feasibility of using TE as a non-invasive diagnostic and prognostic tool in these populations, with very promising results [8–11].

Unfortunately, there are still two issues that need to be resolved in order to apply this technique both in clinical practice and for the design of studies on the prevention of clinical decompensation. First, it is still unclear whether the diagnostic performance of TE shown in diagnostic studies can be translated to clinical settings. The main concern is that these studies have been conducted on patients already pre-selected as harboring established cirrhosis on the basis of unspecific clinical criteria, which could affect significantly the transferability of the performance of the test to patients with asymptomatic liver disease in a real-world situation [12]. And second, available studies focus on the non-invasive diagnosis of high-risk varices, while what is needed for the specific purpose of the prophylaxis of clinical decompensation is the non-invasive identification of patients without high-risk varices (for whom primary prophylaxis is not mandatory).

For these reasons, we performed a prospective, longitudinal, single-center observational study to evaluate the feasibility and accuracy of a systematic strategy based on simple routine parameters and LS measurements, with the specific aim of identifying patients with portal hypertension in an early phase (i.e., without high-risk varices) among a large cohort of all consecutive patients with asymptomatic chronic liver disease in an outpatient clinical setting.

Patients and methods

Study cohort: Setting and patients

The strategy for this study was specifically designed to try to identify patients with portal hypertension, but no large or high-risk esophageal varices. The aim of such a strategy was to select candidate patients for interventional studies on prophylaxis of variceal bleeding and/or clinical decompensation of cirrhosis (PREDESCI, NCT01059396), as well as for other ongoing studies by our group. For this purpose, we considered all consecutive patients with chronic liver disease coming to our outpatient clinics between January 2010 and April 2012. Our outpatient clinics are part of a specialized Liver Unit in a tertiary university hospital in downtown Barcelona, Spain, that serves as the reference center for chronic liver disease (including cirrhosis and its complications) for an area with a population of approximately 450,000 people. The protocol was approved by the Ethics Committee of our institution and all patients gave written informed consent.

Screening-diagnostic strategy, procedures, and definitions

The flow of patients and procedures in the study is depicted in Fig. 1. The study was based on a sequential screening-diagnostic strategy. In previous studies [6,10,13], it has been consistently shown that the likelihood of CSPH in patients with LS <13.6 kPa is very low (<9%). Moreover, even in the presence of CSPH, the HVPG in patients below the 13.6 threshold remains below 12 mmHg [13], and the concurrence of high-risk varices is extremely rare (<4%) [10]. Consequently, the risk of a portal hypertensive decompensation at 1–2 years has been shown to be negligible in these patients [9]. Based on all these data, it was deemed that the systematic use of endoscopic and hemodynamic procedures in patients with LS <13.6 kPa was not clinically justified. For this reason, patients below that threshold in our cohort were screened out, and only those above the 13.6 LS cut-off entered the diagnostic analysis.

Screening phase

All patients coming to the clinics were visited with a recent (less than 1 month old) routine blood analysis and abdominal ultrasonography (US) ordered by either the community referring physician or by the usual treating doctor from our Unit. Liver surface was assessed using high-frequency (5–10 MHz) broadband linear array transducers. Spleen size was determined as spleen bipolar diameter (across the spleen hilium), using multifrequency (1–8 MHz) convex probes. Splenomegaly was defined as spleen diameter over 12 cm. The consistency of ultrasound parameters was further verified independently by 2 of the investigators (SA, JG), who reviewed all the patient's US images at the moment of the first visit.

At baseline (the moment of the first visit), all patients underwent a regular consultation (review of medical history, current symptoms and physical examination). Exclusion criteria to enter the study were: (1) past or present episode of clinical decompensation (ascites, variceal hemorrhage or hepatic encephalopathy); (2) known esophageal varices; (3) known hepatocellular carcinoma; and/or (4) evident collateral circulation on previous imaging studies. If none of these criteria were met, the patient was asked to be included in the study cohort and to undergo a liver stiffness (LS) measurement through TE (Fibroscan®, Echosens, Paris, France) performed by a single operator with experience in more than 500 procedures (LM). LS measurements were performed in a fasting state according to the usual standard procedure [11,14], either at the first visit or within the week after. LS measurements were considered valid if $\geqslant$60% success rate (out of at least 10 measurements) and interquartile range/median LS $\leqslant$0.3 were achieved. Patients with invalid LS measurements or with LS <13.6 kPa were screened out and did not undergo further investigations. Nonetheless, all of these patients were asked for consent to follow-up for ongoing observational studies by our group.

Diagnostic phase

Only those Patients with LS $\geqslant$13.6 kPa entered the diagnostic study and were further evaluated by upper endoscopy and HVPG measurement. Both procedures were performed according to the standard of practice in our center as described previously and in accordance with the recommended standards [15–17]. Endoscopies were performed within 1 month of the first visit by experienced operators who were blinded to the remaining of the patient's procedures. The endoscopic findings were recorded and graded as follows: grade 1, varices were flattened by insufflation; grade 2, varices were nonconfluent and protruding in the lumen despite insufflation; grade 3, confluent varices were not flattened by insufflation. The presence of red signs was also recorded in all patients. According to the criteria proposed at the Baveno V Consensus Conference [3], patients were considered as having large esophageal varices when the grade was 2 or 3. HVPG measurements were performed in a fasted state also within 1 month from the initial consultation with the patient. All measurements were performed in triplicate, and permanent tracings on paper were recorded. The HVPG was classified as follows: $\leqslant$5 mmHg, absence of sinusoidal portal hypertension; 6–9 mmHg, preclinical portal hypertension; $\geqslant$10 mmHg, clinically significant portal hypertension (CSPH).

Statistical analysis

For statistical analyses and presentation of results, an intention-to-diagnose approach was adopted. Following the Standards for the Reporting of Diagnostic accuracy studies (STARD) recommendations (http://www.equator-network.org/), a chart showing the flow of all patients in the study was designed (Fig. 1). A cross tabulation of the results of the index tests (including indeterminate and missing results) by the results of the reference standard was also reported (Table 3). Non-valid results in our study were managed as in usual clinical practice based on other available clinical and imaging data and according to current guidelines [2,3] and were screened out from the diagnostic phase of the study. Missing results of the reference standard (patients who refused to undergo invasive procedures) were handled in the same way. Patients with non-valid and/or missing results of reference standards were followed up until end of September 2013 to assess the development of clinical decompensation. This strategy has been previously recommended to compensate for absence of test and reference standard results in order to provide an additional measure of the clinical yield, safety, and applicability of the diagnostic strategy [12]. Outliers in the diagnostic study were included in all accuracy calculations to keep in line with the pragmatic approach of the study.