Research Article

JOURNAL OF HEPATOLOGY

Cirrhosis

A stepwise algorithm using an at-a-glance first-line test for the non-invasive diagnosis of advanced liver fibrosis and cirrhosis

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Background & Aims: Chronic liver diseases (CLD) are common, and are therefore mainly managed by non-hepatologists. These physicians lack access to the best non-invasive tests of liver fibrosis, and consequently cannot accurately determine the disease severity. Referral to a hepatologist is then needed. We aimed to implement an algorithm, comprising a new first-line test usable by all physicians, for the detection of advanced liver fibrosis in all CLD patients.

Methods: Diagnostic study: 3754 CLD patients with liver biopsy were 2:1 randomized into derivation and validation sets. Prognostic study: longitudinal follow-up of 1275 CLD patients with baseline fibrosis tests.

Results: Diagnostic study: the easy liver fibrosis test (eLIFT), an "at-a-glance" sum of points attributed to age, gender, gamma-glutamyl transferase, aspartate aminotransferase (AST), platelets and prothrombin time, was developed for the diagnosis of advanced fibrosis. In the validation set, eLIFT and fibrosis-4 (FIB4) had the same sensitivity (78.0% *vs.* 76.6%, $p = 0.470$) but eLIFT gave fewer false positive results, especially in patients ≥60 years old (53.8% *vs.* 82.0%, $p < 0.001$), and was thus more suitable as screening test. FibroMeter with vibration controlled transient elastography (VCTE) was the most accurate among the eight fibrosis tests evaluated. The sensitivity of the eLIFT-FM^{VCTE} algorithm (first-line eLIFT, second-line FibroMeter^{VCTE}) was 76.1% for advanced fibrosis and 92.1% for cirrhosis. Prognostic study: patients diagnosed as having "no/mild fibrosis" by the algorithm had excellent liver-related prognosis with thus no need for referral to a hepatologist.

Conclusion: The eLIFT-FM^{VCTE} algorithm extends the detection of advanced liver fibrosis to all CLD patients and reduces unnecessary referrals of patients without significant CLD to hepatologists.

Lay summary: Blood fibrosis tests and transient elastography accurately diagnose advanced liver fibrosis in the large population of patients having chronic liver disease, but these non-invasive tests are only currently available in specialized centers. We have developed an algorithm including the easy liver fibrosis test (eLIFT), a new simple and widely available blood test. It is used as a first-line procedure that selects at-risk patients who need further evaluation with the FibroMeter^{VCTE}, an accurate fibrosis test combining blood markers and transient elastography result. This new algorithm, called the eLIFT-FM^{VCTE}, accurately identifies the patients with advanced chronic liver disease who need referral to a specialist, and those with no or mild liver lesions who can remain under the care of their usual physician.

Clinical trial registration: No registration (analysis of pooled data from previously published diagnostic studies).

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Keywords: Liver fibrosis; Cirrhosis; Non-invasive tests; Algorithms; Liver function tests.

Received 21 October 2016; received in revised form 29 December 2016; accepted 3 January 2017; available online 12 January 2017

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Introduction

Chronic liver diseases (CLD) are very common: worldwide, an estimated 160 million people have chronic hepatitis C [1], 240 million have chronic hepatitis B [2], and 25% of the general population has non-alcoholic fatty liver disease (NAFLD) [3]. CLD can lead to a progressive accumulation of fibrosis in the liver which progressively evolves to cirrhosis and its life-threatening complications such as hepatocellular carcinoma (HCC), liver failure, variceal bleeding, or renal insufficiency. In 2012, driven by the growing worldwide burden of CLD, cirrhosis was responsible for more than 35 million years of lost life and thus became the

eleventh leading cause of mortality among non-communicable diseases [4]. Additionally, HCC has become the sixth leading incident cancer and the second leading cause of cancer-related death worldwide [4].

Both the prognosis and the management of CLD patients are closely linked to the level of liver fibrosis. Treatment of the cause of CLD is mandatory in patients who develop advanced septal fibrosis to prevent further progression to cirrhosis and its complications [1,2,5]. In cirrhotic patients, screening procedures are required for early detection of HCC and identification of large esophageal varices. Liver biopsy is the reference procedure for liver fibrosis evaluation but its invasive nature makes it unsuitable as first-line procedure in the large number of CLD patients. Blood tests and liver stiffness measurement (LSM) by elastography have been recently developed for the non-invasive evaluation of liver fibrosis and provide an exciting alternative to biopsy [6]. However, the high cost of the most accurate blood fibrosis tests limits their widespread use, and liver elastometry is only accessible in specialized centers.

CLD patients are numerous and thus not all of them can be referred to the few specialized hepatology clinics. In practice, most CLD patients are managed by non-hepatologists who encounter challenges in the evaluation of the liver disease that remains silent for many years with normal physical examination and normal routine diagnostic tests. In addition, non-hepatologists have very limited access to the best non-invasive liver fibrosis tests. Resultantly, liver fibrosis is unevaluated in many CLD patients with progressive fibrosis. These patients are finally diagnosed too late when they have reached the stage of cirrhosis complications with an impaired short-term prognosis.

In the present work, we aimed to develop and validate a stepwise algorithm that can be easily instigated by all physicians to facilitate the widespread detection of advanced liver fibrosis in all CLD patients. Such an algorithm should prove very helpful in the regulation of the large flow of CLD patients between primary care and specialized centers, and especially in the identification of CLD patients who needs referral to specialized hepatologists and those who do not.

Patients and methods

The study protocol conformed to the ethical guidelines of the current Declaration of Helsinki. All patients included in the cross-sectional population and the longitudinal cohort gave informed written consent for their participation.

Cross-sectional population

The cross-sectional population was used to develop and validate the new stepwise algorithm. This population was obtained by pooling the data of seven published studies that evaluated non-invasive liver fibrosis tests using liver biopsy as the reference [7–13]. We provide here the main inclusion/exclusion criteria and methods of these seven studies.

Patients

All included patients had CLD without decompensated cirrhosis or HCC. Patient duplication between studies was corrected to ensure that all patients were only included once in the statistical analysis for the present work.

Liver biopsy

All patients had a liver biopsy taken and used as the reference for liver fibrosis evaluation. Pathological examinations were performed in each center by senior experts specialized in hepatology and blinded for patient data. Liver fibrosis was evaluated according to NASH CRN staging in patients with NAFLD, and METAVIR staging in patients with other causes of CLD. Although the two semi-quantitative scoring systems comprise stages from F0 to F4, they do not completely correspond (Table S1). For the present study, we defined "no/mild fibrosis" as NASH CRN F0-2 or METAVIR F0-1, "septal fibrosis" as NASH CRN F3 or METAVIR F2-3, and "cirrhosis" as NASH CRN F4 or METAVIR F4. Advanced fibrosis, which was defined as NASH CRN F $\geq$3 or METAVIR F $\geq$2 (Table S1C), was the primary diagnostic target of the study.

Blood fibrosis tests

Fasting blood samples were taken the day of or within the three months before or after liver biopsy. The data available from the seven studies enabled the calculation of six blood fibrosis tests according to published or patented formulas: Aspartate aminotransferase (AST) to platelet ratio index (APRI [14]), fibrosis-4 (FIB4) [15], Hepascore [16], FibroMeter: virus, second generation (V2G) [17], FibroMeter: virus, third generation (V3G) [18], and FibroMeter with vibration controlled transient elastography (VCTE) [19]. FibroMeter^{V3G} is the same blood fibrosis test as FibroMeter^{V2G} but hyaluronate, a costly and difficult-to-obtain marker, was replaced by the gamma-glutamyl transferase (GGT). We have previously shown that FibroMeter^{V2G} and FibroMeter^{V3G} have comparable diagnostic accuracy in chronic hepatitis C [18]. FibroMeter^{VCTE} is a fibrosis test that combines in a single formula both the blood markers of the FibroMeter^{V3G} with the FibroScan result. We have previously shown that FibroMeter^{VCTE} was significantly more accurate than FibroMeter^{V2G} and FibroScan in chronic hepatitis C [19]. In the present study, APRI and FIB4 were considered as "simple fibrosis tests" since they use common, inexpensive variables and easy-to-calculate formulas. The other fibrosis tests include more expensive parameters in complex equations that require computerized calculation.

FibroScan

LSM with FibroScan was performed in each center by an experienced operator blinded for patient data using the standard M probe. LSM was performed in fasting conditions, the day of or within the three months before or after liver biopsy. Examination conditions were those recommended by the manufacturer [20]. LSM result (kilo Pascal: kPa) corresponded to the median value of the ten valid measurements recorded.

Longitudinal cohort

The prognostic longitudinal cohort was used to validate the clinical significance of the new stepwise algorithm developed in the cross-sectional population. We used a previously-established local database that retrospectively included all consecutive CLD patients seen in the Hepatology Department of the Angers University Hospital for a non-invasive evaluation of liver fibrosis between January 2005 and December 2009 [19]. Exclusion criteria for the present study were: prothrombin time <70% or serum bilirubin $\geq$30 µmol/L (i.e., no need for a fibrosis test to diagnose advanced fibrosis), missing LSM or blood test results, and an interval between blood fibrosis tests and LSM >6 months. Follow-up started the day of the non-invasive evaluation of liver fibrosis and ended January 1st, 2011. Dates and causes of death were obtained from the computerized National Registry of Individuals (CepiDC-Inserm, France). For those patients who could not be matched individually within the national registry, mortality data were obtained from the hospital database, or from the concerned general practitioner.

Statistics

In the cross-sectional population, the diagnostic accuracies of the fibrosis tests were mainly expressed as the area under the receiver operating characteristics (AUROC) and compared using the Delong test [21]. In the longitudinal cohort, the prognostic accuracies of fibrosis tests were evaluated using the Harrell C-index, as previously described [22]. Briefly, the Harrell C-index is an extension of the AUROC for time-to-event (survival) data; it evaluates the concordance between the predicted risk of the event and the observed survival time (discriminative ability). Its results vary from 0 to 1, with a value of 1 indicating a perfect concordance. Survival curves were determined using the Kaplan-Meier method and compared with the log-rank test. Statistical analyses were performed using SPSS version 18.0 software (IBM, Armonk, NY, USA) and SAS 9.1 (SAS Institute Inc., Cary, NC, USA). This study was reported in accordance with the recently published LiverFibroSTARD statements [23].

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