ORIGINAL ARTICLE

Evaluating the risk of hepatocellular carcinoma in patients with prominently elevated liver stiffness measurements by FibroScan: a multicentre study

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Abstract

Background and aims: There are limited data on the significance of liver stiffness measurements (LSM) by transient elastography in the upper extreme end of the measurable spectrum. This multicentre retrospective observational study evaluated the risk of hepatocellular carcinoma (HCC) in patients with LSM ≥20 kPa.

Methods: 432 cirrhosis patients with LSM ≥20 kPa between June 2007 and October 2015 were retrospectively followed-up through electronic records.

Results: A minimum 1-year follow-up was available for 278 patients (177 men; average age 57, range 18–84). LSM ranged from 20.0 to 75.0 kPa (mean 34.6 kPa). Cumulative incidences of HCC were 19 (6.8%), 30 (10.8%) and 41 (14.7%) at 1, 2 and 3 years, respectively. HCC was associated with age (p = 0.003), higher LSM (p = 0.005) and viral aetiology (p = 0.007). Patients were divided into 4 groups based on LSM at entry: 20–25 kPa (n = 74); 25–30 kPa (n = 62); 30–40 kPa (n = 75); >40 kPa (n = 67). Compared to the 20–25 kPa group, the 30–40 kPa group had a hazard ratio (HR) of 3.0 (95% CI, 1.1–8.3; p = 0.037), and the >40 kPa group had a HR of 4.8 (95% CI, 1.7–13.4; p = 0.003).

Conclusions: This study shows an association between LSM at the upper extreme and HCC risk. Physicians may find this beneficial as a non-invasive dynamic approach to assessing HCC risk in cirrhosis patients.

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Introduction

Liver fibrosis is common to all chronic liver disease (CLD).[1] With time, this progressive disruption of hepatic architecture can develop into cirrhosis, characterised by "diffuse conversion of normal liver architecture into structurally abnormal nodules".[2] Cirrhosis is also a premalignant condition for hepatocellular carcinoma (HCC), the 3rd largest global cause of cancer mortality.[3] 80–90% of HCC develop on the background of cirrhosis.

An accurate quantification of the degree of fibrosis is necessary for establishing prognosis and guiding surveillance. The historical gold standard for quantifying fibrosis is liver biopsy, but its invasive nature and potential for complications[4,5] make it unpopular among patients and impractical for serial assessments of CLD. Furthermore, since histological lesions are not uniformly distributed across the liver parenchyma, this allows for large sampling error.[5–9]

List of abbreviations: LSM, liver stiffness measurement; kPa, kilopascal; HCC, hepatocellular carcinoma; CLD, chronic liver disease; ALD, alcoholic liver disease; NAFLD, non-alcoholic fatty liver disease; HBV, hepatitis B virus; HCV, hepatitis C virus; HDV, hepatitis D virus; IQR, interquartile range; S, small; M, medium; XL, extra-large; CI, confidence interval; HR, hazard ratio.

The need for credible alternatives to biopsy has stimulated research into non-invasive methods of fibrosis assessment, including serum biomarkers,[10] axial imaging[11–14] and transient elastography.[15–17] FibroScan™ (Echosens, Paris, France) allows a non-invasive liver stiffness measurement (LSM) by calculating the propagation speed of an elastic sheer wave induced by the transducer, which correlates with liver stiffness (and therefore fibrosis). It is a relatively simple, highly reproducible and operator independent technique which examines an area 100 times that of a biopsy, reducing sampling bias.[18]

Depending on aetiology of liver disease, a LSM between 11.5 and 22.5 kPa indicates cirrhosis.[19–21] Occasionally, patients have much higher FibroScan™ readings, and there are limited data available on their significance. High liver stiffness is not exclusively seen with cirrhosis, and has been linked to several pathologies[22–26] including HCC.[27] Masuzaki *et al.*[28] showed a relationship between rising LSM and the risk of developing HCC. The study assessed a Japanese population, where the incidence of HCC is greater than in Europe,[29,30] and these results may not reflect the risk to a European population. Furthermore, the above study made no attempt to differentiate between LSM at the upper extreme of the scale, instead grouping all values ≥25 kPa together.

This multicenter retrospective observational study aimed to evaluate the risk of HCC in patients with liver stiffness ≥20 kPa. Clinicians may find this helpful in determining how best to follow-up patients with a liver stiffness far higher than the threshold for cirrhosis.

Methods

Transient elastography

Patient records of those with biopsy-proven cirrhosis from the Department of Hepatology, St Mary's Hospital, London (2008 onwards) and the Infectious Disease Department, University Hospital "Policlinico-Vittorio Emanuele", Catania (2007 onwards) were chronologically screened to identify all LSM by FibroScan™ (Echosens' Paris, France) with stiffness values of ≥20 kPa. All LSM were performed by certified staff with experience in FibroScan™ technology. Scans were performed in an outpatient setting, with a typical appointment lasting 10 min. Entries with incomplete FibroScan™ data were excluded from the study. Substandard LSM, defined by manufacturer guidelines as <10 successful attempts, a success rate of <60% (defined as the ratio of successful measurements over the total number of attempts) or an interquartile range of >30% of the median, were not considered an exclusion criteria.

Follow-up

Patients were retrospectively followed-up through imaging studies, according to the EASL guidelines for HCC surveillance.[31] The first line surveillance modality was liver ultrasound, performed biannually in stable cirrhosis patients. Follow-up imaging included US with contrast, triple phase CT, or MRI with gadolinium contrast. HCC was diagnosed considering hyperattenuation in the arterial phase, with washout in the late phase. In the event of an inconclusive study and absence of further imaging, an assumption of no HCC was made. HCC was counted from the time of the first imaging study to positively identify a tumour. The minimum follow-up period was set at 12 months from the original FibroScan™ investigation, and patients were followed for a maximum of 3 years. Data inclusion was stopped (statistically censored) at the last available follow-up, death (if date known, if unknown at last known date alive, e.g. blood test on electronic record), or at 3 years after LSM.

Statistical analysis

Data are expressed as percentages or as mean ± standard deviation (range). Categorical variables were compared with the chi-squared test, and continuous variables compared with Independent Student's T-test (parametric) or Mann–Whitney U test (non-parametric). A two-tailed p value of ≤0.05 was considered significant.

Patients were divided into 4 groups based on baseline kPa value: 20–25 kPa, 25–30 kPa, 30–40 kPa, and >40 kPa. Cumulative incidence of HCC was assessed using the Kaplan Meier approach. Pairwise log rank tests compared differences in survival distributions. A Bonferroni correction was made to adjust for multiple comparisons. Univariate and multivariate Cox proportional hazards regression analysis of age, gender, aetiology and liver stiffness at time of entry was conducted to assess risk factors for HCC. Categorical variables were represented using dummy variables. Hazard ratios for LSM groups were calculated using the 20–25 kPa group as reference. All statistics were performed using IBM© SPSS© Statistics version 22 (IBM, Armonk, New York, USA).

Results

Patient population

Four hundred thirty-two patients (n = 432) with LSM ≥20 kPa were identified for follow-up at the Hepatology Department of St Mary's Hospital (London, UK; n = 261) and the Infectious Disease Department of University Hospital "Policlinico-Vittorio Emanuele" (Catania, Italy; n = 171) between June 2007 and October 2015 (Table 1). There were 286 men and 146 women, with an average age of 56 ± 13 (range 0–84). The predominant underlying aetiology behind their liver disease was HCV (50.7%). Population demographics are shown in Table 1.

Exclusion

Patients were excluded when follow-up data were unavailable for a minimum of 365 days after FibroScan™ (n = 154), unless a new diagnosis of HCC was made within this time. This served to allow a lead-time for HCC development. Of the 154 excluded, 3 patients died of hepatic decompensation, 3 died of non-hepatic