Research Article

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Cirrhosis

Multiparametric magnetic resonance imaging predicts clinical outcomes in patients with chronic liver disease

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Background & Aims: Multiparametric magnetic resonance (MR) imaging has been demonstrated to quantify hepatic fibrosis, iron, and steatosis. The aim of this study was to determine if MR can be used to predict negative clinical outcomes in liver disease patients.

Methods: Patients with chronic liver disease (n = 112) were recruited for MR imaging and data on the development of liver related clinical events were collected by medical records review. The median follow-up was 27 months. MR data were analysed blinded for the Liver Inflammation and Fibrosis score (LIF; <1, 1–1.99, 2–2.99, and ⩾3 representing normal, mild, moderate, and severe liver disease, respectively), T_2^* for liver iron content and proportion of liver fat. Baseline liver biopsy was performed in 102 patients.

Results: Liver disease aetiologies included non-alcoholic fatty liver disease (35%) and chronic viral hepatitis (30%). Histologically, fibrosis was mild in 54 (48%), moderate in 17 (15%), and severe in 31 (28%) patients. Overall mortality was 5%. Ten patients (11%) developed at least one liver related clinical event. The negative predictive value of LIF <2 was 100%. Two patients with LIF 2–2.99 and eight with LIF ⩾3 had a clinical event. Patients with LIF ⩾3 had a higher cumulative risk for developing clinical events, compared to those with LIF <1 ($p = 0.02$) and LIF 1–1.99 ($p = 0.03$). Cox regression analysis including all 3 variables (fat, iron, LIF) resulted in an enhanced LIF predictive value.

Conclusions: Non-invasive standardised multiparametric MR technology may be used to predict clinical outcomes in patients with chronic liver disease.

Keywords: T_1 mapping; Iron corrected T_1; LIF score; LiverMultiScan.
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Abbreviations: MR, magnetic resonance; LIF, Liver Inflammation and Fibrosis score; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; ELF, Extended Liver Fibrosis; MRE, magnetic resonance elastography; ^{1}H-MRS, proton magnetic resonance spectroscopy; HCC, hepatocellular carcinoma; cT_1, iron corrected T_1; LMS, LiverMultiScan.

Introduction

Liver disease in Western populations has reached epidemic proportions, where a third of all adults have some degree of non-alcoholic fatty liver disease (NAFLD) [1]. The estimates for the prevalence of non-alcoholic steatohepatitis (NASH), the more aggressive form of NAFLD, are as high as 12% [2]. Furthermore, viral hepatitis affects over 450 million people worldwide [3,4], and is associated with cirrhosis in 20% of this population. After developing cirrhosis, patients may remain well (“compensated”) for long periods of time, but approximately 5–7% will develop complications (become “decompensated”) annually. Furthermore, annual mortality rates can be as high as 57% once cirrhosis is established [5]. In the face of this epidemic, there is an urgent clinical need for technologies that can identify patients with chronic liver disease, and risk stratify those who will develop complications or die from liver disease. This will facilitate timely therapeutic interventions, liver transplantation, and stratification within clinical studies.

Traditionally, clinicians have used needle biopsy to assess liver fibrosis. However, as this procedure is painful, requires hospitalisation for several hours or more, and is associated with a risk of complications and death, non-invasive methods for liver fibrosis assessment have been developed in the last decade. Furthermore, liver biopsy is associated with both sampling and observer dependent variability [6,7]; therefore the use of this as a gold standard comparator for the development of non-invasive technologies is sub-optimal [8]. A more robust and clinically relevant approach would involve the assessment of whether non-invasive technologies can be used to predict clinically meaningful endpoints.

Broadly, non-invasive techniques can be divided into those based on direct and indirect serum markers of fibrosis and those based on imaging and or elastography. Serum biomarkers are attractive as they are easy to measure and can be repeated over

time. However, they lack specificity as they may be affected by extrahepatic fibrosis. For example, the Extended Liver Fibrosis (ELF) panel reported a sensitivity of 90%, but had a specificity of only 41%, with an area under the receiver operating characteristic curve of 0.80 for the detection of severe fibrosis [9]. A subsequent 7 year follow-up study suggested that ELF score could predict clinical outcomes [10]. However, patients with any disorder associated with extrahepatic fibrosis were excluded from these studies making it difficult to assess how this test could be applied to a general, unselected population.

Liver stiffness measurement using magnetic resonance elastography (MRE), ultrasound-based transient elastography (Fibroscan™), or acoustic radiation force impulse have also been used to assess fibrosis and for predicting clinical outcomes [11–15]. However, ultrasonic elastography cannot be used if there is significant fat or fluid between the chest wall and the liver; failed readings or unreliable results are observed in nearly 20% of patients, particularly those with obesity and the metabolic syndrome [16]. Furthermore, elastography measures have been shown to carry considerable variance [17]. MRE is more accurate than transient elastography [18], but needs additional hardware and is compromised in patients with haemosiderosis.

Overall, despite these advances in non-invasive liver assessment, the drawbacks of the currently available techniques mean that they are not widely available and have not been validated for use as surrogate endpoints in clinical trials. Because of this, several professional and regulatory bodies recognise the need for better stratification tools [19–21].

Magnetic resonance (MR) techniques offer an attractive non-invasive option for liver assessment. These are well established in assessing anatomical morphology, are organ specific and have the capacity to evaluate the whole organ thereby eliminating all the concerns around sampling error. Furthermore, they can be standardised across scanner vendors and magnet strengths so that inter-operator variability is negligible.

T_1 mapping is a MR technique that allows *in vivo* tissue characterisation. At our centre, a multiparametric MR technique has been established, that includes T_1 mapping for fibrosis/inflammation imaging, T_2^* mapping for liver iron quantification and proton magnetic resonance spectroscopy (^{1}H-MRS) for liver fat quantification. The T_1 measurements in our method are adjusted for the iron level, as high iron levels in the presence of fibrosis can lead to "pseudo-normal" T_1 values. This is a quick and truly non-invasive test that does not require injection of any intravenous contrast agent. In a recent study, it has shown good correlation with histological parameters in a cohort of patients with mixed liver disease aetiologies undergoing clinically indicated liver biopsy [22].

The aim of the present study was to assess whether data obtained from this multiparametric MR protocol could be used to predict all-cause mortality and liver related clinical events, irrespective of stage of fibrosis or disease aetiology.

Patients and methods

Study design and patient population

The population under study were those scheduled to have a clinically indicated liver biopsy (n = 116) and adult patients who had cirrhosis diagnosed on biopsy within 5 years of their MRI scan (n = 7). Patients were included irrespective of underlying liver disease aetiology or disease stage. The only exclusion criterion was the presence of MRI contraindications. Patients were recruited from two UK centres (Oxford and Reading) between April 2011 and August 2013. All patients were followed for the development of clinical outcomes except those who were lost to follow-up or had incomplete MR data (n = 11; Fig. 1). Baseline data were collected at the time of recruitment. Outcome data were collected through review of the individual electronic and paper patient records.

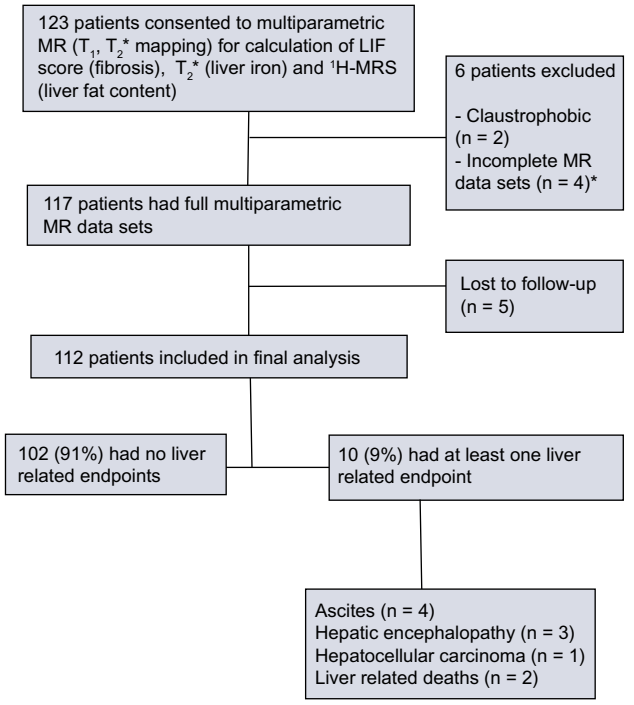

Fig. 1. Study flow chart. The Liver Inflammation and Fibrosis (LIF) score is a standardised continuous score (0–4) derived from liver T_1 and T_2^* values. T_1 primarily reflects the amount of extracellular fluid and can change with inflammation and fibrosis and T_2^* primarily reflects the amount of iron deposition. Liver iron has a confounding effect on T_1, and this is accounted for in the LIF score calculation. *Liver iron concentration from T_2^* maps and hence LIF calculation was not possible in 4 cases. MR, magnetic resonance; ^{1}H-MRS: proton (^{1}H) magnetic resonance spectroscopy; LIF, Liver Inflammation and Fibrosis score.

The study was approved by the UK National Research Ethics Service and the institutional review board and was performed in accordance with the ethical guidelines of the 1975 Declaration of Helsinki. All patients gave written informed consent.

All-cause mortality and liver related clinical events

Both all-cause mortality and liver related clinical events were evaluated. Liver related clinical events were defined as liver related death, the development of hepatocellular carcinoma (HCC) and any new episode of hepatic decompensation (clinically evident ascites, variceal bleeding, and hepatic encephalopathy). Although more than one event per patient was possible and occurred, patients were only counted once in the analysis at the time of the first liver related clinical event. Patients who had evidence of liver related complications at or before enrolment were only counted again if they developed a complication that was distinct from that observed before enrolment, or died. Patients were followed up until their last clinical review or until they died, but the index liver related event as defined above was used in the analysis.

Multiparametric MRI

The MRI technique used in this study has been previously described [22]. Briefly, MR scans were performed in Oxford using a 3-Tesla scanner (Tim Trio, Siemens Healthcare, Germany). Transverse abdominal T_1 and T_2^* MR maps were acquired for the estimation of extracellular fluid and liver iron respectively. Proton magnetic resonance spectroscopy (^{1}H-MRS) was also used to measure liver fat content. Patients attended for their MRI scans after fasting for at least 4 h.