Quantitative magnetic resonance imaging to aid clinical decision making in autoimmune hepatitis

Michael A. Heneghan,a* Elizabeth Shumbayawonda,b Andrea Dennis,b Refah Z. Ahmed,a Mussarat N. Rahim,a Michael Ney,a Loren Smith,c Matt Kelly,b Rajarshi Banerjee,b and Emma L. Culverc

Institute of Liver Studies, King’s College Hospital, NHS Foundation Trust, Denmark Hill, London, United Kingdom
bPerspectum Ltd, Oxford, United Kingdom
cJohn Radcliffe Hospital, Oxford University Hospitals NHS Foundation Trust, Oxford, United Kingdom

Summary

Background In autoimmune hepatitis (AIH), clinical practice and treatment guidelines frequently diverge as a reflection of disease heterogeneity and challenges in achieving standardised care. We sought to explore the utility of multiparametric (mp) MR in patients with AIH, and the impact of this technology on physicians’ decision making and intended patient management.

Methods 82 AIH patients, recruited from two sites between June and November 2019 as part of an observational cohort study, underwent non-contrast MRI alongside their standard clinical investigations. Correlations between iron-corrected T1 (cT1) and other markers of disease were investigated alongside the utility of imaging markers to risk stratify patients in biochemical remission. The impact of mpMR on clinical decision making was evaluated using pairwise t-tests. The discriminatory ability of the imaging markers was assessed using area under the receiver operating characteristic curves (AUCs).

Findings cT1 had a significant impact on clinician intended patient management (p<0.0001). cT1 correlated with ALT (p=0.0005), AST (p=0.0001), IgG (p=0.0005), and liver stiffness (p<0.0001). Patients in deep biochemical remission (N=11; AST/ALT <50% upper limit of normal [ULN] and IgG <12 g/L) had low cT1, while 7/34 in normal biochemical remission (AST/ALT between 50 and 100% of ULN) had high cT1 and were at risk of disease flare. cT1 measures of disease heterogeneity, ALP and bilirubin made the best predictor of those not in biochemical remission (AUC:0.85).

Interpretation This study investigates the impact of mpMR results on intended clinical management in a real world setting. Findings showed that mpMR demonstrated a significant impact on clinical management of AIH and has the potential to inform patient risk stratification.

Funding This paper presents independent research supported by the Innovate UK grant (104,915).

Copyright © 2022 The Authors. Published by Elsevier Ltd. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/)

Keywords: Remission; Fibro-inflammation; Non-invasive imaging; Stratification; cT1

Introduction

Autoimmune hepatitis (AIH) is a challenging condition that presents in both acute and chronic forms in patients of all ages. It remains a diagnosis of exclusion since there is no disease-specific test and one third of patients present with advanced liver disease. Corticosteroids and non-selective immunosuppression are currently the mainstay of treatment. Disease relapse is common and affects up to 80% of patients after treatment withdrawal. Moreover, undesired corticosteroid-related side effects are considerable, and up to 50% of patients can develop cirrhosis despite therapeutic intervention. AIH has a female predominance, with the majority of most patients requiring life-long monitoring.

To-date, liver biopsy is considered essential for diagnosis of AIH in accordance with all clinical guidelines, and can highlight co-existence with non-alcoholic steatohepatitis, viral hepatitis, and variant syndromes. It is also useful for evaluation of treatment response and to guide therapy by quantification of hepatic inflammation and staging of liver fibrosis.

*Corresponding author.
E-mail address: michael.heneghan@nhs.net (M.A. Heneghan).
Monitoring of liver inflammation in AIH relies on non-invasive assessment such as liver biochemistry (alanine transaminase (ALT) activity) and immunoglobulin G (IgG) levels. Liver biochemistry can be insensitive to changes in fibro-inflammation in the liver and one cannot exclude underlying residual active hepatic inflammation in the presence of ‘normal LFTs’ (liver function tests). Some clinical guidelines recommend repeat “on-treatment” histological assessment to confirm complete resolution of histological inflammation to aid in long-term therapeutic management considerations. This has not been universally adopted. In practice, liver biopsy is performed at diagnosis, for an unexplained and persistent flare in liver biochemistry/IgG and when considering treatment cessation or withdrawal. Liver biopsy however is invasive and not liked by patients. This paucity in follow-up histological assessment has resulted in a need for objective, quantitative, reproducible, and accurate non-invasive methods of assessing liver health in this population.

Serum-based biomarker panels, such as FibroTest, serum AST/platelet ratio index (APRI), Fibrosis-4 index (FIB-4) and the enhanced liver fibrosis (ELF) test have been used anecdotally in patients with AIH; their use requires further validation. Non-invasive imaging techniques, including vibration-controlled transient elastography (VCTE; Fibroscan, Echosens, France), magnetic resonance elastography (MRE) and acoustic radiation force impulse imaging (ARFI) are confounded by hepatic inflammation. VCTE has a high coefficient of variation although is often used after 6-months of treatment to monitor disease response and progression of fibrosis.

Multiparametric magnetic resonance (mpMR) techniques have been able to impact clinical practice in medical fields such as oncology (prostate and breast cancer) and cardiology, due to the generation of quantitative biomarkers. mpMR has also demonstrated its utility in clinical pathways for the assessment of liver disease. Iron corrected T1 (cT1) from LiverMultiScan (Perspectum, Oxford) is an objective mpMR measurement of fibro-inflammation with low inter-observer variability and high repeatability over time as well as a very low coefficient of variation in monitoring liver disease at multiple timepoints. cT1 correlates with histology and has been shown to detect early responses to treatment in non-alcoholic fatty liver disease. More recently, cT1 has also shown utility in monitoring disease regression and has correlated with histological fibrosis and inflammation in AIH patients in biochemical remission. Importantly, cT1 outperformed other surrogate markers (VCTE-liver stiffness and elevated liver enzymes) to predict future disease flare in AIH patients, with a cT1 ≥800 ms associated with a ≥20% chance of experiencing a future disease flare, rising to ≥27% chance with a cT1 ≥1000 ms.

The aim of this study was to understand the impact of cT1 on a physician’s intended management plan for patients with AIH. Our objective was to investigate the effect of mpMR results on a physician’s decision making and subsequent intended patient management plans for patient with suspected or confirmed AIH compared with usual standard of care.

Methods

Patient recruitment

82 adult patients (N = 59 from King’s College Hospital NHS Foundation Trust and N = 23 from Oxford...
University Hospitals NHS Trust) with an established biopsy-proven diagnosis of AIH were prospectively recruited into this study between June 2019 and November 2019. Exclusion criteria included: (i) inability or unwillingness to give consent, (ii) those with contraindications to the MR procedure (such as pregnancy or non-MR compatible implants), (iii) those with any clinical doubt to their underlying aetiology of liver disease, or (iv) patients with evidence of current overt hepatic decompensation (such as encephalopathy, gross ascites, or variceal haemorrhage).

Diagnostic criteria
All patients recruited in this study had biopsy confirmed AIH (diagnosed 3.1 years (range: 0–14.4 years) before recruitment). Moreover, at the time of diagnosis, all patients fulfilled the revised,26 and simplified Internatio nal Autoimmune Hepatitis Group (IAIHG)27 criteria with all patients being classed as having probable or definite AIH (score of ≥6).

Ethics statement and registration
Patients gave written informed consent to participate in the study. Local ethical approval was gained via the National Research Ethics Service, West Midlands (Black Country, reference 19/WM/0111), along with appropriate data sharing, confidentiality, and collaboration agreements. The study was registered as a clinical investigation (NCT03979053). Principals of Good Clinical Practice and those of the 1975 Declaration of Helsinki were observed. All patient-identifiable information was kept securely and encrypted within the servers at the study sites.

Study procedures
Patients underwent non-invasive assessment including clinical history, examination, blood panel analysis, VCTE liver stiffness (LS; Fibroscan®; Echosens, France) and non-contrast mpMR. Figure 1 shows a summary of the protocol followed in this study.

Mpmr protocol
The mpMR scanning protocol was installed, calibrated and phantom tested on a 3 T Siemens Prisma MRI scanner (Siemens Healthcare GMBH, Erlangen, Germany) at the Oxford Centre for Magnetic Resonance (OCMR) and a 3 T Siemens Skyra MRI scanner (Siemens Healthcare GMBH, Erlangen, Germany) at Alliance Medical, London. Four single transverse slices were captured throughout the liver centred at the porta hepatis. Anonymised MR data were analysed off-site using LiverMultiScan® software (Persepectum Ltd., United Kingdom) by specialised imaging analysts trained in abdominal anatomy and artefact detection. cT1 maps of the liver were delineated into whole liver segmentation maps using a semi-automatic method, as extensively described by Bachtiar and colleagues,29 and expressed as the median value within the map. cT1 interquartile range (IQR), a measure of the spread of cT1 values across the liver, and the count (expressed as a percentage) of the pixels in the liver map above a predefined threshold of 800 ms (pcT1), both of which represent disease heterogeneity, were also extracted from the whole liver segmentation maps. The mpMR analysis was completed by analysts blinded to the clinical data.

Assessment of clinical impact of cT1
To address the primary objective, clinicians were asked to score the utility of the technology at two stages. The first score, which reflected the anticipated benefit of mpMR, was given immediately after the clinic consultation once the clinician had reviewed the existing patient information and prior to the patient attending the MRI scan. After receiving the mpMR report, the clinicians were asked to provide a second score reflecting the impact of mpMR on the clinical management plan for the patient. For both scores and for each individual patient, a 10-point Likert scale was used to record the clinicians’ level of agreement or disagreement concerning the utility of the technology. On the Likert scale used, a score of 1 indicated no confidence in the utility of LiverMultiScan, whilst a score of 10 indicated complete confidence.

Definitions of disease inactivity and biochemical remission
Clinical guidelines define one of the goals of treatment in AIH to be complete biochemical remission.4,5 As ALT remission has been shown to correlate with outcomes,5 patients in this study were classified into two groups according to biochemistry. Biochemical remission groups were formed around the upper limit of normal (ULN) of aspartate aminotransferase (AST) and ALT1 with those in biochemical remission having AST and ALT less than the ULN (i.e. AST≤40IU/L and ALT≤40IU/L), while those not in biochemical remission were classified as having active disease. Similar to work by Hartl and colleagues,26 to further understand the utility of mpMR to identify the existence of gradations in biochemical remission and to identify those with active sub-clinical disease, patients in biochemical remission were further classified as being either in deep (ALT≤50% ULN (ALT≤20IU/L) and IgG<12 g/L) or normal biochemical remission. Lastly, as a cT1 of >800 ms has previously been shown to relate to increased risk of disease relapse,6 and is indicative of continued active fibro-inflammatory disease8,9 it was
used as a threshold to identify those with active sub-clinical disease (Figure 2).

**Statistics**
Descriptive statistics were used to summarise baseline participant characteristics. Continuous variables were reported as mean and standard deviation and categorical variables were reported as frequency and percentage. The time between diagnosis biopsy and recruitment into the study (disease duration) was also calculated and reported as median and inter-quartile range. For the primary objective, paired t-tests were used to assess the impact of cT1 on clinical decision making by compare the scores given by the clinicians before and after reviewing the mpMR results.

To assess the agreement between non-invasive and biochemical biomarkers, correlations between all markers (median cT1 (cT1), cT1 IQR, pcT1, and LS) with blood tests were analysed using Spearman’s correlation coefficient (rs). Mean differences between those in biochemical remission and those with active disease were compared using the Kruskal Wallis test. Further to this, mean differences between those with low (cT1<800 ms) vs high cT1 (within each biochemical remission group respectively) were evaluated with the Kruskal Wallis tests.

The ability of cT1 to discriminate between those in biochemical remission from those not in biochemical remission were estimated using the area under the receiver operating characteristic curves (AUCs). Sensitivity, specificity, negative and positive predicting values (NPV, PPV respectively) for the predefined cT1 cut-off of 800 ms was calculated, with Youden’s Index used to obtain the best cut-off and related sensitivity, specificity, NPV and PPV for pcT1 and liver stiffness. For the exploratory investigations into possible gradations in biochemical

---

**Figure 1.** The identification, recruitment, and active study procedure followed in this project.
remission, Kruskal Wallis test tests were used to evaluate if any differences existed between those in deep biochemical remission and those in normal biochemical remission.

Descriptive statistics and correlations were performed using all patient’s data, however, subsequent investigations after classification into biochemical remission groups were performed in the patients with both AST and ALT data available for analysis ($N=70$).

All statistical analyses were performed using R version 3.5.3 (R Core Team, Vienna, Austria), and values of $p<0.05$ were considered statistically significant. The Shapiro-Wilk test was used to assess normality of the metrics investigated.

**Figure 2.** (A) Changes in cT1 (ms) associated with increasing fibro-inflammatory burden and differences in cT1 between remission groups. In the images, lower values (cooler colours in maps and colour bar) represent areas with lower cT1 values and therefore lower fibro-inflammation, while higher cT1 values (warmer colours) represent areas of the liver with higher fibro-inflammation. (B) Classification of patients using biochemistry and cT1 to identify the spread of patients with resolved biochemistry that still have active fibro-inflammation.

**Sample size calculation**
The sample size estimation was based on the primary objective and endpoint to assess the effect of MRI results on a physician’s decision making and the number of patients in whom intended clinical management is changed when the MRI results are delivered. According to preliminary data from Arndtz and colleagues subsequently published,²⁵ up to 50% of low-risk patients and up to 23% of high risk patients (as identified by blood serum markers) go on to develop a flare within next 12 months. Thus, in a hypothetical scenario, in a 100 patient cohort where 50 patients are considered to be low risk and 50 are considered to be high-risk, 25 low-risk patients will be incorrectly assigned low risk...
status (instead of high-risk) and will go on to develop a flare. The study also showed that mpMR can benefit up to 36% of patients and thus result in a change in management. Considering the null hypothesis that a clinician can correctly identify patient status (high/low-risk) 25–30% of the time and the worst case scenario where mpMR can benefit 15% patients (small effect size of 0.31–0.34), approximately 60 patients (assuming 80% power, alpha 0.05 and loss rate of 10%) would be required to test our hypothesis, with approximately 80 patients required if a loss rate of 25% is considered.

Role of the funding source
The funding source had no role in the study design, data collection, data analyses, data interpretation, writing of the report and the decision to submit the manuscript for publication. All authors (MAH, ES, AD, RZA, MNR, MN, LS, MK, RB, ELC) has access to the data and jointly took the decision to submit the paper for publication.

Results

Description of cohort
All patients, median age of 52 years (range: 21–81), were consented and recruited over three months between June and October 2019 (Figure 1, Table 1). Seventy-seven percent were female. All participants were on either monotherapy or a combination of therapies at the time of recruitment. The time between the most recent liver biopsy and MRI scan (disease duration) was 23.1 months (IQR:46.7) months.

Clinical assessment
All patients were assessed face-to-face in outpatient clinic. 69/82 (84%) were felt to have stable disease based on clinical parameters, liver biochemistry (+/-immunoglobulin levels), and continuation of treatment regimen. Thirteen out of 82 patients (16%) required a change in medication due to various reasons, including increased/reduced disease activity, planned escalation/de-escalation of therapy, intolerance of medication, or patient choice. 5/13 (6%) had their steroid treatment adjusted (3 decrease, 2 increase) and 9/13 (11%) had a change in their immunosuppressive therapy (6 decrease, 3 increase) (Figure 1).

Surrogate imaging biomarkers and serum markers of AIH activity
cTI correlated significantly with serum markers (ALT \( r_s=0.31, p = 0.005 \), AST \( r_s=0.47, p<0.001 \), IgG \( r_s=0.41, p = 0.001 \), GGT (gamma-glutamyl transferase; \( r_s=0.49, p<0.001 \) and albumin \( r_s= -0.32, p = 0.036 \)), as well as with liver stiffness \( r_s=0.51, p<0.001 \), and disease duration \( r_s=0.32, p = 0.003 \). Furthermore, there were significant correlations between pcT1 and serum ALT \( r_s=0.33, p = 0.001 \), AST \( r_s=0.51, p<0.001 \), IgG \( r_s=0.35, p = 0.003 \), GGT \( r_s=0.5, p<0.001 \) and liver stiffness \( r_s=0.54, p<0.001 \) (Table 2).

Non-invasive imaging and disease activity

Active disease. 25 patients had active disease with 15 having cT1<800 ms. Of these 15, 60% had ALT less than x2 ULN (ALT: 47.9 ± 12.4 IU/L) and according to clinical guidelines have mild disease (Figure 2). The patients with mild disease had significantly lower cT1 IQR (\( p = 0.004 \)), liver stiffness (\( p = 0.04 \)) and pcT1 (\( p<0.0001 \)) compared to those with cT1>800 ms (Figure 3).

Biochemical remission vs active disease.
Those with active disease had significantly higher cT1 \( p = 0.002 \), IgG \( p = 0.01 \), liver stiffness \( p = 0.003 \) and pcT1 \( p = 0.002 \) compared to those in biochemical remission (Figure 4). In the discrimination between biochemical remission and active disease, a cT1 of 800 ms had AUC:0.77 (95% CI: 0.61–0.9), 40% sensitivity, 84% specificity, 67% PPV and 70% NPV. In addition to this, a pcT1 of 48% had AUC:0.76 (95% CI: 0.62–0.9), 50% sensitivity, 94% specificity, 83% PPV and 75% NPV, while a liver stiffness of 5.4 kPa was found to have AUC:0.74 (95% CI: 0%), 75% sensitivity, 69% specificity, 60% PPV and 81% NPV to discriminate between the two biochemical remission groups.

Biochemical remission and active sub-clinical disease.
Of the 45 patients in biochemical remission, 18 were in deep biochemical remission and 27 were in normal biochemical remission (Figure 2). The 7 patients in normal biochemical remission with cT1<800 ms had significantly higher pcT1 \( p = 0.0003 \) and GGT \( p = 0.004 \) when compared to those in normal biochemical remission with cT1>800 ms. Moreover, when compared on a global scale with all other patients in biochemical remission, these 7 patients were found to have significantly higher AST \( p = 0.03 \), cT1 IQR \( p = 0.04 \), GGT \( p = 0.0008 \) and pcT1 (\( p<0.0001 \)) (Figure 5).

Impact of cT1 on clinical decision making
In the first score given immediately after the consultation, but before reviewing the mpMR report, the average score reflecting the anticipated benefit of mpMR was \( 7 \pm 4 \). The average retrospective review, after reviewing the mpMR report, increased significantly by 20% \( \pm 0.0001 \) to \( 9 \pm 2 \). For the first set of scores, 65% were \( \geq 7/10 \) while 35% were \( < 5/10 \), however for the
Table 1: Population demographics showing patient characteristics, blood panel and non-invasive liver assessment results. Statistical differences between those in biochemical remission (AST ≤ 40 IU/L and ALT ≤ 40 IU/L) and those with active disease have also been indicated. P-values for ALT and AST have not been added as these were used to define the biochemical remission groups.

| Whole cohort | Biochemical Remission | Active disease | p-value | Normal limits |
|--------------|-----------------------|----------------|---------|--------------|
| Patient characteristics | | | | |
| Cohort size | 82 | 18 | 27 | 25 |
| Age | 52 ± 16 | 60 ± 13 | 52 ± 14 | 45 ± 17 | 0.058 |
| Body Mass Index (kg/m²) | 27.4 ± 5.6 | 26.0 ± 5.6 | 28.2 ± 4.7 | 26.8 ± 5.0 | 0.751 |
| Serum Liver and Liver function tests | | | | |
| Platelets (10⁹/L) | 222 ± 91 | 257 ± 78 | 228 ± 98 | 205 ± 89 | 0.196 |
| ALP (IU/L) | 73 ± 30 | 69 ± 28 | 69 ± 26 | 82 ± 34 | 0.128 |
| ALT (IU/L) | 55 ± 58 | 26 ± 13 | 54 ± 48 | 74 ± 77 | 0.196 |
| AST (IU/L) | 40 ± 45 | 15 ± 3 | 25 ± 8 | 81 ± 63 | < 0.001 |
| ALP (IU/L) | 41 ± 32 | 23 ± 4 | 28 ± 7 | 70 ± 42 | < 0.001 |
| Serum Liver function tests (µmol/L) | | | | |
| Albumin (g/L) | 13 ± 4.6 | 9.3 ± 1.5 | 13.3 ± 4.7 | 14.9 ± 5.0 | 0.01 |
| Surrogate markers of liver health | | | | |
| Fat (%) | 4.1 ± 2.2 | 3.5 ± 2.0 | 4.0 ± 3.2 | 3.7 ± 4.6 | 0.289 |
| cT1 (ms) | 781 ± 105 | 731 ± 29 | 766 ± 68 | 818 ± 95 | 0.002 |
| Total serum globulins (g/L) | 35 ± 27 | 18 ± 11 | 32 ± 26 | 48 ± 30 | 0.002 |

Table 2: Correlations (R) between cT1 (ms) with serum liver function test results and other surrogate markers of liver health. All significant associations are highlighted in bold.
second set of scores, 78% were ≥ 7/10 and 6% were < 5/10.

Discussion
In this study looking at the utility of using MR imaging in AIH we identified four main findings. Firstly, we managed to further the understanding of gradations in biochemical remission by expanding on the concept of deep biochemical remission and identifying the differences between those in deep biochemical remission and those in normal biochemical remission. Secondly, we highlighted the utility of mpMR results in monitoring AIH patients with further insight into patients in biochemical remission with active subclinical disease. Thirdly, we highlighted the potential utility that quantifying the amount of active fibro-inflammatory disease may have on the phenotypic changes that occur in AIH. Lastly, we highlighted the impact mpMR results has on physicians’ intended plans for patient management in a representative real world AIH population.

Serum liver biomarkers are used to monitor disease activity in AIH transaminases can be normal (or fluctuate) in patients with chronic hepatitis therefore,
liver stiffness, MRE, and ARFI also provide additional information. For instance, VCTE markers (as shown by both cT1 and liver stiffness), they imaging markers correlate significantly with blood tests currently used in clinical practice.39 Findings from this study showed that disease heterogeneity (cT1 IQR and pcT1) correlates with blood markers and varies significantly between biochemical remission groups. Thus, understanding the manner in which disease burden across the liver is related to the level of circulating serum markers could potentially be helpful in the clinical assessment of patients with AIH.

Liver biopsy has traditionally been the preferred strategy prior to drug withdrawal, this procedure may not be mandatory in all adults as a similar relapse frequency has been observed between those with or without a pre-withdrawal liver biopsy.35,36 Patients with ALT levels ≤50% ULN have been shown to have the best outcomes after treatment withdrawal,1 with gradations within the normal range of biochemical remission being shown to be predictive of clinical outcomes.40 Forty percent of our cohort who were in biochemical remission were classified as being in deep biochemical remission and had significantly less active fibro-inflammatory disease compared to those in normal biochemical remission. Moreover, as both cT1 and pcT1 were significantly higher in those with normal biochemical remission, compared to those in deep biochemical remission, including these markers in the evaluation of patients may provide potentially useful information that can be used to improve disease management. cT1 ≥800 ms in patients with biochemical remission is associated with a ≥20% chance of developing a flare in AIH and a cT1> 800 ms has been shown to indicate active sub-clinical disease.29 Of the 45 patients in normal remission, 16% had evidence of active sub-clinical disease. Thus, 16% of patients with resolved biochemical remission in this cohort are potentially at risk of having future disease flares due to persistent fibro-inflammatory activity in the liver that is otherwise undetectable by liver biochemistry.

In this first study assessing the impact of mpMR results on intended clinical management, a 20% increase in physicians’ confidence was observed. Moreover, a decrease of almost 30% (from 35% to 6%) in the lowest ranking scores (scores < 5/10) in the initial results highlight the potential clinically relevant and disruptive information this technology brings. Therefore, as this study only made use of two clinicians, future multisite studies with a range of clinicians should be performed so as to obtain a better understanding of the impact mpMR results may have on physicians’ patient management.

As this was a real world study, concurrent liver biopsy was not included in the study protocol, as this would have deviated from standard of care. Consequently, we acknowledge the limitations to this study; specifically, the inability to assess relationships between cT1 and histological findings. Nevertheless, previous studies have shown significant correlations between cT1 and histology in both adults15,16,24 and paediatrics.29 This cross sectional study only covered a single time point, thus, following this cohort over time will yield a better understanding of the changes associated with these markers as well as the impact they may have on longitudinal disease monitoring. Lastly, as it has been shown that patient management may vary between clinicians,7 future meta-analyses looking at large pooled data across multiple trusts may yield useful information that will support the results presented in this investigation. These studies should also collect data regarding compliance to medication, previous relapses (and their frequency), induction treatment regimens, and other factors which can affect the remission status of a
patient. Statistical analyses following these investigations should control for these covariates within any multivariate models generated so as to ensure that any potential confounding effects these factors have will not influence the outcomes observed.

In conclusion, mpMR quantitative biomarkers have shown a positive impact on clinicians intended management plan as well as utility in characterising the fibro-inflammatory status of those in various gradations of biochemical remission. By identifying differences between those in normal biochemical remission, cT1 has shown promise in the phenotyping and risk stratification of individuals with this orphan disease who may not be identified using serum biochemistry and liver stiffness alone. Future analyses investigating the associations between disease and clinical outcomes should also evaluate the utility of markers of disease heterogeneity.

Data sharing statement
The data and analytic methods used in this study remain the property of the individual study sponsors. All deidentified participant data may be made available to other researchers upon request following permission, investigator support and following a signed data access agreement.

Funding
This paper presents independent research supported by the Innovate UK grant (104915).

Contributions
Conceptualisation: MK, AD, RB, MAH
Data collection: MAH, RZA, MNR, MN, LS, ELC
Data curation: RZA, LS, ES
Data analysis: ES
Funding acquisition: MK, AD, RB
Writing original draft: ES
Writing — Review & Editing: ES, MAH, ELC, AD, MK, RB, MN, MNR
All authors reviewed, discussed, and agreed with manuscript.

Declaration of interests
ES, AD, MK and RB are employees of Perspectum. Perspectum Ltd is a privately funded commercial enterprise that develops medical devices to address unmet clinical needs, including LiverMultiScan®. MAH, RZA, MNR, MN, LS and ELC have no conflicts of interest to declare.

Acknowledgements
The investigators gratefully thank the patients for their participation.

References
1 Heneghan MA, Yeoman AD, Verma S, Smith AD, Longhi MS. Autoimmune hepatitis. Lancet. 2015;382:1433–1444.
2 van den Brand FF, van der Veen KS, Lissenberg-Witte BI, et al. Adverse events related to low dose corticosteroids in autoimmune hepatitis. Aliment Pharmacol Ther. 2019;50:1120–1126.
3 Gleeson D, Heneghan M. British society of gastroenterology (BSG) guidelines for management of autoimmune hepatitis. Gut. 2011;60:1611–1629.
4 European Association for the Study of the Liver. EASL Clinical practice guidelines: autoimmune hepatitis. J Hepatol. 2015;63:971–1004.
5 Mack C, Adams D, Assis DN, et al. Diagnosis and management of autoimmune hepatitis in adults and children: 2019 practice guidance and guidelines from the American association for the study of liver diseases. Hepatology. 2019. https://doi.org/10.1002/hep.31651:1–119.
6 Manns M, Caza A, Gorham J, Krawitt E, Mieli-Vergani G, Vergani D. Diagnosis and management of autoimmune hepatitis. Hepatology. 2010;51:2193–2213.
7 Dyson JK, Wong LL, Bigramurume T, et al. Inequity of care provision and outcome disparity in autoimmune hepatitis in the United Kingdom. Aliment Pharmacol Ther. 2018;48:931–960.
8 Poynard T, Banerjee R, Sellwood J, et al. Relative performances of FibroTest, Fibroscan, and biopsy for the assessment of the stage of liver fibrosis in patients with chronic hepatitis C: a step toward the truth in the absence of a gold standard. J Hepatol. 2012;56:541–548.
9 Wai C, Greenson J, Fontana R, et al. A simple noninvasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C. Gastroenterology. 2005;130:58–596.
10 Shah A, Lydecker A, Murray K, Tetti B, Contos M, Sanay A. Comparison of noninvasive markers of fibrosis in patients with nonalcoholic fatty liver disease. Clin Gastroenterol Hepatol. 2009;7:1104–1112.
11 Parkes J, Guha I, Roderick P, et al. Enhanced liver fibrosis (ELF) test accurately identifies liver fibrosis in patients with chronic hepatitis C. J Viral Hepat. 2012;19:23–31.
12 Messroghli DR, Moin JC, Ferreira VM, et al. Clinical recommendations for cardiovascular magnetic resonance imaging of active chronic hepatitis C. J Viral Hepat. 2016;23:230–239.
13 Marino MA, Helbich T, Baltzer P, Pinker-Domenig K. Multiparametric MRI of the breast: a review. J Mag Reson Imaging. 2018;47:301–315.
14 Bjurlin MA, Carroll PR, Eggener SE, et al. Update of the standard operating procedure on the use of multiparametric magnetic resonance imaging for the diagnosis, staging and management of prostate cancer. J Urol. 2020;197:706–712.
15 Banerjee R, Pavlides M, Tunnicliffe E, et al. Multiparametric magnetic resonance for the diagnosis, staging and management of prostate cancer. Radiography. 2018;50:1120–1126.
16 Pavlides M, Banerjee R, Tunnicliffe E, et al. Multiparametric magnetic resonance for the assessment of non-alcoholic fatty liver disease severity. Liver Int. 2017;37:1065–1073.
17 Bradley CR, Cox EF, Scott RA, et al. Multigland assessment of compensated cirrhosis patients using quantitative magnetic resonance imaging. J Hepatol. 2018;69:1015–1024.
18 Everett RJ, Trehelb TA, Fukui M, et al. Extracellular myocellular volume in patients with aortic stenosis. J Am Coll Cardiol. 2020;75:104–116.
19 Bachtar V, Kelly M, Willham H, et al. Repeatability and reproducibility of multiparametric magnetic resonance imaging of the liver. PLoS ONE. 2015;10:e0214521.
20 Harrison S, Dennis A, Fiore M, et al. Utility and variability of three non-invasive liver fibrosis imaging modalities to evaluate efficacy of RE-MD-02 in subjects with NASH and bridging fibrosis during a phase-2 randomized clinical trial. PLoS ONE. 2018;13:e0201054.
21 Eddowes P, Mcdonald N, Davies NI, et al. Utility and cost evaluation of multiparametric magnetic resonance imaging for the assessment of non-alcoholic fatty liver disease. Aliment Pharmacol Ther. 2018;47:631–644.
22 McDonald N, Eddowes P, Hodson J, et al. Multiparametric magnetic resonance imaging for quantification of liver disease: a two-centre cross-sectional observational study. Sci Rep. 2018;8:9189.

www.thelancet.com Vol 46 Month April, 2022 10
23 Blake L, Duarte RV, Cummins C. Decision analytic model of the diagnostic pathways for patients with suspected non-alcoholic fatty liver disease using non-invasive transient elastography and multiparametric magnetic resonance imaging. BMJ Open. 2016;6:e010507.

24 Harrison S, Rossi S, Paredes A, et al. NGM282 improves liver fibrosis and histology in 12 weeks in patients with nonalcoholic steatohepatitis. Hepatology. 2020;71:1198–1212.

25 Arndtz K, Shumbayawond E, Hodson J, et al. Multiparametric MRI imaging, autoimmune hepatitis, and prediction of disease activity. Hepatol Commun. 2021. https://doi.org/10.1002/hep4.1687.

26 Alvarez F, Berg PA, Bianchi FB, et al. International autoimmune hepatitis group report: review of criteria for diagnosis of autoimmune hepatitis. J Hepatol. 1999;31:929–938.

27 Henness EM, Zeniya M, Czaja AJ, et al. Simplified criteria for the diagnosis of autoimmune hepatitis. Hepatology. 2008;48:169–176.

28 Hartl J, Hanno E, Weiler-Normann C, et al. Patient selection based on treatment duration and liver biochemistry increases success rates after treatment withdrawal in autoimmune hepatitis. J Hepatol. 2015;62:642–646.

29 Janowski K, Shumbayawonda E, Dennis A, et al. Multiparametric MRI as a non-invasive monitoring tool for children with autoimmune hepatitis. J Pediatr Gastroenterol Nutr. 2021;72(1):108–114. Jan 1.

30 Terziroli Beretta-Piccoli B, Mieli-Vergani G, Vergani D. Autoimmune hepatitis: standard treatment and systematic review of alternative treatments. World J Gastroenterol. 2017;23:6030–6048.

31 Hartl J, Ekhen H, Sebode M, et al. Usefulness of biochemical remission and transient elastography in monitoring disease course in autoimmune hepatitis. J Hepatol. 2018;68:754–763.

32 Venkatesh S, Yin M, Ehman R. Magnetic resonance elastography of liver: technique, analysis, and clinical applications. J Magn Reson Imaging. 2011;33:444–455.

33 Loomba R, Wolfson T, Ang B, et al. Magnetic resonance elastography predicts advanced fibrosis in patients with nonalcoholic fatty liver disease: a prospective study. Hepatology. 2014;60:1920–1928.

34 Karlas T, Pfrepper C, Rosendahl J, et al. Acoustic radiation force impulse (ARFI) elastography in acute liver failure: necrosis mimics cirrhosis. Z Gastroenterol. 2011;49:443–448.

35 Bota S, Herkner H, Sporea I, et al. Meta-analysis: ARFI elastography versus transient elastography for the evaluation of liver fibrosis. Liver Int. 2013;33:1148–1147.

36 Morishita N, Hiramatsu N, Oze T, et al. Liver stiffness measurement by acoustic radiation force impulse is useful in predicting the presence of esophageal varices or high-risk esophageal varices among patients with HCV-related cirrhosis. J Gastroenterol. 2014;49:1173–1182.

37 Rider O, Banerjee R, Rayner J, et al. Investigating a liver fat: arterial stiffening pathway in adult and childhood obesity. Arterioscler Thromb Vasc Biol. 2016;36:198–203.

38 Pavlides M, Banerjee R, Sellwood J, et al. Multiparametric magnetic resonance imaging predicts clinical outcomes in patients with chronic liver disease. J Hepatol. 2016;65:308–315.

39 Yuan X, Duan SZ, Cao J, Gao N, Xu J, Zhang L. Noninvasive inflammatory markers for assessing liver fibrosis stage in autoimmune hepatitis patients. Eur J Gastroenterol Hepatol. 2019;31:1467–1474.

40 Heneghan MA, Allan ML, Bornstein JD, Muir AJ, Tendler DA. Utility of thiopurine methyltransferase genotyping and phenotyping, and measurement of azathioprine metabolites in the management of patients with autoimmune hepatitis. J Hepatol. 2006;45:584–591.