



Prognostic value of multiparametric magnetic resonance imaging, transient elastography and blood-based fibrosis markers in patients with chronic liver disease

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Abstract

Background & Aims: Liver cT_1 , liver T_1 , transient elastography (TE) and blood-based biomarkers have independently been shown to predict clinical outcomes but have not been directly compared in a single cohort of patients. Our aim was to compare these tests' prognostic value in a cohort of patients with compensated chronic liver disease.

Methods: Patients with unselected compensated liver disease aetiologies had baseline assessments and were followed up for development of clinical outcomes, blinded to the imaging results. The prognostic value of non-invasive liver tests at prespecified thresholds was assessed for a combined clinical endpoint comprising ascites, variceal bleeding, hepatic encephalopathy, hepatocellular carcinoma, liver transplantation and mortality.

Results: One hundred and ninety-seven patients (61% male) with median age of 54 years were followed up for 693 patient-years (median (IQR) 43 (26–58) months). The main diagnoses were NAFLD (41%), viral hepatitis (VH, 25%) and alcohol-related liver disease (ArLD; 14%). During follow-up 14 new clinical events, and 11 deaths occurred. Clinical outcomes were predicted by liver $cT_1 > 825$ ms with HR 9.9 (95% CI: 1.29–76.4, $P = .007$), TE > 8 kPa with HR 7.8 (95% CI: 0.97–62.3, $P = .02$) and FIB-4 > 1.45 with HR 4.09 (95% CI: 0.90–18.4, $P = .05$). In analysis taking into account technical failure and unreliability, liver $cT_1 > 825$ ms could predict clinical outcomes ($P = .03$), but TE > 8 kPa could not ($P = .4$).

Conclusions: We provide further evidence that liver cT_1 , TE and serum-based biomarkers can predict clinical outcomes, but when taking into account technical failure/unreliability, TE cut-offs perform worse than those of cT_1 and blood biomarkers.

KEYWORDS

¹H-MRS, iron-corrected T_1 , Liver MultiScan, T_1 mapping, T_2^* mapping

1 | BACKGROUND AND AIMS

Chronic liver diseases (CLDs) affect an estimated 1.5 billion people worldwide,¹ with the predominant causes being non-alcoholic fatty liver disease (NAFLD),² chronic viral hepatitis (VH) B and C³ and alcohol.⁴ Liver fibrosis is the final common pathway of injury in CLDs. Once fibrosis progresses to cirrhosis, each year approximately 5%-7% will become decompensated⁵ (develop variceal bleeding, ascites and hepatic encephalopathy). Cirrhosis is the 11th most common cause of mortality worldwide⁶ and liver cancer is reported as the 4th most common cause of cancer-related mortality.⁷

In the face of this public health epidemic there is an unmet clinical need to stratify disease severity in patients with CLD and to flag patients at risk of decompensation as early as possible. Liver biopsy is used routinely in clinical practice to assess fibrosis stage and inform prognosis,⁸ but is unsuitable for routine longitudinal follow-up of patients because of its invasive nature, associated risk and cost.

The magnetic resonance imaging (MRI) parameter T_1 , when corrected for iron content (cT_1)⁹ can quantify extracellular water content, which rises with fibrosis and inflammation. Liver cT_1 correlates with liver fibrosis¹⁰ and severity of steatohepatitis,¹¹ has excellent repeatability and reproducibility,¹² and is used in the UK Biobank population health study as the reference for liver fibroinflammatory disease.¹³ Liver cT_1 , when stratified into groups according to a liver inflammation and fibrosis (LIF) score, was found to predict clinical outcomes in a general hepatology outpatient setting by Pavlides *et al.*¹⁴ Liver cT_1 is no longer converted into the LIF score and refinement of the algorithm used to generate liver cT_1 now enables it to be standardised across MRI scanner field strengths and vendors. Liver T_1 has also been shown to be associated with development of clinical outcomes in other cohorts^{15,16}

Transient elastography (TE) correlates with fibrosis^{17,18} and can predict clinical outcomes.¹⁹⁻²¹ Fibrosis-4 (FIB-4), aspartate aminotransferase to platelet ratio index (APRI) and AST/ALT ratio are commonly used markers of liver fibrosis/inflammation and have also been shown to predict clinical outcomes in patients with CLD.²²⁻²⁵ To date there has been no study evaluating the prognostic significance of MRI, TE and blood-based markers alongside histology as a reference.

Using a larger cohort of patients with CLD, over longer follow-up than Pavlides *et al.*, the primary aim of this study was to assess the prognostic value of liver cT_1 . Secondary aims were to assess the relative prognostic value of other liver-related biomarkers, including liver fat measured by MR proton spectroscopy (^1H -MRS), liver iron measured by T_2^* , transient elastography (TE), histological fibrosis stage and blood-based composite scores (FIB-4, APRI and AST/ALT ratio).

2 | PATIENTS AND METHODS

2.1 | Patient selection

This study follows up patients from two cohort studies primarily assessing the role of MRI in liver disease assessment (details in

Lay summary

Liver disease affects people in different ways with some more likely to get worse than others. Liver biopsy involves passing a needle into the body to collect a sample of the liver. Liver biopsy helps assess how severe the liver disease is and the likelihood it will get worse in the future. Liver biopsies, however, are expensive and carry a risk of bleeding and other complications. There is, therefore, a need for alternative non-invasive tests that can inform clinical decision making as a liver biopsy would, but without the risks. In this study, we assessed whether 3 types of non-invasive test could predict which patients' liver disease would worsen in the future. We found that magnetic resonance imaging (MRI) scans, measurement of liver stiffness (called transient elastography (TE)) and blood-based tests can all help identify patients who are more likely to get worse liver disease in the future.

Table S1). Patients referred for a clinically indicated liver biopsy, or with a known diagnosis of liver cirrhosis, were eligible to take part. Patients were recruited from hepatology services in a teaching hospital and large district general hospital in the UK between May 2011 and July 2017. Patients with contraindications to MRI scanning were excluded. The studies were approved by the United Kingdom National Research Ethics Service (UK NRES references 13/SC/0243 and 11/H0504/2) and were conducted according to the declaration of Helsinki. All patients gave written and informed consent.

At baseline, patients underwent multiparametric MRI scans, TE and blood sampling following a minimum of 4 hours fasting.

2.2 | MRI protocol

All MRI scans were carried out at the University of Oxford Centre for Clinical Magnetic Resonance Research (OCMR) on a 3T Siemens Tim Trio scanner (Erlangen, Germany). Patients underwent the LiverMultiScanTM (Perspectum Diagnostics Ltd, Oxford, UK) acquisition protocol for T_1 and T_2^* mapping and ^1H -MRS, as previously described.^{9,10}

2.3 | MR Analysis

Spectroscopic data were fitted using the OXSA toolbox²⁶ implementation of the AMARES algorithm²⁷ with an in-house MATLAB (The Mathworks, Natick, MA, USA) script.²⁸ Liver fat fraction was calculated as the fat signal divided by the total fat and water signal.

LiverMultiScanTM is a software product, developed specifically to measure T_1 , T_2^* (iron content) and cT_1 (liver fibroinflammation), and was used for the image analysis in this study. Images were analysed

by trained analysts blinded to the clinical and histological data (for details, see Supplementary methods; for example images, see Figure S1).

In previous publications,¹⁴ cT_1 was tri-linearly mapped to a discrete scoring system graded from 0 to 4 named the LIF score in an attempt to align with histological assessment gradations. The LIF score is no longer supported by LiverMultiScanTM, and here we report cT_1 values.

2.4 | Histological assessment

All liver biopsies were performed as part of the patients' clinical care using 18G needles for percutaneous biopsies and 19G needles for transjugular biopsies (quality and timing reported in Supplementary Information). All biopsies were included in the analysis as they were used to inform clinical care irrespective of the core length or number of portal tracts. All biopsies were assessed for the Ishak stage by a specialist liver histopathologist blinded to the imaging data. Fibrosis severity was defined as mild (Ishak F0-2), moderate (Ishak F3-4) and severe (Ishak F5-6).

2.5 | Blood samples

Blood samples were taken on the same day as the MRI scan. Simple scores for serum-based fibrosis markers Fibrosis-4 (FIB-4),²⁹ aspartate aminotransferase/alanine aminotransferase (AST/ALT) ratio and AST to platelet ratio index (APRI)³⁰ were calculated.

2.6 | Transient elastography (liver stiffness)

Transient elastography (TE) measurements of liver stiffness were performed using Fibroscan® (Echosens, Paris) by trained operators with no prior experience. The M probe was used first and, if unable to obtain a measurement, the XL probe was then used. For a successful measurement, 10 valid readings were required and, as per recommended guidelines, unreliable readings were defined as having an IQR/median > 0.3, or success rate < 60%. Failure was defined as no measurement obtained using either M or XL probes.

2.7 | Clinical follow up

Outcome data were extracted from the patients' electronic medical records. The primary clinical endpoint was a composite endpoint comprising ascites, variceal bleeding, hepatic encephalopathy, hepatocellular carcinoma (HCC), liver transplantation and mortality. A secondary endpoint was all-cause mortality. Patient records were reviewed by two researchers (blinded for review) blinded to the patients' MRI and liver-related biomarker results until the patients' latest medical evaluation, until they died, or

were censored at 72 months maximum follow-up. Disagreements were adjudicated by a senior clinician (blinded for review). Patients were considered "lost to follow-up" if they did not return for any clinical follow-up after their baseline assessments. Where multiple events occurred, only the first event was counted in analysis. Patients were excluded if they had decompensated liver disease at baseline as a non-invasive liver test is unlikely to be needed in these patients.

2.8 | Statistical analysis

Baseline statistics are described as mean \pm standard deviation (SD) for normally distributed variables and median (interquartile range (IQR)) for non-normally distributed variables. The primary outcome was survival of the composite endpoint, hereafter, termed a 'clinical event'. All-cause mortality was a secondary endpoint. Survival analysis was carried out on all the available data for each outcome with each biomarker, missing results were excluded from analysis and no imputation performed. Kaplan-Meier curves were compared using the log-rank test to evaluate significance of survival differences of binary and grouped cut-offs. All p values quoted for binary cut-offs were calculated using the log-rank test. Cox proportional hazards analysis was used to calculate hazard ratios (HRs) for grouped and continuous variables. Where impossible to obtain a hazard ratio in cut-off analysis (because of zero events occurring in a group), sensitivity, specificity, positive predictive value (PPV) and negative predictive values (NPV) were reported. Receiver Operator Curve (ROC) analysis was performed for all continuous variables for the identification of patients who developed a new clinical event.

The primary variable of interest was liver cT_1 . Cut-off values were predefined with $cT_1 > 825$ ms corresponding to the previously reported LIF score ≥ 2 ¹⁴ and the best (Youden index) cut-off was also assessed. Liver cT_1 was also grouped using the cut-offs corresponding to the 90% sensitivity and 90% specificity for identification of clinical events. To determine the importance of iron correction, we also assessed uncorrected liver T_1 at 825 ms and the best cut-off (Youden index) for prediction of events as there were no previously reported cut-offs at 3T.

Secondary variables were liver iron as measured by T_2^* , liver fat as measured by $^1\text{H-MRS}$, liver stiffness as measured by TE, Ishak fibrosis stage, APRI, FIB-4 and AST/ALT. Cut-off values were chosen based on the literature (see Supplementary methods). Effect of treatment for underlying liver disease, presence of type 2 diabetes, body mass index (BMI) >30 kg/m² and age were also analysed for prediction of outcomes.

Given the spatial heterogeneity of disease often seen in autoimmune hepatitis (AIH) and biliary liver disease, which could affect the reliability of MRI and TE through sampling error, subgroup analysis was conducted for event-free survival in patients with only the 3 main liver disease aetiologies (NAFLD, ArLD and VH) where disease distribution is more homogenous.

To address the influence of technical rate of failure/unreliability of tests, separate intention to diagnose (ITD) analysis was conducted for event-free survival taking into account all attempted measurements, including technical failures and unreliable results. Unreliable results were included, and failed attempts were assigned either as false positive or false negative depending on the patient's outcome, generating 3 x 2 tables (Table S2).³¹

Non-invasive tests were assessed for event-free survival by multivariate Cox proportional hazards analysis in variables with sufficient data available.

Statistical significance was set at $P < .05$. Analysis was performed, and plots generated using R Statistical software.³²

3 | RESULTS

3.1 | Cohort characteristics

Two-hundred-and-thirty-five patients were included, of which 17 (7%) were lost to follow up and 21 (9%) were excluded for having decompensated liver disease at baseline (Figure 1). In total, 197 patients were followed up for a total of 693 patient-years with a median (IQR) follow-up of 43 (26-58) months.

Baseline characteristics for the whole cohort and for those who had/did not have clinical events are shown in Table 1. The three most common aetiologies of chronic liver disease were NAFLD ($n = 85$, 43%), ArLD ($n = 22$, 11%) and VH ($n = 50$, 25%). Overall, 178 (90%) patients had liver biopsy, in whom fibrosis was mild, moderate and severe in 95 (48%), 28 (14%) and 55 (28%) respectively. Fifty-nine patients had their underlying liver disease treated during the follow-up period—these included patients with chronic hepatitis C achieving a sustained virological response (SVR) ($n = 29$), patients with chronic hepatitis B achieving viral suppression ($n = 8$), patients regularly consuming harmful amounts of alcohol achieving complete abstinence

($n = 3$) and patients undergoing bariatric surgery who lost $> 10\%$ body weight ($n = 9$).

There were 14 new clinical events. Mortality occurred in 11 patients of which five patients died from non-liver-related causes (Table S3). Concordance of clinical event reporting between adjudicators was 93% (see Supplementary information for details).

Patients who had clinical events were older and had higher prevalence of ArLD, more severe fibrosis by histology and non-invasive biomarkers (serum scores, liver stiffness and liver cT_1), higher AST, ALP, GGT and bilirubin and lower albumin and platelets than patients without clinical events (Table 1).

3.2 | Survival analysis by biomarker

3.2.1 | Liver cT_1

3.2.1.1 | Whole cohort

MR scanning was successful in 182 of 197 (92%) patients, but failed in 15 (3 had claustrophobia, 1 did not fit in the scanner and 13 scans were of poor quality).

On univariate Cox regression, liver cT_1 had HR 1.007 (95% CI: 1.003-1.011, $P = .001$, Table S4) for event-free survival (0.7% increase in risk for every 1 ms increase in cT_1 ; equivalent to HR 1.91; 91% doubling of risk per 100 ms). Liver cT_1 had HR 1.007 (doubling of risk per 100 ms, 95% CI: 1.002-1.012, $P = .007$) for all-cause mortality.

The prespecified cut-off of liver $cT_1 > 825$ ms could predict event-free survival with HR 9.9 (95% CI: 1.29-76.2, $P = .007$) and all-cause mortality with HR 7.74 (95% CI: 0.98-61.2, $P = .02$, Figure 2A-B, Table S5). Liver $cT_1 > 825$ ms correctly identified 12/13 (92%) clinical events and 9/10 (90%) deaths.

The best cut-off for cT_1 was > 840 ms, which predicted event-free survival with HR 12.1 (95% CI: 1.57-93.1, $P = .002$, Figure 2C, Table S5) and all-cause mortality with HR 9.4 (95% CI: 1.19-74.2, $P = .01$).

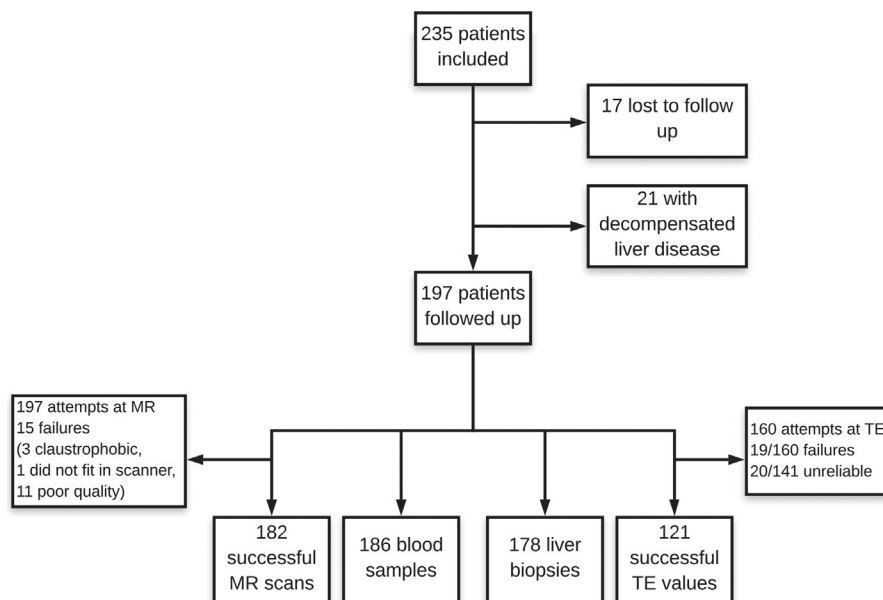


FIGURE 1 Flow diagram of study

TABLE 1 Baseline patient characteristics

	All (n = 197)	Event free (n = 183)	With events (n = 14)	P value
Age (years)	53 (44-59)	51 (44-59)	61 (57-69)	.004
Male	123 (62)	112 (61)	11 (79)	.198
BMI (kg/m ²)	28.4 (24.8-34.0)	28.4 (25.1-33.6)	31.9 (24.7-34.8)	.528
T2DM	42 (21)	37 (20)	5 (36)	.143
Excess alcohol use	31 (16)	26 (14)	5 (36)	.027
Treatment during follow-up period	59 (30)	56 (31)	3 (21)	.472
Primary disease aetiology				
Viral hepatitis	50 (25)	47 (26)	3 (21.5)	.255
NAFLD	85 (43)	80 (44)	5 (36)	.348
ArLD	22 (11)	19 (10)	3 (21.5)	.201
PSC/PBC/AIH	16 (8)	15 (8)	1 (7)	.713
Other ^a	24 (13)	22 (12)	2 (14)	.216
Histological fibrosis; Ishak stage				
Mild; F0-2	95 (48)	93 (51)	2 (14)	<.0001
Moderate; F3-4	28 (14)	28 (15)	0 (0)	
Severe; F5-6	55 (28)	44 (24)	11 (79)	
No biopsy	19 (10)	18 (10)	1 (7)	
Blood results				
ALT (IU/L)	49 (30-92)	51 (30-92)	46 (29-81)	.906
AST (IU/L)	41 (28-68)	39 (28-66)	55 (45-90)	.013
Albumin (g/L)	44 (41-46)	44 (42-47)	39 (35-44)	.0004
ALP (IU/L)	174 (130-238)	170 (125-233)	301 (178-406)	.0110
Bilirubin (μmol/L)	11 (8-16)	10 (7-15)	24 (14-34)	.0003
GGT (IU/L)	72 (35-144)	67 (33-122)	345 (90-409)	.0013
Platelets (x 10 ⁹ L)	196 (151-267)	201 (155-269)	105 (74-130)	.0005
Serum biomarkers				
FIB-4	1.59 (0.92-2.69)	1.51 (0.88-2.48)	5.46 (4.25-10.45)	<.0001
AST/ALT	0.87 (0.60-1.17)	0.83 (0.59-1.13)	1.27 (1.16-1.79)	.0027
APRI	0.53 (0.31-0.95)	0.50 (0.30-0.88)	1.11 (0.92-2.18)	.0003
Liver stiffness (kPa)	8.0 (5.6-14.6)	7.8 (5.5-10.9)	29.9 (15.1-35.3)	.0010
Liver cT ₁ (ms)	840 (787-925)	837 (786-923)	901 (871-1068)	.0033
Liver fat (%)	4.90 (1.45-10.74)	5.00 (1.43-10.88)	4.28 (1.70-6.90)	.435
T2* (ms)	19.4 (14.0-22.5)	19.2 (13.9-22.6)	20.8 (18.4-21.1)	.495

Results shown are median (interquartile range) or n (%). P values quoted for the differences between patients with events and no events using the Wilcoxon non-parametric test.

Abbreviations: alanine aminotransferase, AST; alcohol-related liver disease, PSC; alkaline phosphatase, GGT; ALT; aspartate aminotransferase, ALP; AST-platelet ratio index, cT₁; autoimmune hepatitis; BMI; body mass index, T2DM; fibrosis-4 score, APRI; gamma-glutamyltransferase, FIB-4; iron-corrected T₁; non-alcoholic fatty liver disease, ArLD; primary biliary cholangitis, AIH; primary sclerosing cholangitis, PBC; type 2 diabetes mellitus, NAFLD.

^aOther included cryptogenic cirrhosis, no specific features, sarcoid, cholestasis and haemochromatosis.

Liver cT₁ when stratified into groups showed significant increase in risk of clinical events with increasing cT₁ thresholds ($P < .001$, Figure 2D, Table S6).

In ITD analysis, liver cT₁ > 825 ms predicted event-free survival with HR 4.64 (95% CI: 1.04-20.8, $P = .03$) and cT₁ > 840ms with HR 5.57 (95% CI: 1.24-25.0, $P = .01$).

3.2.1.2 | NAFLD/ArLD/VH subgroup

In the NAFLD/ArLD/VH subgroup ($n = 148$), liver cT_1 predicted event-free survival with HR 1.007 (95% CI: 1.002-1.011, $P = .005$, Table S7).

Liver $cT_1 > 825$ ms predicted event-free survival ($P = .006$), identifying all 11 events (Figure 3A, Table S8). When stratified into groups, liver cT_1 showed significant increase in risk of clinical events with increasing cT_1 thresholds ($P = .0048$) (Figure 3B, Table S9).

In ITD analysis liver $cT_1 > 825$ ms could predict event-free survival ($P = .009$), identifying all events.

3.2.2 | Liver T_1

3.2.2.1 | Whole cohort

Uncorrected liver T_1 had HR 1.006 ($P = .006$, 95% CI: 1.002-1.01) for event-free survival and HR 1.007 ($P = .007$, 95% CI: 1.002-1.0011) for all-cause mortality.

Liver $T_1 > 825$ ms was not predictive of event-free survival ($P = .08$) or all-cause mortality ($P = .06$) and identified 10/13 (77%) clinical events correctly (Figure 4A, Table S5).

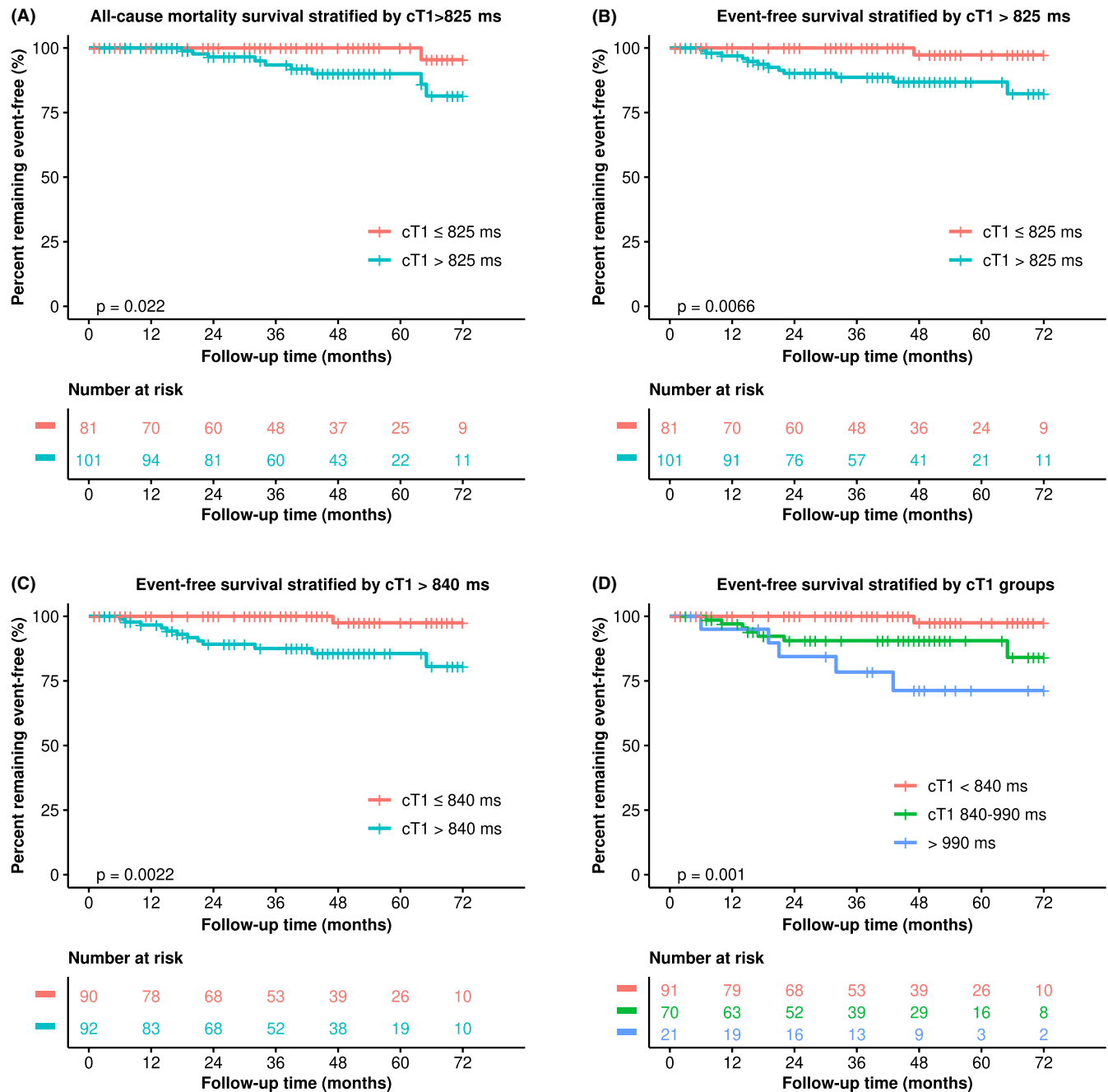


FIGURE 2 Kaplan-Meier plots for survival of clinical events stratified by liver cT_1 . Plots show (A) survival from all-cause mortality, (B) event-free survival, each stratified by liver $cT_1 > 825$ ms, (C) event-free survival stratified by $cT_1 > 840$ ms and (D) event-free survival stratified by cT_1 groups (<840 ms, $840-990$ ms and > 990 ms) in $n = 182$ patients with chronic liver disease. P values for differences between survival curves were generated by the log-rank test

The best cut-off for liver T_1 was > 868 ms, which predicted event-free survival with HR 5.47 (95% CI: 1.50-20.0, $P = .004$, 10/13 (77%) events identified, Figure 4B, Table S5) and all-cause mortality with HR 7.2 (95% CI: 1.53-34.3, $P = .004$).

In ITD analysis ($n = 197$, 14 events) neither liver $T_1 > 825$ ms nor $T_1 > 868$ ms could predict event-free survival ($P = .2$ and 0.07 respectively).

3.2.2.2 | NAFLD/ArLD/VH subgroup

T_1 predicted event-free survival in the NAFLD/ArLD/VH subgroup with HR 1.005 (95% CI: 1.001-1.009, $P = .02$).

$T_1 > 825$ ms was unable to predict event-free survival in the NAFLD/ArLD/VH subgroup ($P = .09$, Figure 4A, Table S8). $T_1 > 868$ ms was able to predict event-free survival in the NAFLD/ArLD/VH subgroup with HR 6.17 (95% CI: 1.33-28.7, $P = .008$, Figure 4B) as well as in ITD analysis HR 5.32 (95% CI: 1.14-24.7, $P = .02$), in both cases identifying 9/11 (82%) events.

3.2.3 | Liver iron and liver fat

Neither liver iron nor liver fat was predictive of clinical outcomes in either the whole cohort or the subset of NAFLD/ArLD/VH (Tables S4, S5, S7 and S8).

3.2.4 | Histology

3.2.4.1 | Whole cohort

Biopsies were performed in 178/197 (90%) patients. In those with biopsies there were 13 clinical events and 11 deaths.

As a semi-continuous variable, Ishak stage could predict event-free survival with HR 1.99 between stages (95% CI: 1.32-3.01, $P = .001$, Table S10, Figure S2) and all-cause mortality with HR 1.82 (95% CI: 1.21-2.74, $P = .004$).

Ishak stage $\geq F5$ predicted event-free survival with HR 12.6 (95% CI: 2.80-57.1, $P < .0001$, 11/13 (85%) events identified) and all-cause mortality with HR 9.75 (95% CI: 2.11-45.1, $P = .004$, 9/11 (82%) events identified).

When grouped into mild, moderate and severe fibrosis, Ishak stage showed an increase in risk of clinical events ($P = .002$, Table S10, Figure S2). Patients with moderate fibrosis showed no greater risk of clinical events than those with mild fibrosis.

3.2.4.2 | NAFLD/ArLD/VH subgroup

In the NAFLD/ArLD/VH subgroup ($n = 142$), Ishak stage could predict event-free survival ($P < .001$, Table S8).

Ishak fibrosis stage $\geq F5$ was predictive of event-free survival ($P < .0001$), identifying 10/10 (100%) events.

3.2.5 | Transient elastography

3.2.5.1 | Whole cohort

TE was attempted in 160/197 (81%) patients with technical failure observed in 19 (12%). From the remaining 141 measurements, unreliable values were observed in 20 (14%) with 121 (76%) reliable TE measurements remaining.

TE predicted event-free survival with HR 1.062 (95% CI: 1.03-1.09, $P < .001$) and all-cause mortality with HR 1.069 (95% CI: 1.03-1.11, $P < .001$).

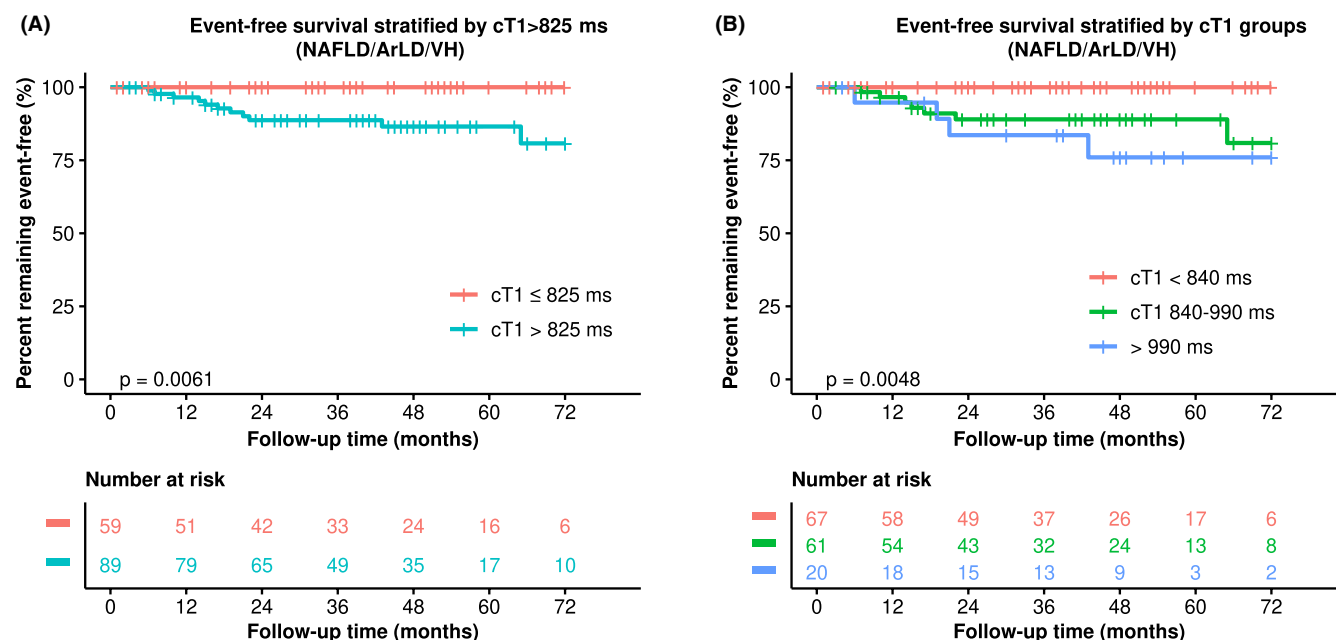


FIGURE 3 Kaplan-Meier plots for survival of clinical events stratified by liver cT_1 in a subset of patients with NAFLD, ArLD and viral hepatitis (VH). Patients ($n = 148$) were stratified by (A) liver $cT_1 > 825$ ms and (B) by cT_1 groups of < 840 ms, 840-930 ms and > 930 ms P values for differences between survival curves were generated by the log-rank test

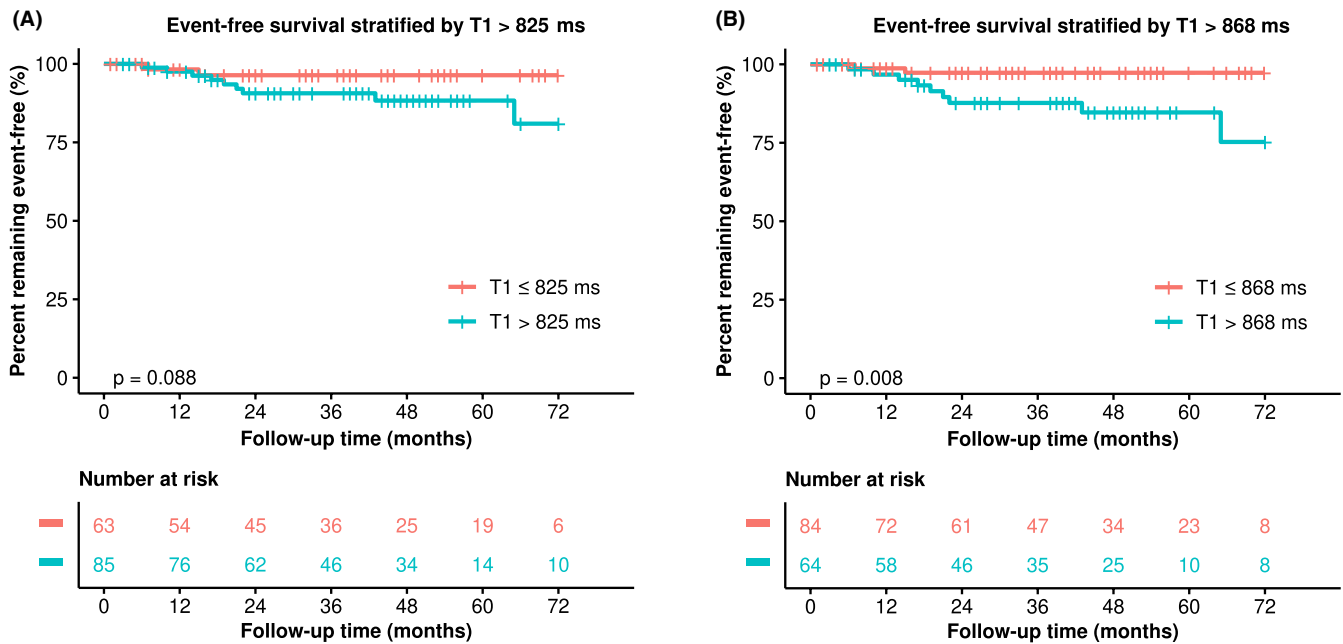


FIGURE 4 Kaplan-Meier plots for survival of clinical events stratified by liver T_1 . Patients ($n = 182$) were stratified by (A) liver $T_1 > 825$ ms and (B) $T_1 < 868$ ms P values for differences between survival curves were generated by the log-rank test

TE > 8 kPa could predict all-cause mortality ($P = .008$) identifying all deaths and event-free survival ($P = .02$), identifying 8/9 (89%) clinical events.

When stratified into groups, TE showed significant increase in risk of clinical events with increasing TE thresholds ($P < .0001$, Table S11, Figure S3).

In ITD analysis, TE > 8 kPa could not predict event-free survival ($P = .4$).

3.2.5.2 | NAFLD/ArLD/VH subgroup

In the NAFLD/ArLD/VH subgroup, TE was attempted in 126/157, failed in 14/126 (11%) and was unreliable in 15/112 (13%) (total failed and/or unreliable in 29/126 (23%).

In the 97 patients with reliable measurements, TE predicted liver event-free survival with HR 1.083 (95% CI: 1.039-1.129, $P < .001$).

TE > 8 kPa was not predictive of event-free survival ($P = .06$), identifying 6/7 (86%) events and not predictive of event-free survival in ITD analysis ($P = .5$).

When stratified into groups, TE showed significant increase in risk of liver events with increasing TE thresholds ($P < .001$, Table S12).

3.2.6 | Serum-based fibrosis markers

3.2.6.1 | Whole cohort

FIB-4 predicted event-free survival with HR: 1.24 (95% CI: 1.15-1.34, $P < .001$) and all-cause mortality with HR 1.25 (95% CI: 1.14-1.37, $P < .001$). APRI did not predict event-free survival ($P = .8$) nor all-cause mortality ($P = .995$). AST/ALT ratio predicted event-free survival with HR 2.61 (95% CI: 1.61-4.21, $P < .001$) and all-cause mortality with HR 3.11 (95% CI: 1.79-5.40, $P < .001$).

FIB-4 > 1.45 predicted event-free survival with HR 4.11 (95% CI: 0.91-18.56, $P = .05$, 11/13 (85%) events identified, Figure S4). APRI > 1 did not predict event-free survival ($P = .07$). AST/ALT ratio > 1 predicted event-free survival with HR 6.09 (95% CI: 1.67-22.2, $P = .002$, 10/13 (77%) events identified, Figure S5).

ITD analysis results were exactly the same as there were no failed tests.

3.2.6.2 | NAFLD/ArLD/VH subgroup

In the patients with serum blood tests available, there were $n = 148$, with 11 clinical events occurring.

FIB-4 could all predict event-free survival with HR 1.52 (95% CI: 1.29-1.79, $P < .001$). APRI could predict event-free survival with HR 1.93 (95% CI: 1.35-2.75, $P < .001$). AST/ALT ratio could predict event-free survival with HR 3.34 (95% CI: 1.97-5.68, $P < .001$).

FIB-4 > 1.45 could predict event-free survival with HR 7.08 (95% CI: 0.90-56, $P = .03$, 9/10 (90%) events identified), APRI > 1 could predict event-free survival HR 4.37 (95% CI: 1.23-15.6, $P = .01$, 6/10 (60%) events identified) and AST/ALT > 1 could predict event-free survival with HR 18.3 (95% CI: 2.32-144, $P < .001$, 9/10 (90%) events identified).

The details of the intention to diagnose analysis for all biomarkers are included in the supplement (Tables S13-S19).

3.2.7 | Traditional risk factors

Age was predictive of event-free survival ($P = .008$, HR: 1.073, 95% CI: 1.02-1.13) and all-cause mortality (HR 1.08, 95% CI: 1.02-1.15, $P = .02$). Neither presence of type 2 diabetes nor BMI > 30 kg/m²

nor treatment for underlying liver disease was predictive of event-free survival or all-cause mortality.

3.3 | Multivariate analysis

TE was excluded as a result of insufficient quantity of data. No more than two variables were assessed together because of the low number of events per variable (EPV).

3.3.1 | Continuous variables

Liver cT_1 showed a trend towards being predictive of event-free survival independently of liver T_1 . Liver cT_1 was predictive of event-free survival independently of APRI score. Liver cT_1 was not predictive of event-free survival independently of either FIB-4 or AST/ALT ratio, (Table 2). Liver cT_1 was predictive of event-free survival independently of Age (Table S20).

3.3.2 | Binary cut-offs

Liver $cT_1 > 825$ ms was predictive of event-free survival independently of $T_1 > 825$ ms. Liver $cT_1 > 825$ ms was predictive of event-free survival independently of FIB-4 > 1.45 and AST/ALT > 1 but not APRI > 1 , (Table 3).

All multivariate analysis results should be taken with caution as EPV varied between 6 and 7 rather than the recommended 10.

4 | DISCUSSION

We have shown further evidence with 693 patient-years of follow-up that liver cT_1 can predict all-cause mortality and event-free survival. The prognostic values of uncorrected liver T_1 , TE, Ishak fibrosis stage and blood-based markers of liver disease severity were also assessed in the same cohort. Liver $cT_1 > 825$ ms correctly identified 12/13 (92%) of clinical events and performed even better when the patient cohort was restricted to NAFLD, ArLD and VH, identifying all liver events.

Higher liver T_1 has been shown in a previous study to be associated with the development of liver-related clinical outcomes, albeit in a cohort of patients with CLD with normal liver iron content.¹⁵ In our study there were two patients correctly identified by liver $cT_1 > 825$ ms who developed liver events who were missed by uncorrected $T_1 > 825$ ms. This reduced the correct classification percentage from 92% to 77%. The best T_1 cut-off was > 868 ms, which could not predict clinical events in ITD analysis, whereas cT_1 's best cut-off of > 840 ms could. As liver iron content itself (as measured by MRI T_2^*) was not predictive of clinical outcomes, these results underscore the utility of the iron correction method. This is especially important given the prevalence of elevated liver iron content in the general population³³ and in patients with ArLD and NAFLD.

Although excess liver fat can accelerate fibrosis progression in certain patients,³⁴ our results showed no association of liver fat with clinical outcomes. This supports other studies that have shown histological liver fibrosis is the only parameter independently associated with poorer outcomes.⁸

TABLE 2 Cox proportional hazards multivariate analysis for event-free survival—continuous variables

	Hazard ratio	95% CI	P value	Number of observations and events
Liver cT_1 and T_1				
cT_1	1.0072	1.00-1.015	.053	182 observations, 13 events
T_1	0.9996	0.99-1.006	.897	
Cox model	-	—	.004	
Liver cT_1 and APRI				
cT_1	1.0057	1.001-1.010	.010	172 observations, 12 events
APRI	0.9977	0.926-1.08	.953	
Cox model	-	—	.03	
Liver cT_1 and FIB-4				
cT_1	1.004	0.998-1.009	.215	171 observations, 12 events
FIB-4	1.390	1.19-1.62	<.0001	
Cox model	-	—	<.0001	
Liver cT_1 and AST/ALT				
cT_1	1.004	1.000-1.008	.065	173 observations, 12 events
AST/ALT	2.267	1.34-3.85	.002	
Cox model	—	—	<.0001	

TABLE 3 Cox proportional hazards multivariate analysis for event-free survival—binary cut-offs

	Hazard ratio	95% CI	P value	Number of observations and events
Liver cT ₁ > 825 ms and T ₁ > 825 ms				
cT ₁ > 825 ms	18.6	1.73-199	.016	182 observations, 13 events
T ₁ > 825 ms	0.47	0.10-2.12	.327	
Cox model	—	—	.01	
Liver cT ₁ > 825 ms and APRI > 1				
cT ₁ > 825 ms	7.7	0.97-61.7	.054	172 observations, 12 events
APRI > 1	2.1	0.65-6.60	.215	
Cox model	—	—	.01	
Liver cT ₁ > 825 ms and FIB-4 > 1.45				
cT ₁ > 825 ms	8.1	1.04-63	.046	171 observations, 12 events
FIB-4 > 1.45	2.9	0.63-13	.171	
Cox model	—	—	.01	
Liver cT ₁ > 825 ms and AST/ALT > 1				
cT ₁ > 825 ms	10.7	1.4-83	.023	173 observations, 12 events
AST/ALT > 1	9.7	2.1-44	.003	
Cox model	—	—	<.0001	

In comparison to Ishak fibrosis stage F5-6, which could identify 11/13 (85%) of clinical events, cT₁ > 825 ms identified 12/13 (92%) events. Liver cT₁ > 825 ms also had a similarly high NPV to biopsy for the exclusion of patients with events (99% vs 98%), indicating its suitability as a screening test.

Here, liver cT₁ but not TE at their respective prespecified cut-offs could predict event-free survival—this is likely because of the lower number of events assessed by reliable TE results, as on univariate analysis TE was strongly predictive of developing clinical events. Additionally, when failed/unreliable results were accounted for, TE > 8 kPa was unable to predict liver event-free survival, whereas liver cT₁ > 825 ms could. This was not a true intention-to-diagnose analysis as there were no data collected on patients excluded at the outset as a result of MRI contraindications, therefore, the success rates of MRI and TE in the general CLD population may be different. Our reported TE failure rates are comparable to studies in NAFLD,²² but higher than in other prognostic studies conducted in cohorts with no or smaller (<13.5%) proportions of NAFLD patients.¹⁹⁻²¹ Our cohort contained a significant proportion (43%) of NAFLD patients (including patients scheduled for bariatric surgery), in which it is reported that TE performs less well and can reach failure/unreliability rates of 20%.³⁵ This is an important consideration with NAFLD now the most prevalent CLD. The inexperience of the operators may have influenced the high failure/unreliability rate, as has been reported in previous studies.^{35,36}

A distinct advantage of cT₁ therefore is its technical success rate, also reported as 98% vs 85% for TE in a study including patients with obesity and ascites.³⁷ In our study, liver cT₁ failed mainly in those who either were unable to enter the scanner (claustrophobia) or with extremely high iron (haemochromatosis), degrading the T₂* signal. Liver cT₁ also has excellent test-retest repeatability and reproducibility

metrics¹² compared with a high coefficient of variation for TE.³⁸ In clinical practice, if a TE measurement is unreliable/fails, patients are often biopsied. Liver cT₁ would be a useful diagnostic alternative to TE—or as a second-line test after TE in failed cases—to avoid unnecessary biopsies. Liver cT₁ will perhaps be most useful in NAFLD/ArLD/VH where we have shown it has the most prognostic value and has been shown in other studies to be cost-effective in the non-invasive risk stratification³⁹ and diagnostic pathway of NAFLD.⁴⁰

In this study, the serum-based composite biomarkers FIB-4 performed well overall with AST/ALT performing well in the subset of patients with NAFLD/ArLD/VH. FIB-4 has performed well in tertiary care settings,^{41,42} often performing better in patients with hepatitis C^{23,42} than NAFLD²²/ArLD.²⁴ AST/ALT ratio's prognostic ability has also been limited to few studies in patients with viral hepatitis,^{25,43} so its excellent performance here must be taken in context of those results. Blood tests are cheap, easily repeatable and not susceptible to 'technical failure', however, guidelines⁴⁴ suggest that they should not be used in isolation as a result of their reduced specificity for liver disease but should be combined with other modalities.

Liver cT₁ is likely to have a greater impact earlier rather than later in the screening process for the detection of early liver fibroinflammatory disease and help in monitoring these patients non-invasively. Studies of even larger cohorts may bring out these differences in the future.

We have shown liver cT₁ performs especially well in the most prevalent CLDs, namely, NAFLD, ArLD and VH, with cT₁ cut-offs correctly identifying all liver events. These particular diseases represent a significant financial cost to the UK's social and healthcare systems.⁴⁵ Accurate, cost-effective stratification of these patients with non-invasive biomarkers would allow significant savings in time and money and an increase in patient comfort. There is also an unmet need for reliable

non-invasive endpoints in NASH drug development. Liver cT₁ can differentiate simple steatosis from NASH,¹¹ and the prognostic value of liver cT₁ shown in this study provides further evidence to support the use of liver cT₁ for prognostic enrichment in NASH drug trials.

We conducted multivariate analysis which indicated liver cT₁ to perform as well as T₁, better than APRI, but worse than FIB-4 and AST/ALT. However, analysis also showed that at the prespecified cut-offs, liver cT₁ performed better than T₁ and FIB-4 and similarly to AST/ALT and APRI. Meaningful cut-offs are desirable in clinical use, indicating liver cT₁ has independent clinical prognostic relevance. These multivariate results should be taken with caution as the number of events per variable was lower than the minimum recommended threshold⁴⁶ and therefore may yield results with high margin of error.

Limitations of this study included no fixed follow-up time point. This means that the AUC analyses, sensitivities, specificities, PPVs and NPVs generated in cut-off analysis should be taken with caution because unlike in Cox proportional hazards and Kaplan-Meier analysis, the effect of patients being censored at different time points is not taken into account. Our patient cohort included a wide range of liver disease severity and aetiologies from patients with mild fibrosis to those with cirrhosis. Future studies should examine the prognostic value of liver cT₁ alongside other non-invasive tests in prespecified liver disease severity groups.

In conclusion, liver iron-corrected T₁ (cT₁), TE and serum-based blood biomarkers can identify patients at risk of developing clinical outcomes in a cohort with mixed CLD aetiologies, typical of general hepatology cohorts, but when taking into account technical failures of MRI and TE, MRI and blood markers perform better than TE. Further multicentre studies should be carried out to validate our results.

CONFLICTS OF INTEREST

ANAJ, EMT, MK, EB, SN, RB and MP are shareholders in Perspectum Ltd. RB is on the board of directors of Perspectum. RB, AD and MK are employees of Perspectum. EMT, EB, SN, RB and MP have filed patent applications related to the use of MRI for the assessment of liver disease. CL, EAS, JCB, JC, JC and EAS have nothing to declare.

AUTHORS' CONTRIBUTIONS

MP, RB, SN and EB designed the study. ANAJ and EAS collected outcome data. EMT developed the iron correction method. ANAJ and AD performed the statistical analysis. CL, RB, JCB, JC, JC, EB and MP recruited patients to the study. ANAJ, CL, MK, SN, EB, RB and MP drafted the manuscript. All authors reviewed the manuscript critically and have approved the final version.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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