Perspectum

cT1 as a Reasonably Likely Surrogate Endpoint in MASH clinical trials

Rajarshi Banerjee, CEO

BM BCh MA(Oxon) MRCP(UK) MPH DPhil

4th April 2025

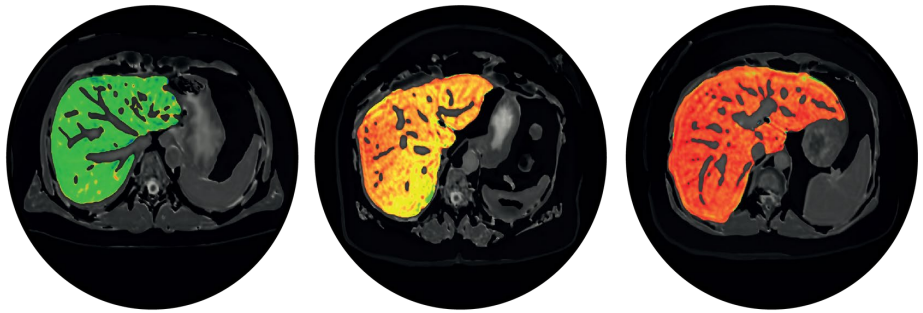
Disclosures and disclaimers

Rajarshi Banerjee is CEO and shareholder of Perspectum

Materials presented are for educational and scientific exchange only. Not for sales or promotional use

The information presented herein reflects a potential context of use (COU) for cT1 to be applied in clinical trials as a monitoring biomarker and a reasonably likely surrogate endpoint.

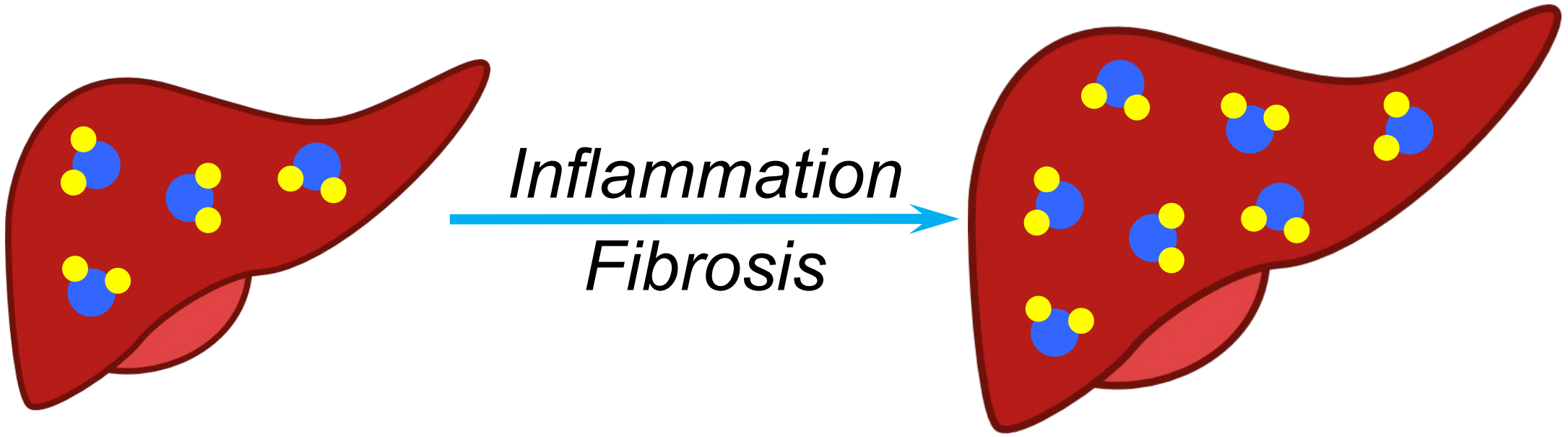
Contents



- What is cT1?
- Biological plausibility
- Diagnostic accuracy
- Prognostic accuracy
- Sensitivity to change

T1 as a Biomarker for MASH

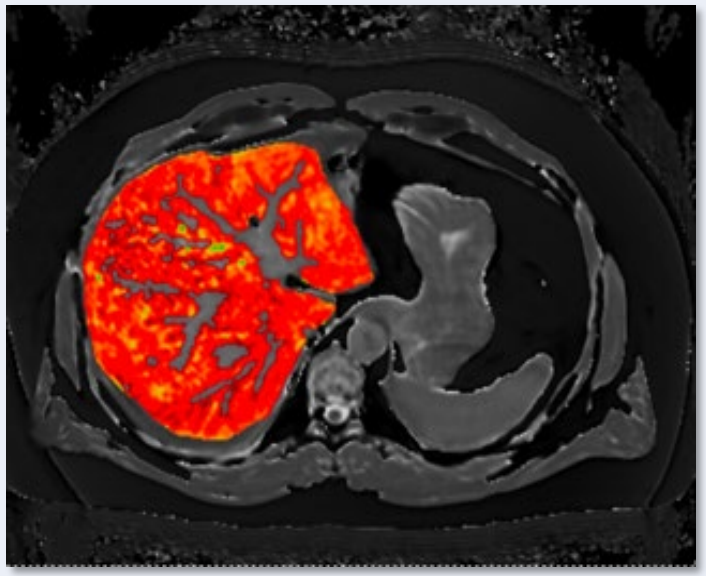
Fundamental magnetic property of tissue



Increased water content
…increased T1

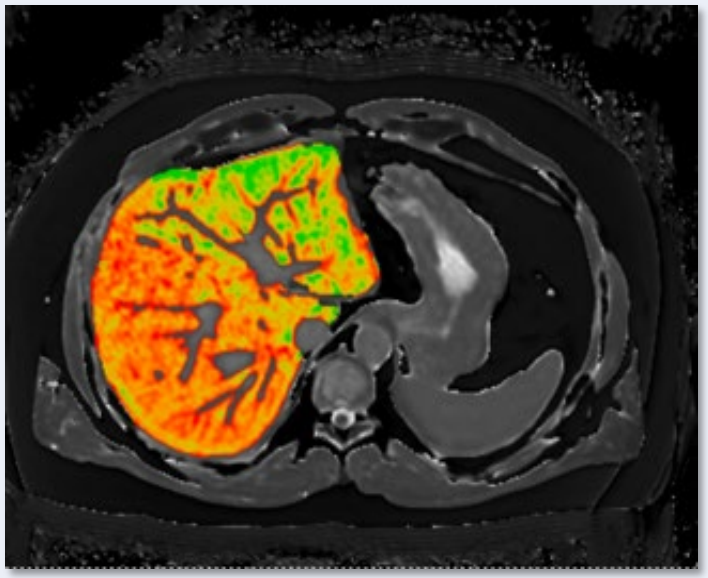
A “Virtual Biopsy” of the Liver

Start of treatment



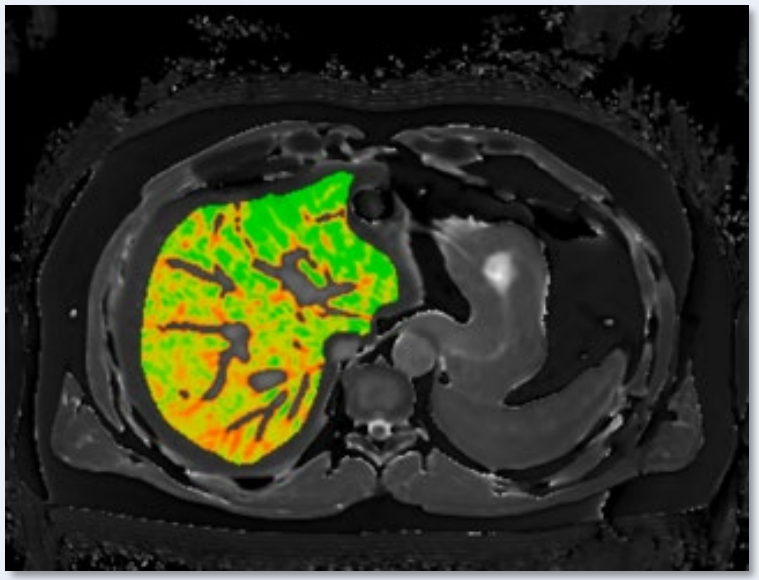
cT1 – 1041 ms

Week 6



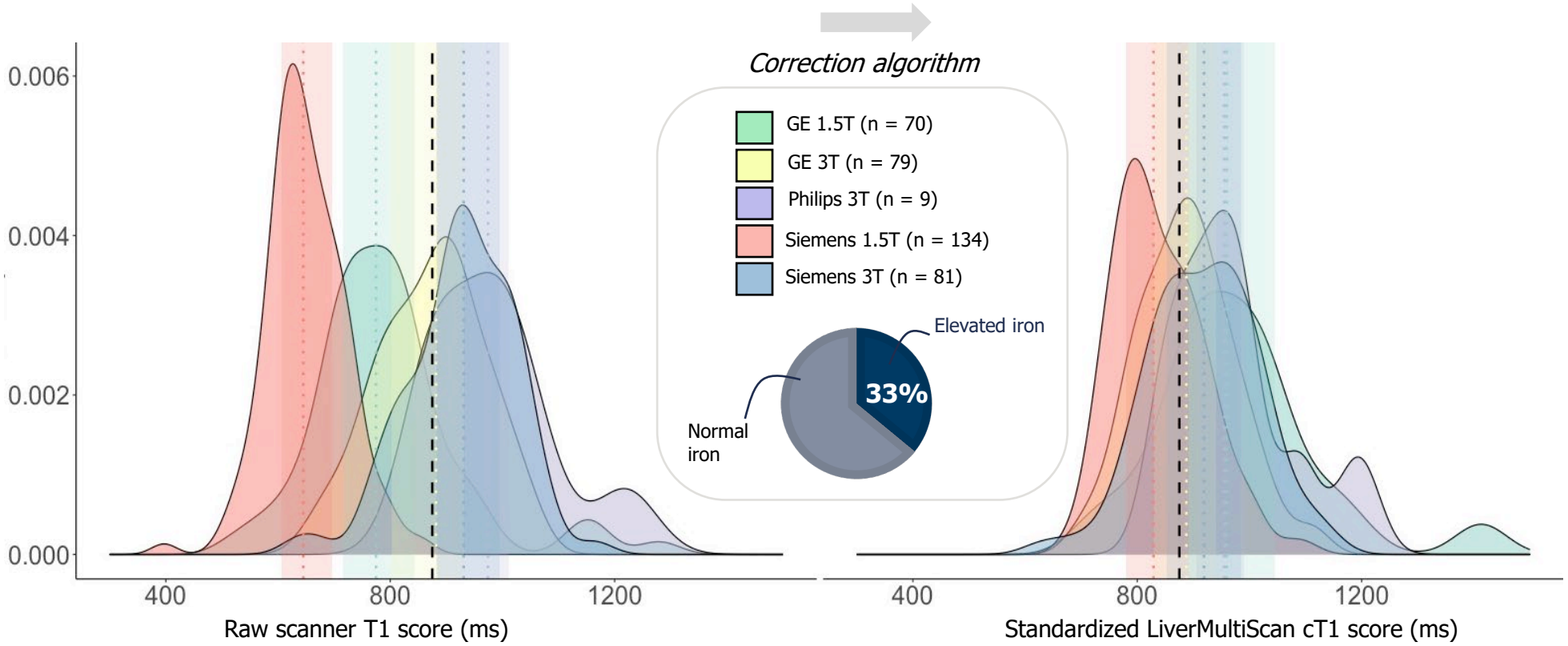
cT1 – 864 ms

Week 12



cT1 – 772 ms

cT1 as a standardised biomarker for MASH

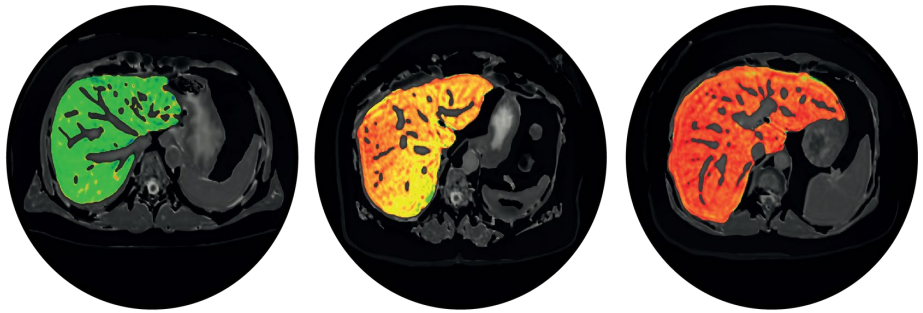


- cT1 upper limit of normal is 800ms
- cT1 optimal threshold for at-risk MASH is 875ms
- cT1 ≥ 875ms identified approximately twice the number of patients with biopsy confirmed at-risk MASH compared to T1 ≥ 875ms

Fig 1. The colored dotted lines represent the medians, and the shaded regions represent the interquartile range of T1 and cT1 across each scanner.

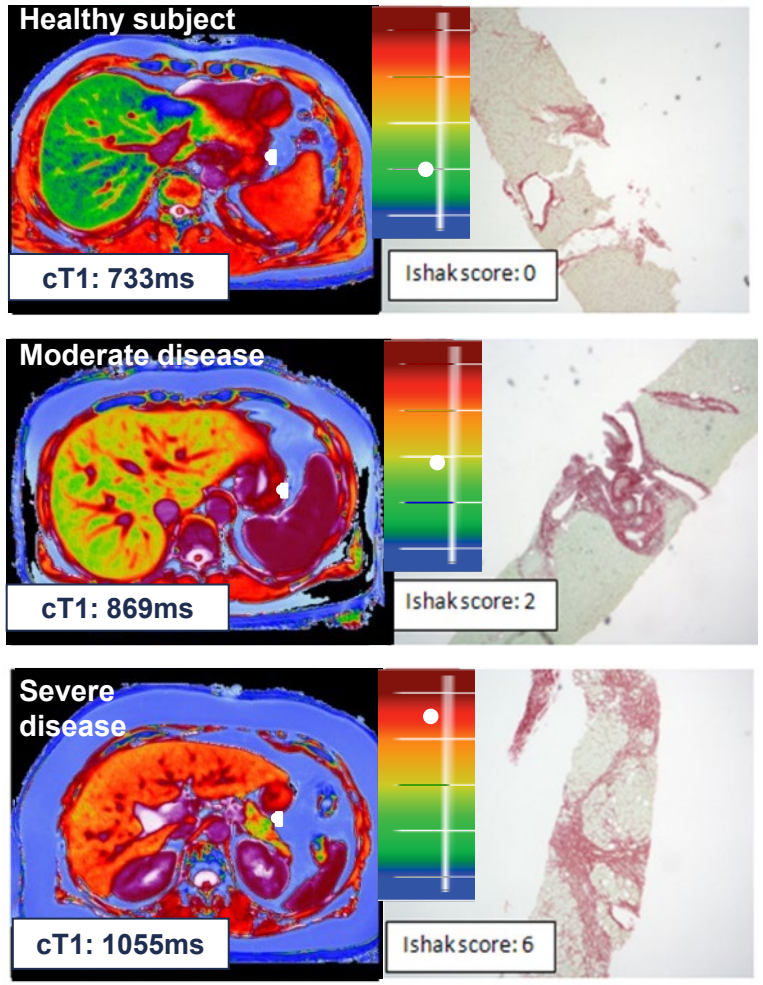
Nadziruddin, I., et al. Hepatology; 2024; 80 (S1). **Presented at AASLD 2024**

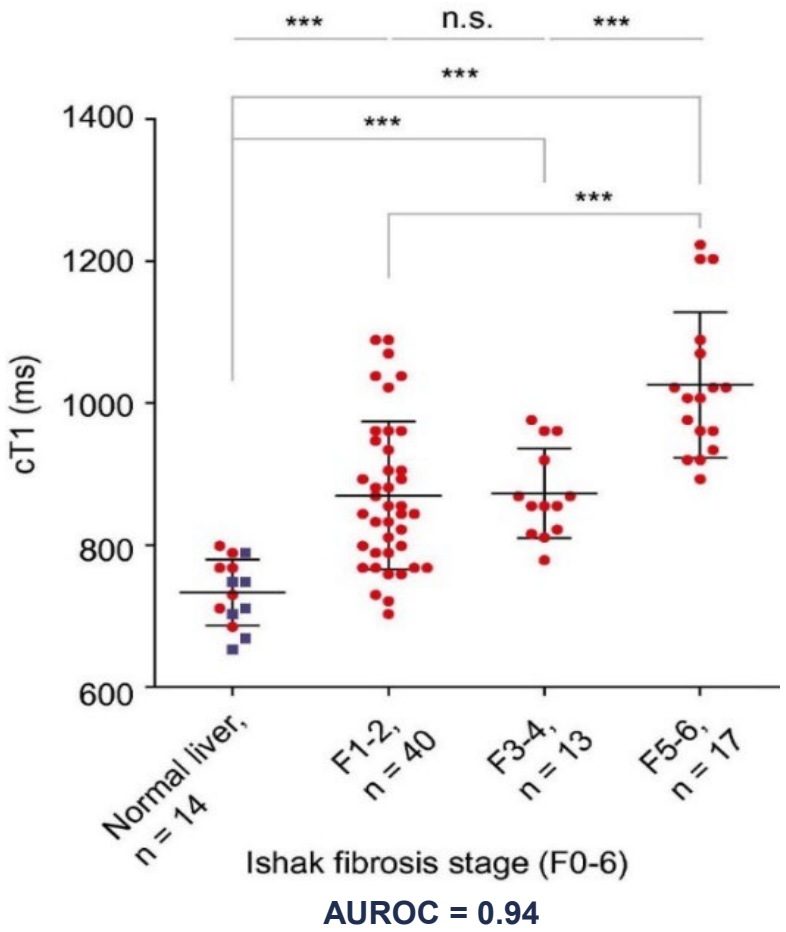
Contents



- What is cT1?
- Biological plausibility
- Diagnostic accuracy
- Prognostic accuracy
- Sensitivity to change

Clinical validation study shows cT1 can stage chronic liver disease, compared to histology





- Prospective single-center study in subjects with various liver diseases (n=79):

Study population diagnosis	
Viral hepatitis	31 subjects
Steatohepatitis	31 subjects
Other	17 subjects

- Severity of disease was staged using **Ishak fibrosis score (F0-6)**; widely accepted for fibrosis & necroinflammation in viral hepatitis C
- Sub-analysis was performed on steatohepatitis patients using **NAFLD Fibrosis Stage (F0–F4)**

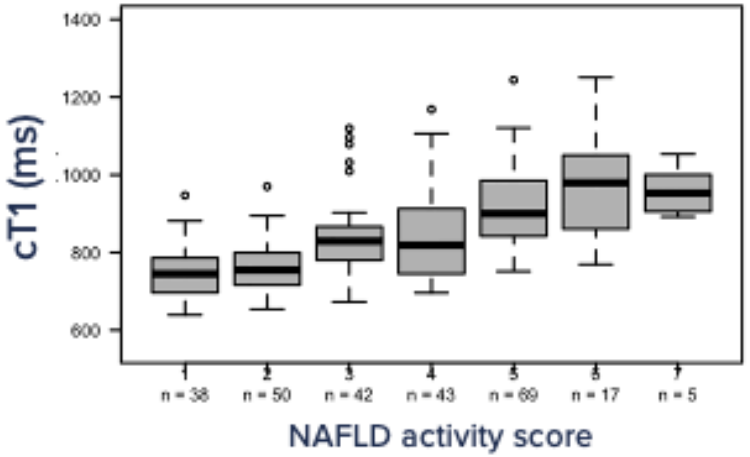
Banerjee et al. Journal of Hepatology; 2014; vol 60

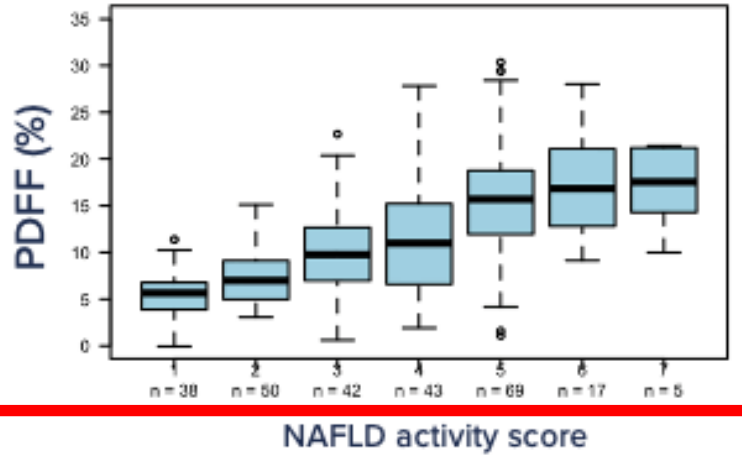
Correlations Between MRI Biomarkers PDFF and cT1 With Histopathological Features of Non-Alcoholic Steatohepatitis

Andrea Dennis[1], Matt D. Kelly[1], Carolina Fernandes[1], Sofia Mouchti[1], Jonathan A. Fallowfield[2], Gideon Hirschfield[3], Michael Pavlides[4,5,6], Stepl Manu V. Chakravarthy[8], Rajarshi Banerjee[1] and Arun Sanyal[9]*

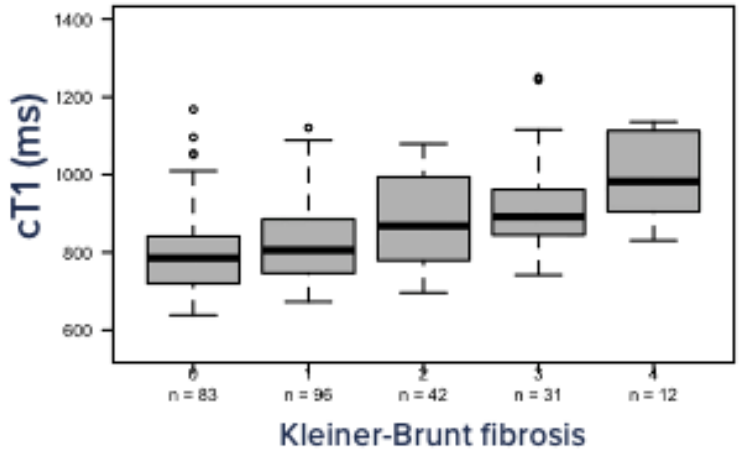
frontiers in Endocrinology

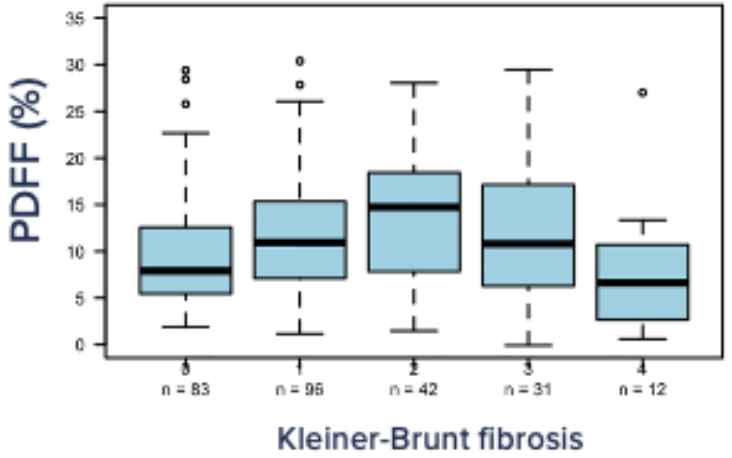
Associations with NAFLD activity score →



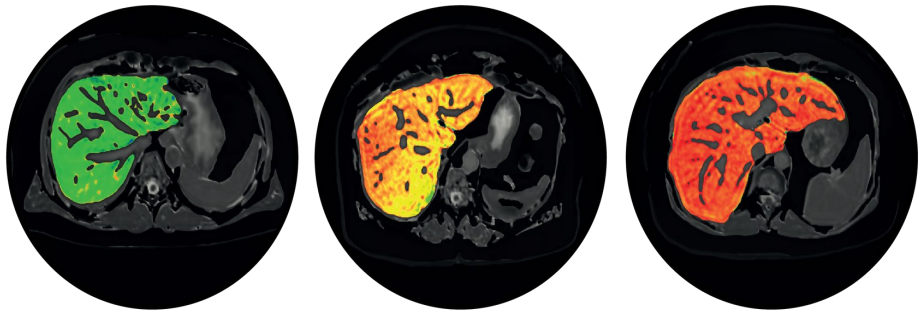


Associations with fibrosis →





Contents



- What is cT1?
- Biological plausibility
- Diagnostic accuracy
- Prognostic accuracy
- Sensitivity to change

cT1 for diagnosing MASH

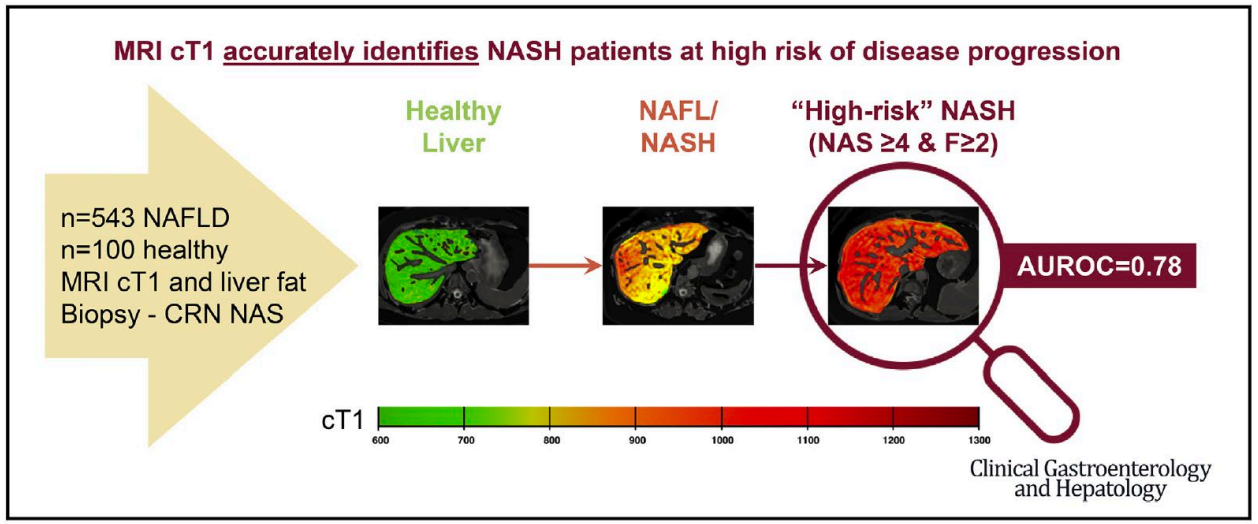
Clinical Gastroenterology and Hepatology 2022;20:2451–2461

SYSTEMATIC REVIEWS AND META-ANALYSES

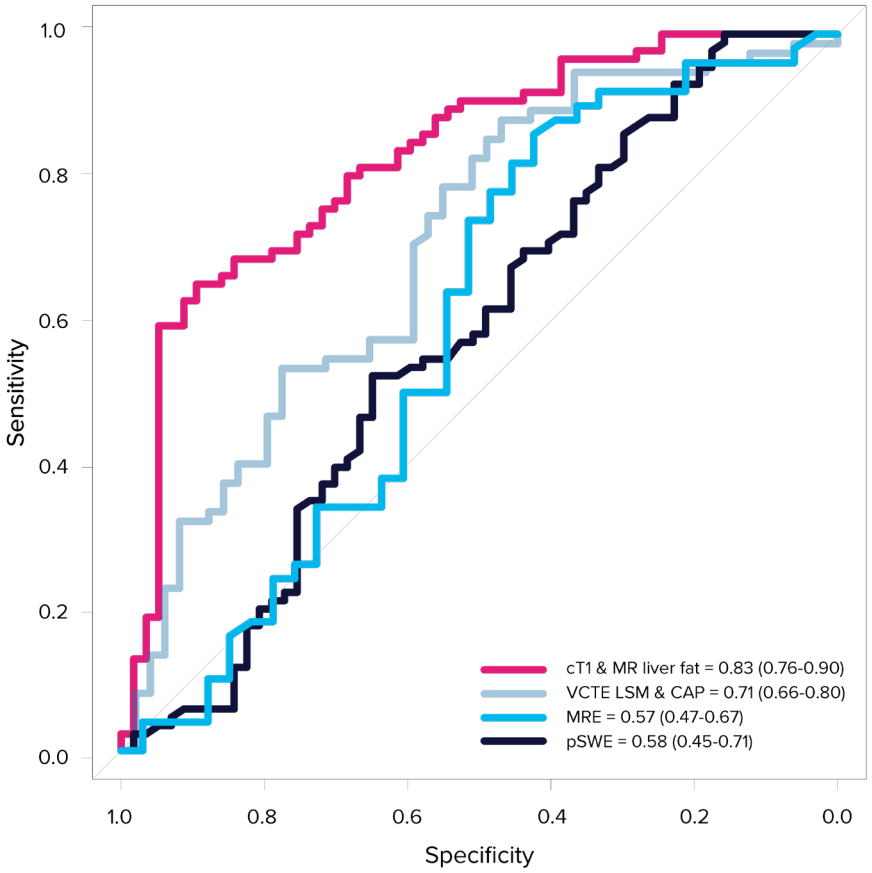
Siddharth Singh, Section Editor

Clinical Utility of Magnetic Resonance Imaging Biomarkers for Identifying Nonalcoholic Steatohepatitis Patients at High Risk of Progression: A Multicenter Pooled Data and Meta-Analysis

Anneli Andersson,[*] Matt Kelly,[*] Kento Imajo,[‡] Atsushi Nakajima,[‡] Jonathan A. Fallowfield,[§] Gideon Hirschfield,[||] Michael Pavlides,[¶,#,**] Arun J. Sanyal,[‡‡] Mazen Noureddin,[§§] Rajarshi Banerjee,[*] Andrea Dennis,[*] and Stephen Harrison[¶]



AUROC curves for diagnosing NASH
(n= 144 biopsy confirmed NAFLD patients)

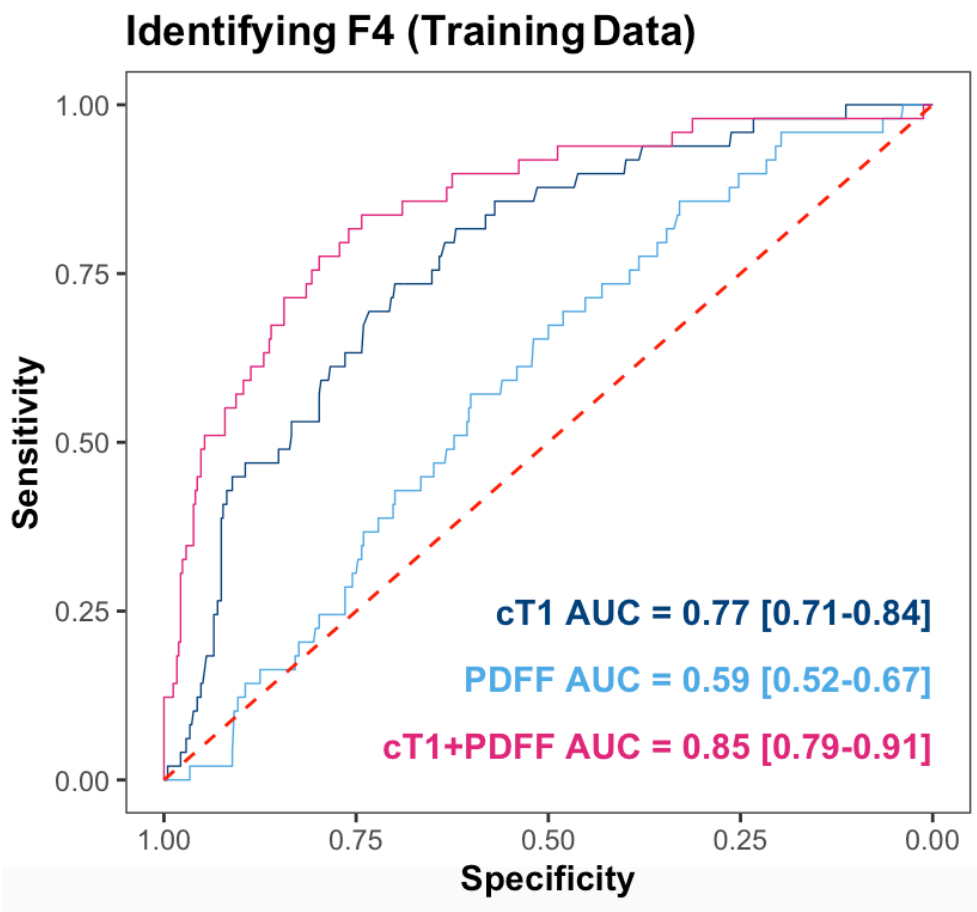


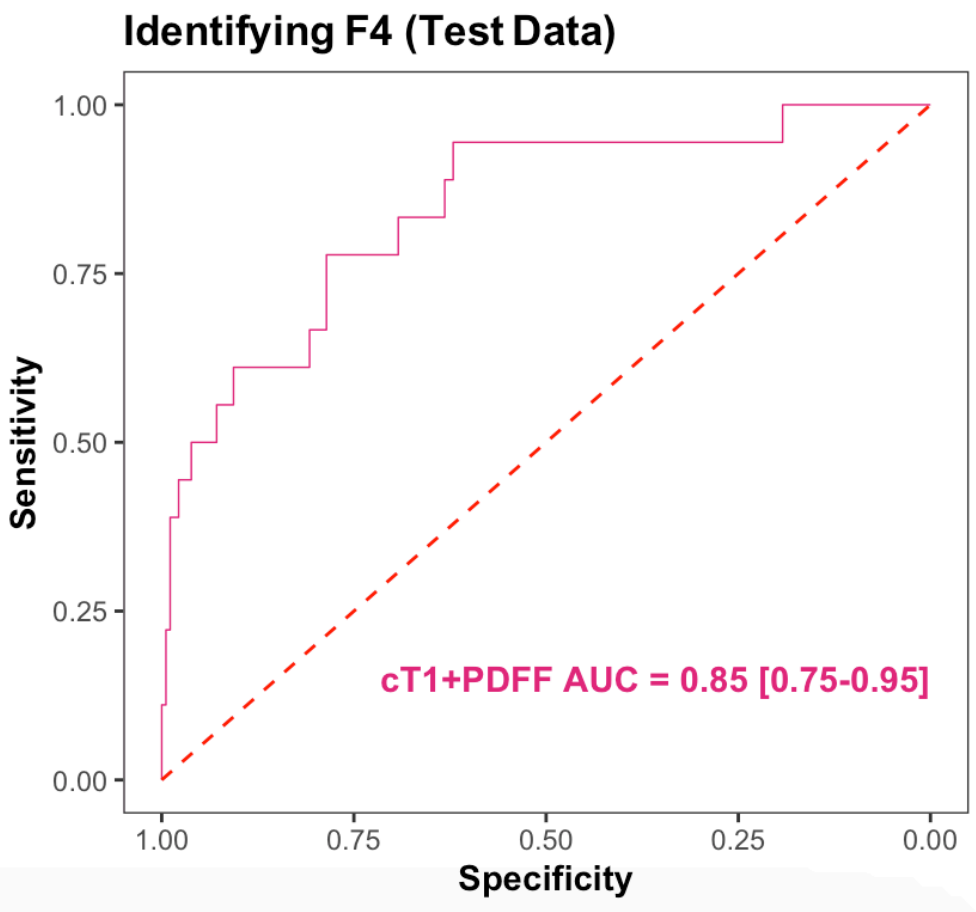
Perspectum

Andersson A, et al. Clinical Gastroenterology and Hepatology. 2022; 20.

Imajo K, et al. World J Gastroenterol. 2021; 27(7)

Combining cT1 with PDFF for the exclusion of patients with cirrhosis

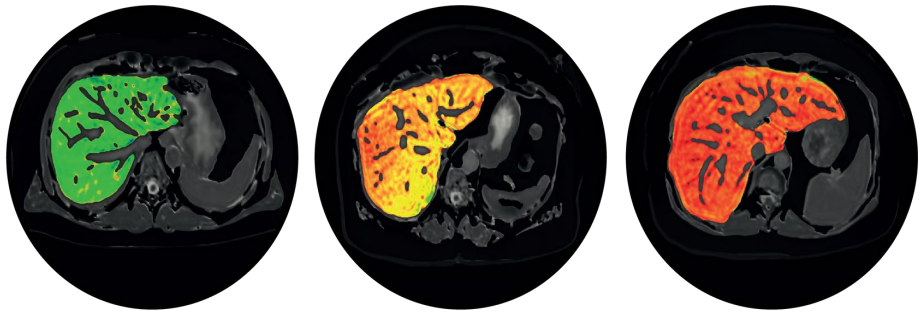




Data were N= 465 in training and N=200 in the validation data sets. F4 confirmed by biopsy

Data unpublished

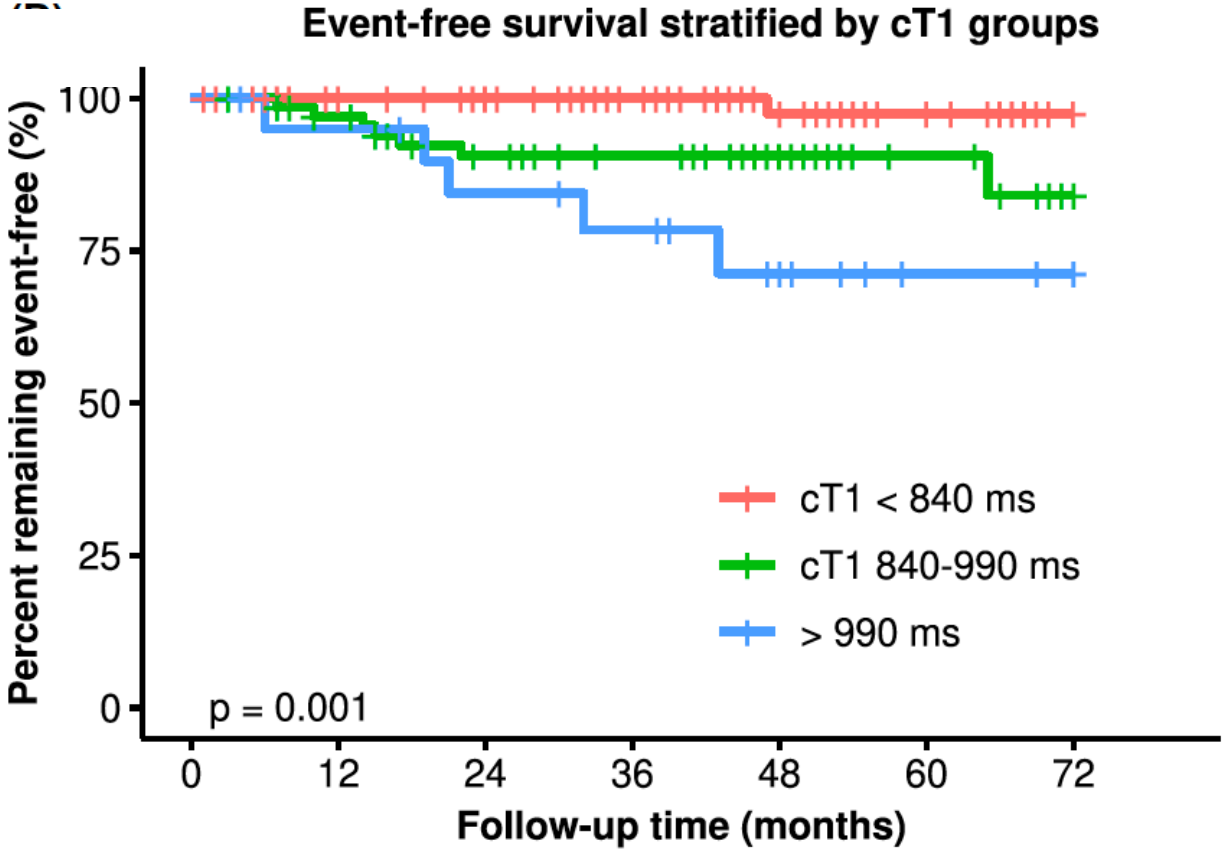
Contents



- What is cT1?
- Biological plausibility
- Diagnostic accuracy
- Prognostic accuracy
- Sensitivity to change

cT1 is prognostic in patients with chronic liver disease

- 182 patients with chronic liver disease; 85 with MASLD
- Average follow up time 43 (26-58) months
- 14 liver related events; 11 liver related deaths



3.2.1 | Liver cT_1

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 > 840ms, 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).

3.2.2 | Liver T_1

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).

3.2.3 | Liver iron and liver fat

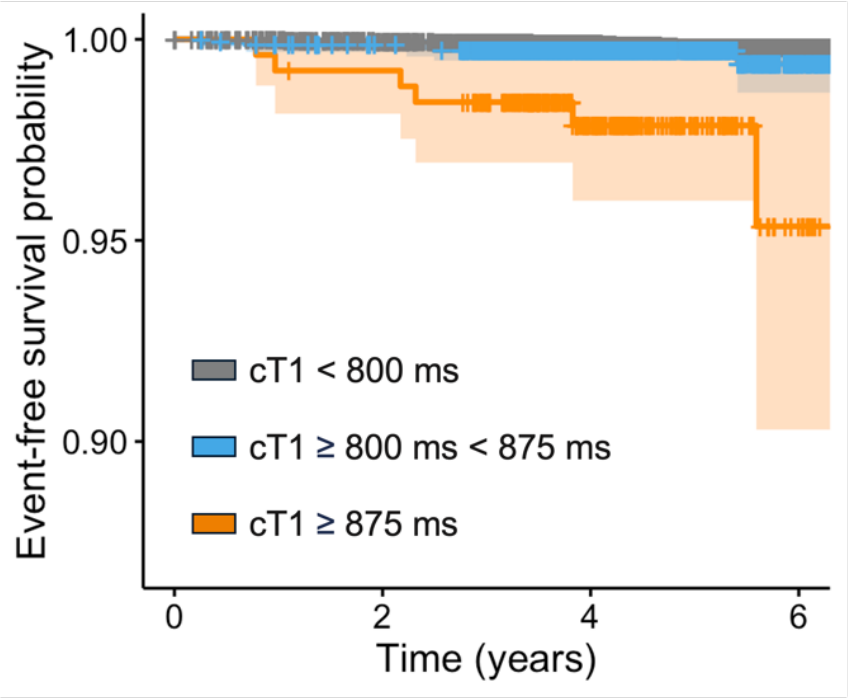
Neither liver iron nor liver fat was predictive of clinical outcomes in either the whole cohort or the subset of NAFLD/ArLD/VH (Tables S4, S5, S7 and S8).

Jayaswal, A., et al. (2020). Liver International, 40(12)

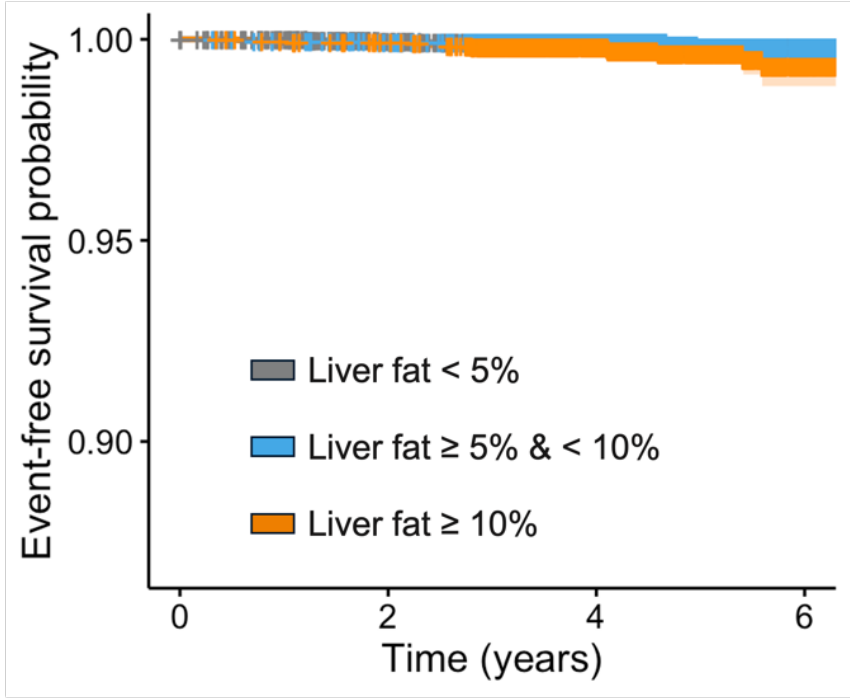
cT1 is prognostic in patients with chronic liver disease

- 28,841 UK biobank participants
- 6,223 with MASLD
- 2,325 with repeat scans
- 12 liver related events; 131 liver related hospitalisations

Major Liver Events: cT1 level



Major Liver Events: LFC level

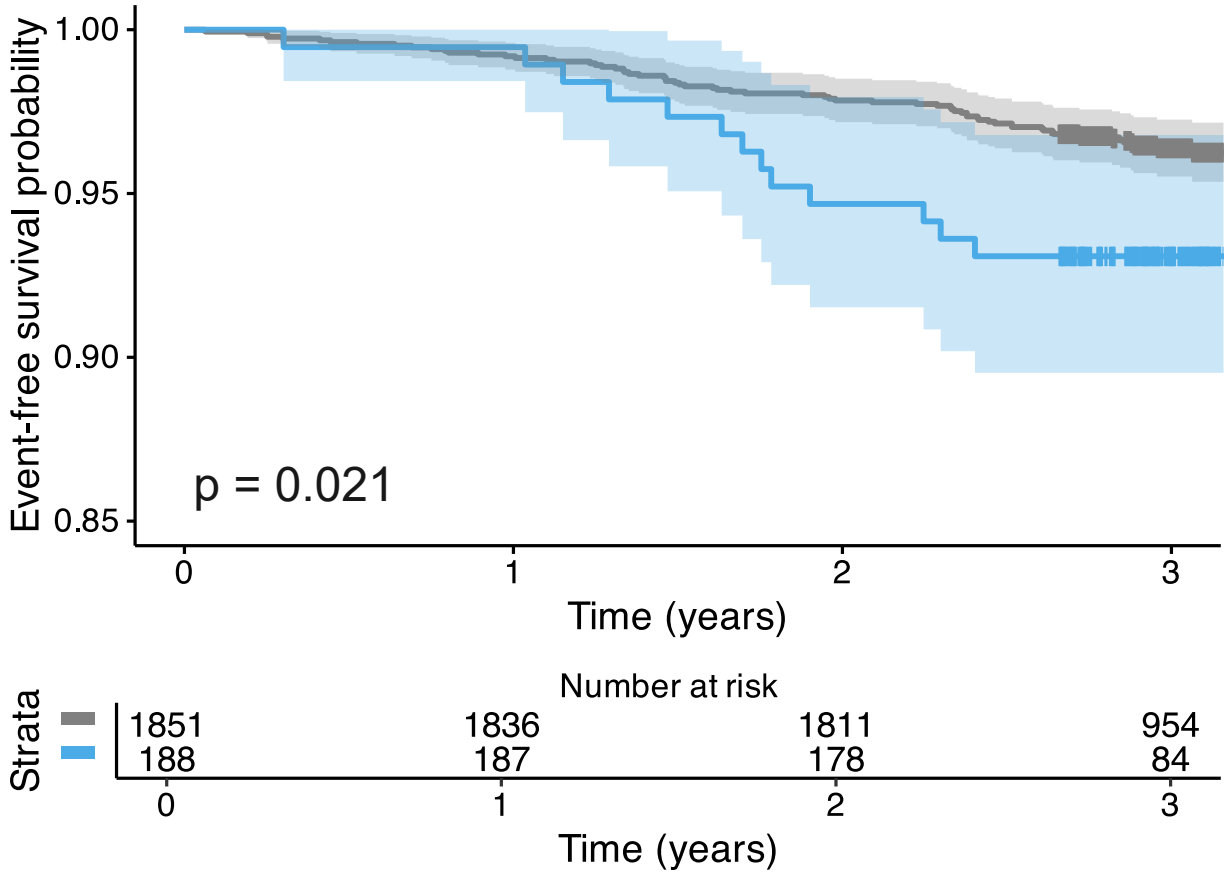


- **Elevated cT1, but not LFC**, is associated with major liver and CVD events, and all-cause mortality
- **cT1 > 875 ms** is associated with major liver events in the general population and MASLD sub-set

Jackson, et al. Nature Medicine; 2025 (in press)

Increase in cT1 over time is associated with increased risk of CVD outcomes

- 2,325 with repeat scans, n at risk = 2,039



ΔcT1 < 45 ms

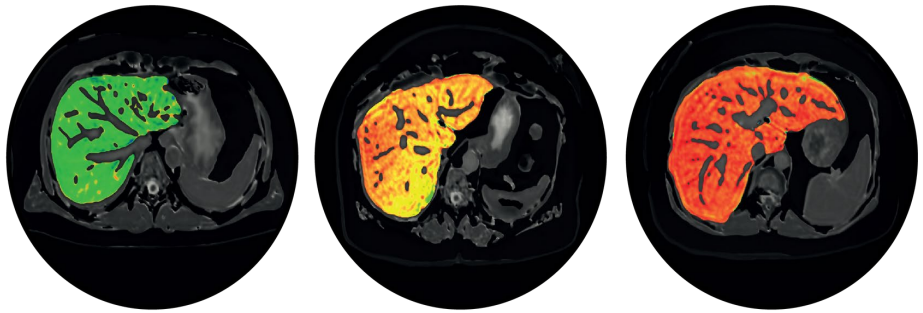
ΔcT1 ≥ 45 ms

HR = 2.1 (1.1, 3.7)

Outcomes: First occurrence of cardiovascular related hospitalisation or MACE
HR: multivariate adjusted Cox proportional Hazard ratio, adjusted for age, sex, BMI, type 2 diabetes and dyslipidemia status

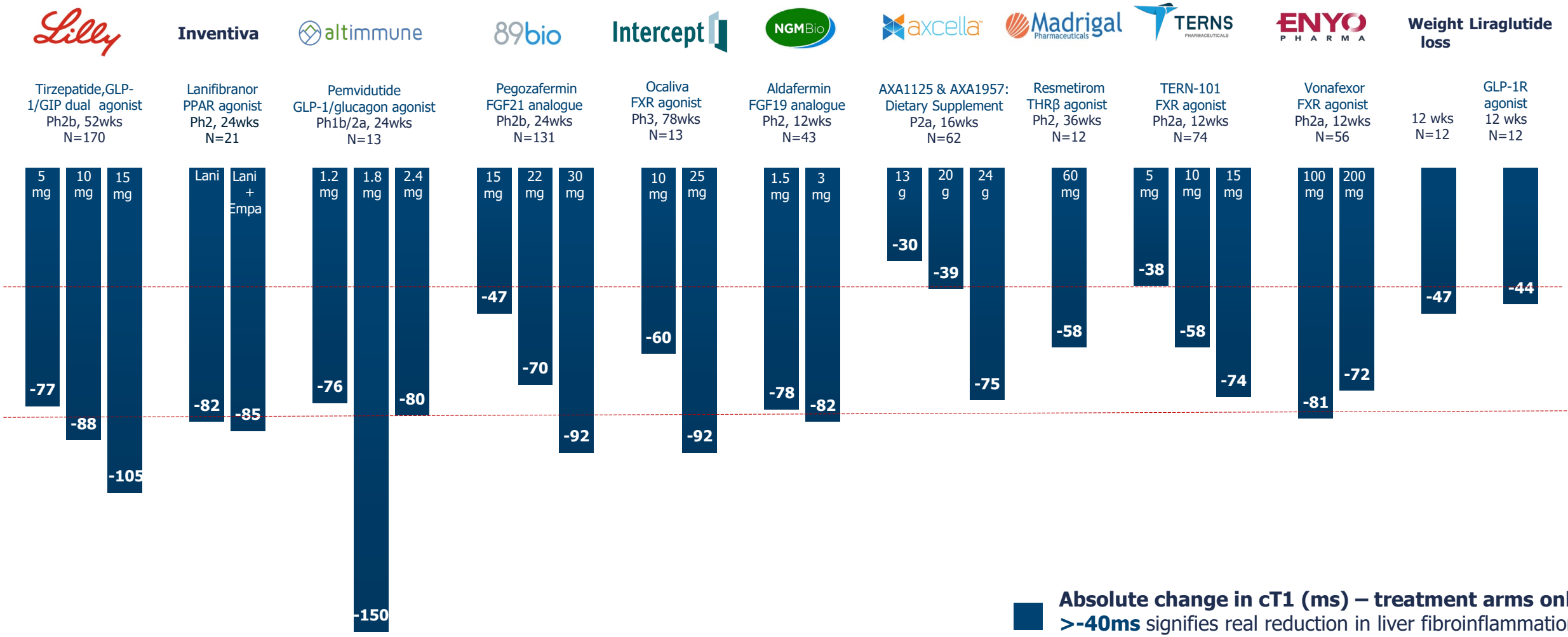
Jackson, et al. Nature Medicine; 2025 (in press)

Contents



- What is cT1?
- Biological plausibility
- Diagnostic accuracy
- Prognostic accuracy
- Sensitivity to change

cT1 change detection in MASH clinical trials



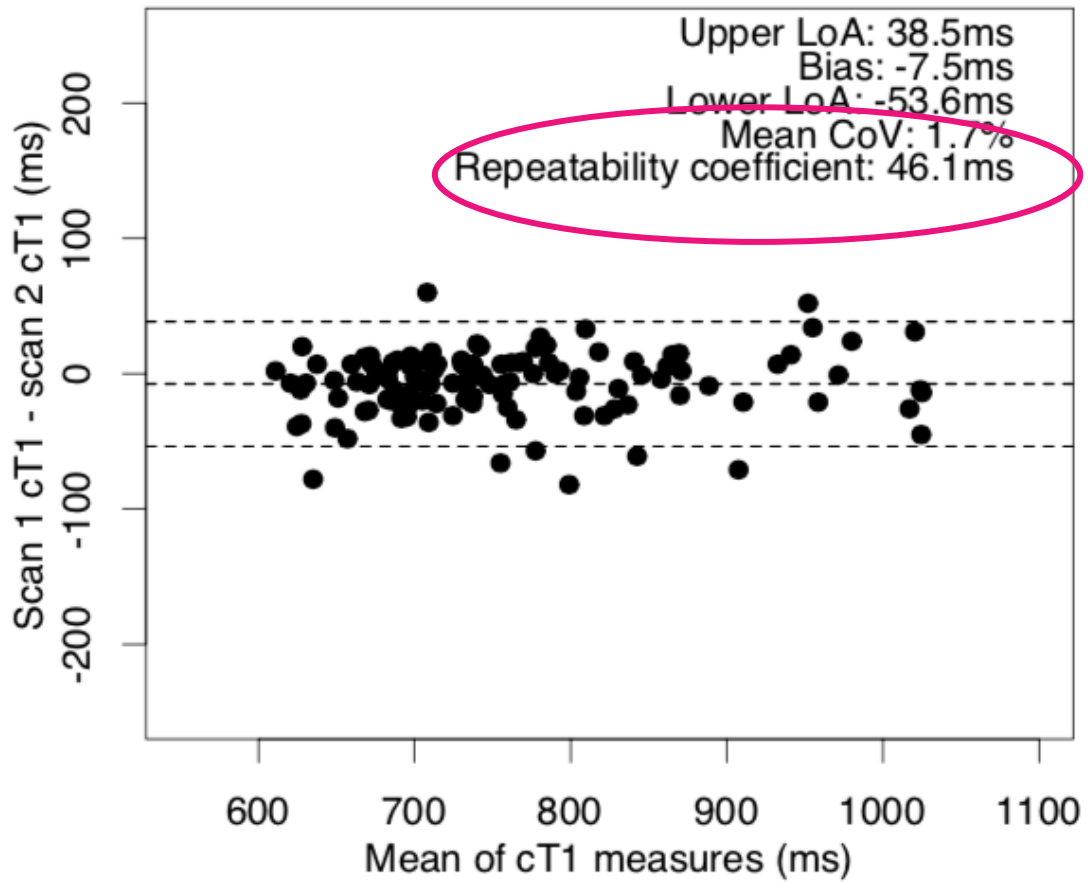
Absolute change in cT1 (ms) – treatment arms only
>-40ms signifies real reduction in liver fibroinflammation
>-80ms is equivalent to a 2-point change in NAS (score)

Measuring a real change with cT1

RESEARCH ARTICLE

Repeatability and reproducibility of multiparametric magnetic resonance imaging of the liver

- Observational study on 60 participants (32 health volunteers and 29 with chronic liver disease)
- cT1 repeated measurements have low bias and high repeatability.
- **Based on these results, a longitudinal change in cT1 of > ~46 ms represents true change with 95% certainty**.

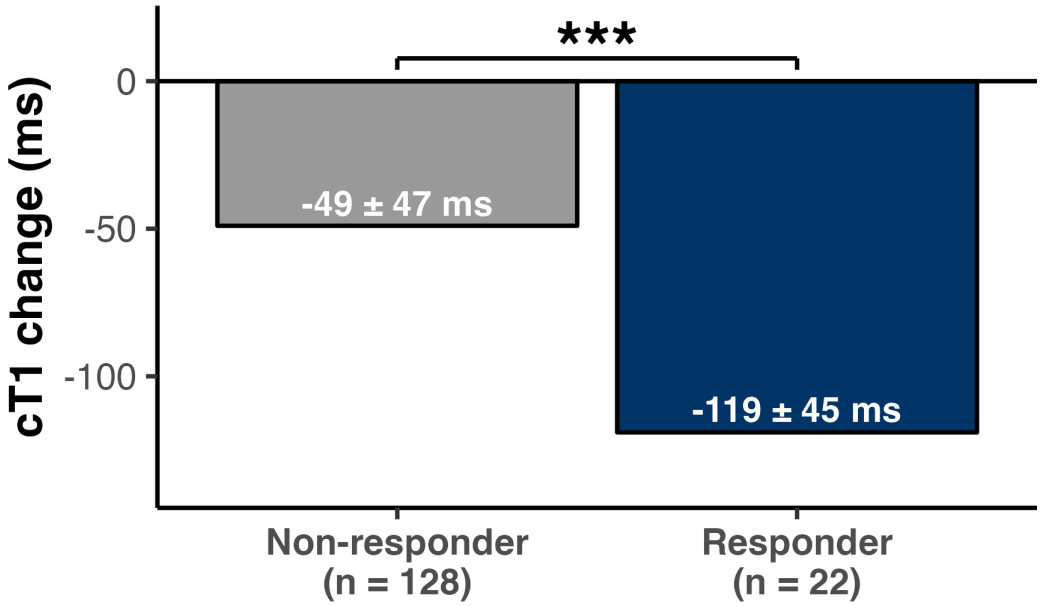


Bachtair et al, PlosOne, 2019

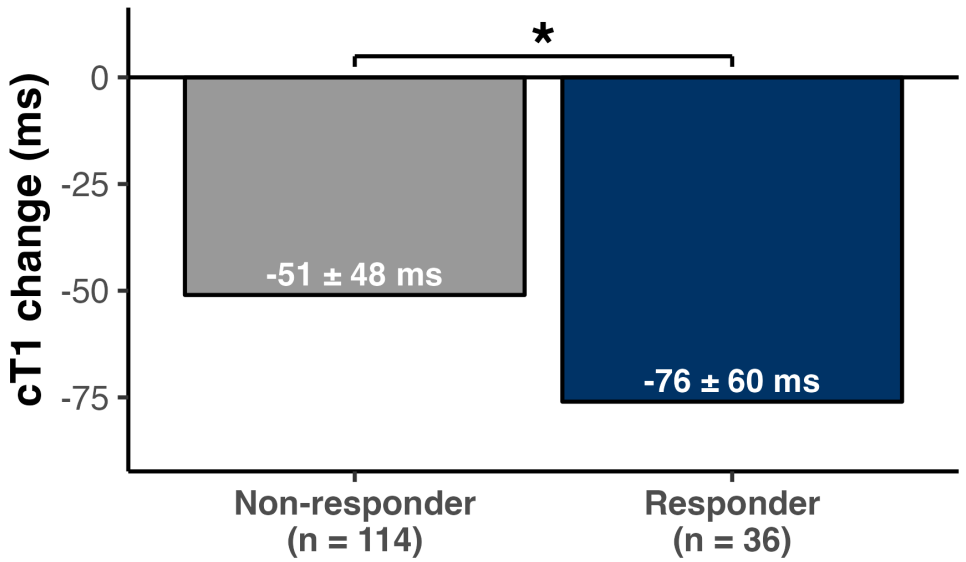
Recommended threshold for reduction in cT1 of >80ms is associated with histological response

150 patients from three MASLD/MASH-confirmed cohorts were included.

MASH resolution and no worsening in fibrosis



Improvement in fibrosis of 1 stage with no worsening in MASH



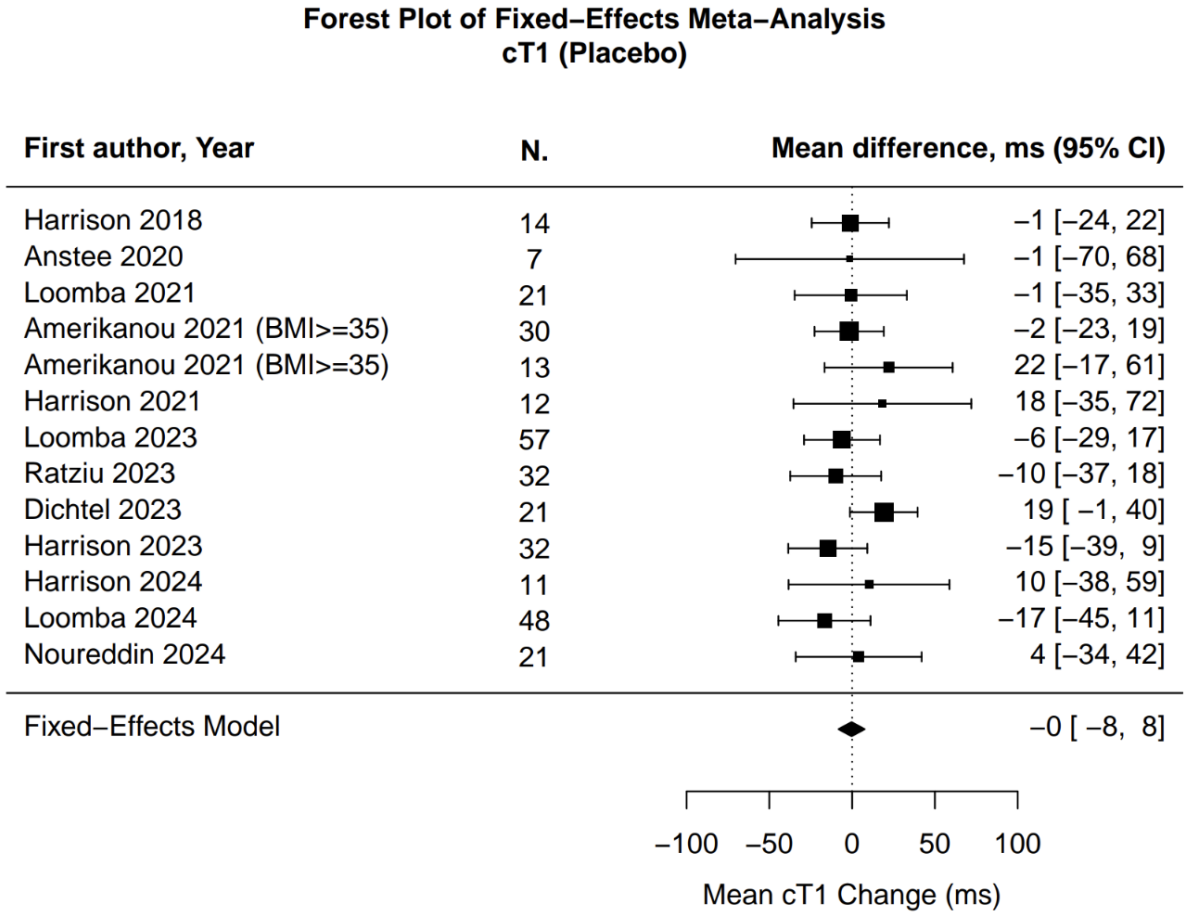
The optimal threshold (Youden's index) for separating responders from non-responders was reduction in cT1 >-82ms for MASH resolution and reduction of cT1 >-68ms for fibrosis improvement

Alkhouri, N., et al. Journal of Hepatology. 2025, 82

Negligible placebo response in cT1, alongside significant reduction across various interventions

16 STUDIES

1134 INDIVIDUALS WITH MASLD



Proportion cT1 responders (≥80ms change) in placebo arm was 8%, markedly lower than published for histological endpoints (15-25%).

Andersson et al, Clinical Gastroenterology and Hepatology. 2025 (in press)

communications medicine

A Nature Portfolio journal

Article

https://doi.org/10.1038/s43856-025-00796-9

Utility and cost-effectiveness of LiverMultiScan for MASLD diagnosis: a real-world multi-national randomised clinical trial

Check for updates

A list of authors and their affiliations appears at the end of the paper

Abstract

Background: Increasing prevalence of metabolic dysfunction–associated liver disease (MASLD) and metabolic dysfunction–associated steatohepatitis (MASH) poses a growing healthcare burden. Noninvasive diagnostic tools to replace liver biopsy are urgently needed. We investigated the utility and cost-effectiveness of including multiparametric magnetic resonance imaging (mpMRI) to the management of adults with suspected MASLD multi-nationally.

Methods: RADIcAL-1, a 1:1 randomised controlled trial (standard-of-care [SoC] *vs*. imaging arm [IA; SoC+mpMRI]) included 802 participants from Germany, Netherlands, Portugal and

Plain language summary

Steatotic liver disease is a global health problem which needs better diagnostic pathways. Here, we compared the number of doctor visits, the speed of diagnosis, and whether the cost of adding an MRI scan (LiverMultiScan) is justified by the improvement in patients' quality of life across Germany, the Netherlands, Portugal, and the

Take home messages

- cT1 is a biologically plausible measure of poor liver health related to MASLD
- cT1 is a prognostic biomarker when measured at baseline
- Risk of liver-related events (LRE) is significantly increased in MASLD patients with cT1 ≥875ms
- When assessed serially, an increase in cT1 is associated with an increased risk of CV events
- Absolute change in cT1 from baseline is significantly different in the active arms compared to placebo arms and in trials involving drugs with different mode of actions
- Improvement in cT1 is associated with a high likelihood of achieving histological response
- **cT1 shows considerable promise as a potential Reasonably Likely Surrogate Endpoint in MASH clinical trials**

Global footprint and strong ties with numerous sites