Clinical utility of MRI biomarkers for identifying NASH patients' high risk of progression: A multi-center pooled data and meta-analysis

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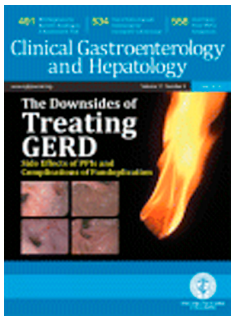

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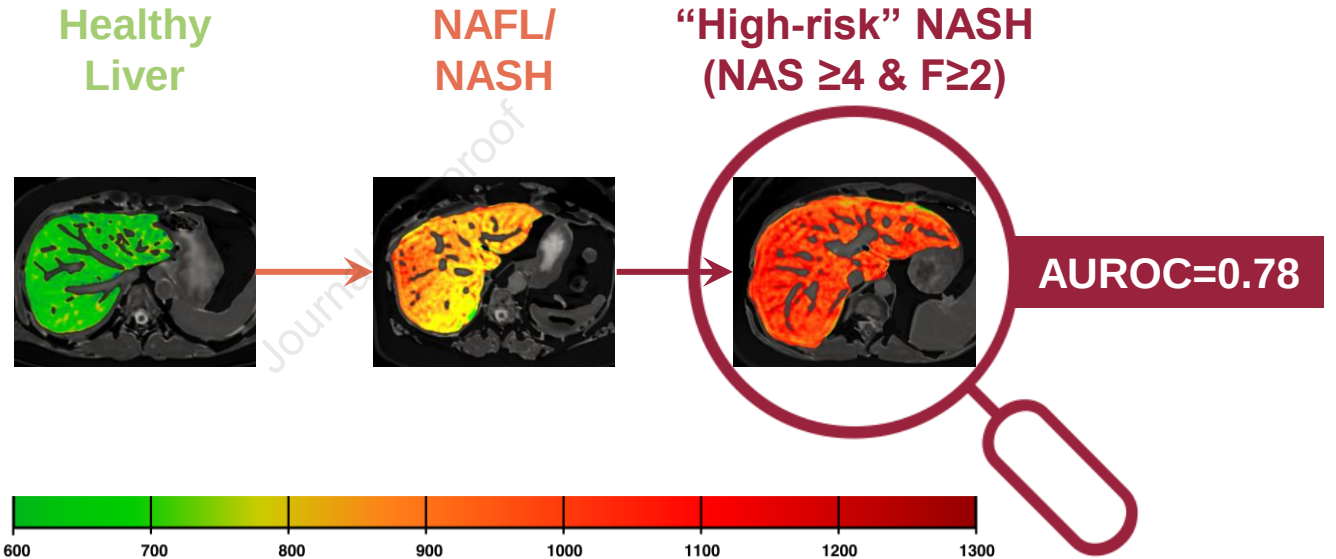
MRI cT1 accurately identifies NASH patients at high risk of disease progression

n=543 NAFLD
n=100 healthy
MRI cT1 and liver fat
Biopsy - CRN NAS



Clinical Gastroenterology and Hepatology

Clinical utility of MRI biomarkers for identifying NASH patients at high risk of progression: A multi-center pooled data and meta-analysis

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Conflicts of Interest: Perspectum Ltd is a privately funded commercial enterprise that develops medical devices to address unmet clinical needs, including LiverMultiScan®. RB is the CEO and founder of Perspectum. AA, MK and AD are employees of Perspectum. MP is a shareholder in Perspectum and has filed patent applications in the field of MRI for the assessment of liver disease. SH is a paid consultant for Echosens, Sonic Incytes and Fibronostics. GH has consulted for Intercept, Genfit, GSK, Cymabay, Pliant, Roche and Mirum. **Other authors do not have any conflicts of interest related to this work**

Abbreviations: high-risk NASH – participants with elevated NAS (NAS≥4) and significant fibrosis (F≥2); AUROC – area under the receiver operating characteristics; BMI – body mass index; cT1 – corrected T1; F – fibrosis; IQR – interquartile range; MRI – magnetic resonance imaging; NAS – NAFLD activity score; NAFLD – non-alcoholic fatty liver disease; NAFL – non-alcoholic fatty liver; NASH – non-alcoholic steatohepatitis; NASH; CRN – NASH Clinical Research Network; NPV – negative predictive value; PDFF – proton density fat fraction; PPV – positive predictive value; ROC – receiver operating characteristics; ROI – region of interest

Abstract:

Background and aims: Non-alcoholic fatty liver disease (NAFLD) is increasing in prevalence worldwide. NAFLD is associated with excess risk of all-cause mortality, and its progression to non-alcoholic steatohepatitis (NASH) and fibrosis accounts for a growing proportion of cirrhosis and hepatocellular cancer and thus is a leading cause of liver transplant worldwide. Non-invasive precise methods to identify patients with NASH and NASH with significant disease activity and fibrosis when the disease is still modifiable are crucial. The aim of this study was to examine the clinical utility of cT1 versus MRI liver fat for identification of NASH participants with NAS ≥4 and F ≥2 ("high-risk" NASH).

Methods: Data from five clinical studies (n=543) with participants suspected of NAFLD were pooled or used for individual participant data meta-analysis. The diagnostic accuracy of the MRI biomarkers to stratify NASH patients was determined using Area Under the Receiver Operating Characteristic curve (AUROC).

Results: A stepwise increase in cT1 and MRI liver fat with increased NAFLD severity was demonstrated, and cT1 was significantly higher in NASH participants with fibrosis grade ≥2 (high-risk NASH). The diagnostic accuracy (AUROC [95% CI]) of cT1 to identify those with NASH was 0.78 [CI: 0.74-0.82], for liver fat was 0.78 [CI: 0.73-0.82], and when combined with MRI liver fat was 0.82 [CI: 0.78-0.85]. The diagnostic accuracy of cT1 to identify those with high-risk NASH was good (AUROC: 0.78 [CI: 0.74-0.82]), was superior to MRI liver fat (AUROC: 0.69 [CI: 0.64-0.74]) and was not substantially improved by combining it with MRI liver fat (AUC: 0.79, [CI: 0.75-0.83]). The meta-analysis showed similar performance to the pooled analysis for these biomarkers.

Conclusions: This study demonstrates that quantitative MRI derived biomarkers cT1 and liver fat are suitable for identifying those with NASH, and cT1 is a better non-invasive technology than liver fat to identify NASH patients at greatest risk of disease progression. MRI cT1 and liver fat therefore have important clinical utility to help guide appropriate use of interventions in NAFLD and NASH clinical care pathways.

Keywords:

Liver*MultiScan*; cT1; PDFF; NAFLD; non-invasive; quantitative MRI

Introduction:

Non-alcoholic fatty liver disease (NAFLD) is increasing in prevalence worldwide and its progression to non-alcoholic steatohepatitis (NASH) and fibrosis accounts for a growing proportion of cirrhosis and

hepatocellular cancer [1]. NAFLD patients have a nearly 2 fold higher risk of overall mortality compared to population comparators [2], with risk of extra hepatic cancer and cirrhosis increasing in a dose dependent relationship with worsening histological severity [2]. Those with a NASH Clinical Research Network (NASH CRN) fibrosis stage of 2 or higher have a significantly increased risk of liver related and all-cause mortality [3–5]. It is a key goal in the field to identify patients with NASH and NASH with elevated NAFLD activity score (NAS) and presence of significant fibrosis (referred to here as high-risk NASH), as they need to be monitored in secondary clinical care and will most likely benefit from disease-specific drug therapies currently under development [6,7] or respond to lifestyle interventions. Despite this, there is still a lack of consensus in guidelines about how to identify such patients and liver biopsy is currently the clinical reference standard. Biopsy however is a suboptimal method as a public health approach because of the sheer numbers of patients with NAFLD (20-30% of the adult population[8]) and is not a preference of either patient or clinician due to the high incidence of pain [9] and due to the risk of complications, including rare cases of mortality [10,11]. There is therefore a critical need to identify NASH patients, particularly those at high risk of disease progression, with alternative non-invasive diagnostic methods.

Whilst there are many good non-invasive markers of fibrosis available, such as magnetic resonance elastography (MRE), shear wave elastography (SWE) and vibration controlled transient elastography from ultrasound (VCTE), these markers alone are not sensitive to NASH *per se* [12], owing to the fact they are not sensitive to earlier features of disease (e.g. steatosis, inflammation and ballooning). Similarly, blood based biomarkers such as FIB-4 and ELF have good performance to rule-out advanced fibrosis but have been reported to show limited performance in detecting NASH [13]. Quantitative multiparametric MRI are non-invasively derived metrics, which can be used to objectively evaluate and monitor liver tissue characteristics. Proton density fat fraction (PDFF, also referred to here as MRI liver fat) has been demonstrated as a reliable, accurate metric for quantifying liver fat and identifying patients with NAFLD

[14–17]. MRI liver fat strongly correlates with histological steatosis, but because liver fat declines with advanced fibrosis[18–20], it cannot be used to stage disease severity or to identify patients with NASH who have significant fibrosis. Iron-corrected T1 mapping (cT1) has been shown to correlate with fibroinflammatory activity on biopsy and to have high diagnostic accuracy to identify patients with NAFLD, NASH and NASH with higher stages of fibrosis [21–25].

Both MRI liver fat and cT1 are already used as endpoints in several clinical interventional NASH studies to assess severity of liver disease and to monitor response to treatment [26–28] and both have been used as screening tools or as criteria for inclusion in NASH trials to identify the target population [NCT02548351, NCT02443116, NCT03900429 among others]. The goal of this study was to comprehensively evaluate the diagnostic accuracy of cT1 and MRI liver fat to identify those with NASH and high-risk NASH, who are at higher risk of disease progression, in a population with suspected NAFLD.

Methods

Design and Study Participants

Data from N=543 participants from five observational studies were pooled and included in a retrospective analysis, from which N=517 have been previously reported on [23,29–32] in either diagnostic accuracy or prevalence of NAFL assessment. Participants were enrolled at routine patient visits in secondary or tertiary care, at sites in the UK, US and Japan, and those with any other known chronic liver disease except NAFLD were excluded from this analysis. All the clinical investigations were conducted in accordance with the Declaration of Helsinki 2013, approved by local relevant institutional review boards and written informed consent was obtained from all participants. All analyses in this study were done from the individual data points and not extracted from published results of the primary studies. To allow

for comparison to those without liver disease, 100 participants with MRI liver fat below 5% and a BMI below 25kg.m^{-2} from the UK Biobank imaging sub-study, further described elsewhere[33], were identified and selected as healthy controls. These controls were only included in the boxplots in figure 1, to visualize MRI biomarkers at different disease severities, but not included in the pooled dataset that was used for all other analyses. All participants underwent abdominal multiparametric MRI examination with the Liver*MultiScan* image acquisition protocol [21,22,34]. Perspectum is the only vendor of Liver*MultiScan*® and for this study all the relevant observational studies that were conducted using this technology were included. Full details on methods are reported in the supplementary material.

Statistical Analyses

Analyses were performed using R software version 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria). Median with interquartile range (IQR) used to describe continuous variables, and frequency and percentage for categorical variables. The correlation of cT1 and MRI liver fat with histological parameters was explored using Spearman's Rank correlation coefficient (r_s) and a p-value < 0.05 was considered statistically significant. The difference in cT1 or MRI liver fat between different histological stages and grades of disease severity were compared using non-paired Mann-Whitney U test or Kolmogorov-Smirnov (KS) test for two group comparisons and Kruskal-Wallis test for multi-group comparison. Diagnostic accuracy for identifying patients with biopsy confirmed disease was explored using area under receiver operating characteristic curves (AUROC) [35] A logistic regression model was used to combine cT1 and MRI liver fat in order to assess their combined ability to classify NASH and high-risk NASH participants. Biomarker performance was assessed according to sensitivity and specificity for pre-selected cut-offs as well as for the cut-off related to the optimal combination of sensitivity and specificity according to the Youden's index [36]. DeLong test was used to determine the significance of differences

between ROC curves [37]. Modelled positive and negative predictive values were calculated as described by Altman et al. [38]. Meta-analysis was performed on individual participant data and the cluster adjusted AUROC was computed with the random-effects (RE) model of the *metafor* package in R and represented in a forest plot.

Results

In the pooled participant dataset used in this study, the median age was 56 [50-63] years, 42% were female and 61% had a Body Mass Index (BMI) ≥ 30kg.m^{-2}. The descriptive statistics in Table 1 demonstrate that the study population comprised a diverse spectrum of histological severity, although relatively few individuals had fibrosis stage 4 or lobular inflammation grade 3. The statistics of each individual study has been summarized in Supplementary Table 1. An overview of the cT1 (fibro-inflammation) and MRI liver fat values in patients at different stages of NAFLD is shown in Figure 1. There was a significant increase in both MRI metrics as the severity of disease increased from healthy controls to NASH, via biopsy confirmed non-NAFLD and NAFL. In addition, cT1 was significantly higher in patients classified by biopsy as high-risk NASH. In contrast, MRI liver fat values were comparable for identifying high-risk NASH patients.

Table 1: Descriptive statistics on full pooled individual participant data, as well as divided by those with NAS≥4&F≥2 versus those without. Significance difference represented a p<.05.

*Figure 1: [A] Boxplot comparison of cT1 in controls, and patients suspected of NAFLD with confirmed non-NAFLD, NAFL and NASH, [B] Boxplot comparing cT1 in high-risk (NAS≥4 & F≥2) and low-risk NASH. [C] Boxplot comparison of liver fat (PDFF) in controls, and patients suspected of NAFLD with confirmed non-NAFLD, NAFL and NASH, [D] Boxplot comparing MRI liver fat (PDFF) in high-risk (NAS≥4 & F≥2) and low risk NASH. *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001*

Identifying patients with NASH using cT1 and MRI liver fat

cT1 and MRI liver fat correlated with NASH CRN histological scoring of steatosis, lobular inflammation, ballooning and the composite NAS, Supplementary Table 2. The diagnostic accuracy to discriminate patients with biopsy confirmed NASH from those without as measured by AUROC was 0.78 [CI: 0.74-0.82] for cT1 and 0.78 [CI: 0.73-0.82] for MRI liver fat, with no significant difference between the two ROC curves (Figure 2 [A]). Combining cT1 and MRI liver fat in a bivariate logistic regression model enhanced the AUROC to 0.82 [0.78-0.85], which was significantly higher (P<.001) than either biomarker alone. Biomarker performance for discriminating those with NASH from simple NAFLD was assessed using a cut-off of cT1≥800ms, MRI liver fat ≥5% or a combination of both. These cut-off values have been described previously as indicators for recommending further diagnostic evaluation [39,40]. Using the cut-off of cT1≥800ms to discriminate those with NASH resulted in a sensitivity of 75%, specificity of 66% and PPV and NPV both of 71%. Using the cut-off of MRI liver fat ≥5% to discriminate those with NASH resulted in a sensitivity of 92%, specificity of 40%, PPV of 63% and NPV of 82%. We also explored the diagnostic accuracy of each biomarker to discriminate between those with NAFL and the healthy controls, resulting in an AUROC for cT1 of 0.89 [CI: 0.88-0.91] and for MRI liver fat of 0.83 [CI: 0.81-0.84]. For cT1, the optimal cut-off (Youden's index) was cT1≥740 ms with a specificity and sensitivity of 82% and 84% respectively. For MRI liver fat, the optimal cut-off was MRI liver fat ≥4% with a specificity and sensitivity of 70% and 85% respectively. The healthy controls had median [IQR] cT1 and MRI liver fat values of 687ms [619-755ms] and 2% [0 - 3.2%], respectively. The patients suspected of NAFL had median cT1 and MRI liver fat values of 814ms [680 – 948ms] and 9% [0-18.5], respectively.

Table 2. Diagnostic accuracy of cT1 to identify patients with high-risk NASH at pre-specified thresholds.

Figure 2: ROC curves and AUROC in legend for [A] NASH (NAS≥4) using MRI liver fat (PDFF), cT1 and the combination of cT1 and MRI liver fat; [B] high-risk NASH (NAS≥4 & F≥2), using MRI liver fat, cT1 and the combination of cT1 and MRI liver fat. [C] Correlation between cT1 and fibrosis score, [C] Correlation between MRI liver fat (PDFF) and fibrosis score

Stratifying high-risk NASH patients with cT1

There was a significant moderate correlation between cT1 and fibrosis (r_s=0.50, p < 0.001) with significant differences in cT1 between each of the fibrosis stages (Figure 2 [C]). MRI liver fat showed a weak correlation with fibrosis (r_s=0.15, p < 0.001), and exhibited a non-linear relationship with a trend to decrease at higher fibrosis stages, demonstrated by the absence of a significant difference in MRI liver fat (PDFF) between fibrosis stages F0 and F4 or F1 and F3, (Figure 2[D]).

The diagnostic accuracy of cT1 to identify high-risk NASH demonstrated with AUROC (Figure 2[B]) was 0.78 [CI: 0.74-0.82] with a sensitivity of 78%, specificity of 67% and negative predictive value (NPV) of 88% at the optimal rule-out cut-off of 825 ms; sensitivity of 59%, specificity of 81% and PPV of 55% for a cut-off value of cT1≥875ms; and sensitivity of 39%, specificity of 90% and PPV of 60% at the higher rule-in cut-off value of 925 ms (Table 2). The AUROC for MRI liver fat was significantly (p<0.001) lower (0.69 [CI: 0.64-0.74]) than for cT1 (Figure 2 [B]) with a sensitivity of 68% and a specificity of 62% at the cut-off value of 10%. By combining cT1 and MRI liver fat in a bivariate logistic regression model, MRI liver fat showed no significant additional value to the use of cT1 alone for identifying high-risk NASH patients.

Using the rule-out and rule-in cut-off values of 825 ms and 925 ms, the proportion of patients with a cT1 in between these thresholds was 27% and the PPVs and NPVs for various cT1 cut-off values were modelled for test populations with different prevalence of high-risk NASH (Table 3). This demonstrated a PPV of 80% for the rule-in cut-off value of 925 ms when the disease prevalence in the tested population reached 50%, with a NPV of 75% for the rule out cut-off value of 825ms for the same prevalence.

Table 3: Modelled positive and negative predictive values (PPV and NPV) for cT1 at simulated prevalence of high-risk NASH, based on performance in the pooled dataset (n=543).

Meta-analysis of individual clinical studies combined

A meta-analysis was performed using the individual participant data from the five clinical studies. The performance data for identifying high-risk NASH from the individual studies is presented in a forest plot (Figure 3) and the cluster adjusted AUROC for cT1, MRI liver fat (PDFF) and the combination to identify high-risk NASH were 0.73 [CI: 0.68-0.78], 0.69 [CI: 0.63-0.75] and 0.75 [CI: 0.70-0.80] respectively. The combined datasets showed an acceptably low level of heterogeneity in cT1 and MRI liver fat based on the funnel plots in Supplementary Figure 1, while the combination had a slightly higher heterogeneity across studies.

Figure 3: Forest Plots of the 5 individual studies and the resulting random effect model summary AUROC for cT1, liver fat (PDFF) and the combination, to identify high-risk NASH.

Discussion:

This study analyzed pooled individual participant data from 5 studies to create the largest cohort of suspected NAFLD patients to date that have undergone Liver*MultiScan* paired with biopsy, to validate the utility of quantitative multiparametric MRI in the diagnosis of those with NASH, and those with NASH with fibrosis (high-risk NASH). Our results revealed good diagnostic performance for both cT1 and MR liver fat to identify patients with NASH and superior performance for cT1 to identify those with NASH at higher risk of disease progression.

Both cT1 and MRI liver fat correlated with the inflammatory components of the NAS, lobular inflammation and ballooning. In NASH patients however, the fibrosis stage has been shown to predict progression of disease [5] and clinical outcome [4,41]. Being able to identify those at risk of both inflammatory and fibrotic NASH who have increased risk of overall mortality [2] is important for developing more effective strategies for prevention, surveillance and intervention [42]. As previously demonstrated [18,20,43], we confirm that MRI liver fat decreases with higher grades of fibrosis, displaying a parabolic relationship with the fibrosis score. Consequently, and as expected, MRI liver fat showed a substantially lower AUROC of 0.69 [CI: 0.64-0.74] than cT1 (0.78 [CI: 0.74-0.82]) for the identification of patients with high-risk NASH, which was not significantly changed when MRI liver fat and cT1 were combined. Changes in the NAS have been shown to correlate with changes in fibrosis and high baseline NAS has been associated with greater progression to advanced fibrosis[5], thus being able to identify NASH patients with severe disease activity, even with fibrosis <2 may be an untapped opportunity to avoid missing patients who are at risk of progressing to higher stages of fibrosis and clinical outcomes. cT1 has previously been shown to non-invasively predict who are likely to progress to severe disease, such as liver-related clinical events and poor outcomes [34] at a cT1 cut-off value of 825 ms. The threshold was previously determined to have 90% sensitivity to rule out those with high-risk NASH [25]. In this current analysis, with high-risk NASH prevalence of 29%, a cT1 cut-off value of 825ms was again an optimal rule-out threshold, with an NPV of 88%. This performance is superior to that shown for NIS-4 and FIB-4, and equivalent to VCTE or FAST, in other studies [44–47]. Of note, the same cut-off value for ruling out high-risk NASH and for prediction of clinical outcomes is a superior feature of cT1 compared to many blood biomarkers for which higher thresholds are typically required for outcome prediction [48]. Focusing on identifying those with high-risk NASH, cT1 ≥875ms was associated with disease activity and significant fibrosis, but cT1 ≥925 ms was the optimal rule-in threshold with 90% specificity, minimal false positives and a relatively good PPV of 60%. It is important to highlight however that the PPV is highly dependent on the prevalence of disease in

the assessed population, and different clinical scenarios will have different disease prevalence's. By modeling the expected PPV in a variety of disease prevalence populations, given the sensitivities and specificities from this study, the PPV of cT1 would be 80% for a disease prevalence of 50%. This is higher than VCTE, NFS, FAST and equivalent to NIS-4 and FIB-4 for high-risk NASH and a similar disease prevalence [44–47]. The diagnostic performance of cT1 for separating NAFLD from NASH in this study showed good sensitivity and specificity at a cT1 cut-off value of 800ms. This result further justifies the use of a previously defined cut-off value of cT1 ≥ 800ms, below which no further diagnostic evaluation is warranted [39,40]. The healthy participants from the UK biobank imaging study had a cT1 range of between 619-755ms suggesting that 800ms can be considered as the upper limit of normal for cT1.

The aim of using different cut-off values to identify high-risk NASH is to maximize effective clinical decision making and confidence by reducing false negatives when ruling out disease, reducing false positives when ruling in disease, and minimizing the number of patients that fall in between the cut-off values. Many non-invasive tests face the issue of indeterminate results, due to technical failures or separate rule-in and rule-out cut-off values, with indeterminate results of 30-45% and above reported for classifying high-risk NASH [47,49]. This may be a consequence of tests being originally developed for fibrosis staging in general, rather than for NASH with presence of fibrosis. A high ratio of indeterminate results could lead to increased referral for further confirmatory testing, leading to a higher burden on the healthcare system and patient, including unnecessary biopsies. In this study, we demonstrate that cT1 has good diagnostic ability to identify high risk NASH but also a low indeterminate range with only 27% falling between the rule-in and rule-out cut-off values, a feature complimented by the high technical robustness of multiparametric liver MRI compared to other imaging technologies [29,31].

It must be acknowledged that a perfect biomarker for NASH has not been developed yet, and currently there is a wealth of research activity in the pursuit of such a test. Whilst cT1 showed good diagnostic accuracy for identifying those with NASH and NASH with significant fibrosis, there was still overlap in the range of cT1 values between the groups along the NAFL – NASH – High risk NASH continuum and thus opportunity to improve performance further. Composite biomarkers such as the FAST test, which combines liver stiffness from VCTE, controlled attenuation parameter (CAP) as a marker of fat and AST [44], or MRE shear stiffness combined with either the FIB-4 score [50] or MRE damping ratio and PDFF [51], have been reported to give a better diagnostic accuracy than individual metrics alone. Similarly, blood based tests such as the ADAPT score (Pro-C3, AST and diabetes status) are also being explored as composite biomarkers [52]. In fact, cT1 in combination with AST and fasting glucose (cTAG, [53]) has also been shown to outperform cT1 on its own for detecting patients with high-risk NASH. Despite these advances however, cT1 appears to be the best performing individual imaging biomarker for identifying those with NASH with significant fibrosis.

The future of tests for NASH in the clinical pathway is currently a source of discussion amongst key opinion leaders. Whilst generally the clinical pathways for those with NAFLD focus on staging fibrosis to identify those who would benefit from surveillance for HCC and cirrhosis, more recently the importance of also identifying those who have progressed from simple steatosis to NASH has been highlighted, particularly as the risk of liver and non-liver related clinical events is increased with such progression [2] and because lifestyle interventions have been shown to be effective in improving liver health [54]. It has also been acknowledged that disease burden and economic impact of NASH worldwide are huge [55,56] and that earlier diagnosis and care of NASH patients could reduce future healthcare costs. However, the absence of a suitable diagnostic for NASH means the majority of health economic analyses suffers from a lack of NASH specific data [57]. Currently, however, there are no suitable blood tests for identifying NASH

as reported by the LITMUS consortium. Vali et al [58] investigated a number of blood-based biomarkers for their suitability to diagnose NASH from a large sample of over 680 participants. Their analysis concluded that no single biomarker showed sufficient accuracy for discriminating NASH, reporting an AUC of 0.64 for FIB-4 and AUC of 0.62 for ELF [13]. Reasonable performance for discriminating NASH from NAFLD has been reported for ultrasound methods such as CAP [12]. However, unless CAP is combined with liver stiffness, it is poor at discriminating those with NASH with significant fibrosis (F≥2) [12].

Tests for NASH are now being recommended to be integrated into multidisciplinary care pathways [59] given the often concurrent presence of type II diabetes and obesity. As such, it may be suggested that cT1 be incorporated into such pathways for those with risk factors for NASH [40] and in particular for those with failed or indeterminate screening tests. This is because cT1 has (i) good diagnostic accuracy for high-risk NASH, (ii) strong NPV for ruling out and good PPV for ruling in high-risk NASH, even at low prevalence, as well as a (iii) low number of indeterminate values. Early economic models exploring risk stratification pathways with cT1 alone or in combination with other non-invasive technologies have demonstrated cost-effectiveness over biopsy or ultrasound-based imaging technologies alone [60–62], particularly in the scenario of following a failed or indeterminate ultra-sound test [62] and for the avoidance of unnecessary liver biopsies[60,62]. In fact, MRI biomarkers to avoid unnecessary liver biopsies were employed in a recent 16 week phase 2a clinical trial (NCT03976401), in which only patients with ≥30% reduction in MRI liver fat were deemed eligible for end-of-treatment biopsy [63] resulting in 17 biopsies avoided in the placebo arm of the study.

A great strength of this study is the large number of individual participant datasets with suspected NAFLD from multiple sites in Asia, Europe and North America, collected on all major MRI scanner models and at different field strengths. The strength of the results from this study are further emphasized by the high

diagnostic performance despite heterogeneous clinical pathways, at a relatively low overall prevalence of high-risk NASH that is closer to a real-world NAFLD care setting. A limitation related to the pooling of these studies is the variable number of participants from each study and the lack of centrally read histology for all participants, which could potentially lead to a bias in the data. However, this has been addressed by performing a meta-analysis of the individual studies, which resulted in a similar summary diagnostic accuracy for the multiparametric MRI biomarkers to identify high-risk NASH patients and showed no significant bias for cT1 between the studies.

In summary, these results show that both MRI liver fat and cT1 are effective biomarkers for identifying those with NASH however cT1 is superior in identifying NASH patients at greatest risk of disease progression and thus has the potential to reduce unnecessary biopsies by providing an accurate and reliable alternative in the clinical care pathway.

Conclusion:

This large, pooled analysis and meta-analysis using 543 individual participant datasets from five independent studies, with data acquired across the world and on all major scanner models, demonstrates good diagnostic accuracy of multiparametric MRI biomarkers cT1 and MRI liver fat (PDFF) to identify patients with NASH and of cT1 alone to identify NASH patients who are at higher risk of disease progression.

References:

1. Estes C, Razavi H, Loomba R, Younossi Z, Sanyal AJ. Modeling the epidemic of nonalcoholic fatty liver disease demonstrates an exponential increase in burden of disease. Hepatology. 2018;

2. Simon TG, Roelstraete B, Khalili H, Hagström H, Ludvigsson JF. Mortality in Biopsy-Confirmed Nonalcoholic Fatty Liver Disease: Results From A Nationwide Cohort. Gut. 2021;70(7):1375–82.

3. Dulai PS, Singh S, Patel J, Soni M, Prokop LJ, Younossi Z, et al. Increased risk of mortality by fibrosis stage in nonalcoholic fatty liver disease: Systematic review and meta-analysis. Hepatology. 2017;

4. Ekstedt M, Hagström H, Nasr P, Fredrikson M, Stål P, Kechagias S, et al. Fibrosis stage is the strongest predictor for disease-specific mortality in NAFLD after up to 33 years of follow-up. Hepatology. 2015;

5. Kleiner DE, Brunt EM, Wilson LA, Behling C, Guy C, Contos M, et al. Association of Histologic Disease Activity With Progression of Nonalcoholic Fatty Liver Disease. JAMA Netw open. 2019;

6. Konerman MA, Jones JC, Harrison SA. Pharmacotherapy for NASH: Current and emerging. Journal of Hepatology. 2018.

7. FDA CDER. Noncirrhotic nonalcoholic steatohepatitis with liver fibrosis: developing drugs for treatment. Guid Ind. 2018;(December).

8. Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease—Meta-analytic assessment of prevalence, incidence, and outcomes. Hepatology. 2016;64(1):73–84.

9. Thomaides-Brears H, Alkhouri N, Allende D, Harisinghani M, Noureddin M, Reau N, et al. Incidence of Complications from Percutaneous Biopsy in Chronic Liver Disease: A Systematic Review and Meta-Analysis. Dig Dis Sci. 2021;

10. Thomaides-Brears H, Alkhouri N, Allende D, Harisinghani M, Noureddin M, Reau NS, et al. Meta-Analysis of Complications from Liver Biopsy: A 2010-2020 Update for Chronic Liver Disease. Hepatology. 2020;72(S1):1528.

11. Friedman LS. Controversies in liver biopsy: Who, where, when, how, why? Current Gastroenterology Reports. 2004.

12. Imajo K, Tetlow L, Dennis A, Shumbayawonda E, Mouchti S, Kendall TJ, et al. Quantitative multiparametric magnetic resonance imaging can aid non-alcoholic steatohepatitis diagnosis in a Japanese cohort. World J Gastroenterol. 2021;27(3):0–0.

13. Vali Y, Lee J, Schattenberg J, Romero-Gomez M, Tiniakos D, Bedossa P, et al. Comparative diagnostic accuracy of blood-based biomarkers for diagnosing NASH vs. NAFL: phase 1 results of the LITMUS project. PO-919. J Hepatol. 2021;75(2):S201–S293.

14. Yokoo T, Serai SD, Pirasteh A, Bashir MR, Hamilton G, Hernando D, et al. Linearity, bias, and precision of hepatic proton density fat fraction measurements by using MR imaging: A meta-analysis. Radiology. 2018;286(2):486–98.

15. Middleton MS, Heba ER, Hooker CA, Bashir MR, Fowler KJ, Sandrasegaran K, et al. Agreement Between Magnetic Resonance Imaging Proton Density Fat Fraction Measurements and Pathologist-Assigned Steatosis Grades of Liver Biopsies From Adults With Nonalcoholic Steatohepatitis. Gastroenterology. 2017;153(3):753–61.

16. Noureddin M, Lam J, Peterson MR, Middleton M, Hamilton G, Le TA, et al. Utility of magnetic resonance imaging versus histology for quantifying changes in liver fat in nonalcoholic fatty liver disease trials. Hepatology. 2013;58(6):1930–40.

17. Beyer C, Hutton C, Andersson A, Imajo K, Nkajima A, Kiker D, et al. Comparison between magnetic resonance and ultrasound-derived indicators of hepatic steatosis in a pooled NAFLD cohort. PLoS One. 2020;In press:1–19.

18. Dennis A, Kelly MD, Fernandes C, Mouchti S, Fallowfield JA, Hirschfield G, et al. Correlations Between MRI Biomarkers PDFF and cT1 With Histopathological Features of Non-Alcoholic Steatohepatitis. Front Endocrinol (Lausanne). 2021;11(January):1–10.

19. Doycheva I, Cui J, Nguyen P, Costa EA, Hooker J, Hofflich H, et al. Non-invasive screening for NAFLD and advanced fibrosis in diabetes in primary care setting by MRI and MRE. Aliment Pharmacol Ther. 2016;43(1):83–95.

20. Permutt Z, T.-A. Le, Peterson MR, Seki E, Brenner DA, Sirlin C, et al. Correlation between liver histlology and novel MRI in adult patients with NAFLD. 2013;36(1):22–9.

21. Banerjee R, Pavlides M, Tunnicliffe EM, Piechnik SK, Sarania N, Philips R, et al. Multiparametric magnetic resonance for the non-invasive diagnosis of liver disease. J Hepatol. 2014;61(1):69–77.

22. Pavlides M, Banerjee R, Sellwood J, Kelly CJ, Robson MD, Booth JC, et al. Multiparametric magnetic resonance imaging predicts clinical outcomes in patients with chronic liver disease. J Hepatol. 2016;64:308–15.

23. Pavlides M, Banerjee R, Tunnicliffe EM, Kelly C, Collier J, Wang LM, et al. Multiparametric magnetic resonance imaging for the assessment of non-alcoholic fatty liver disease severity. Liver Int. 2017;37(7):1065–73.

24. Thomaides-Brears HB, Lepe R, Banerjee R, Duncker C. Multiparametric MR mapping in clinical decision-making for diffuse liver disease. Abdom Radiol [Internet]. 2020;45(11):3507–22. Available

from: https://doi.org/10.1007/s00261-020-02684-3

25. Dennis A, Mouchti S, Kelly M, Fallowfield J, Hirschfield G, Pavlides M, et al. A composite biomarker using multiparametric magnetic resonance imaging and blood analytes accurately identifies patients with non-alcoholic steatohepatitis and significant fibrosis. Sci Rep. 2020;In press:1–11.

26. Harrison SA, Rossi SJ, Paredes AH, Trotter JF, Bashir MR, Guy CD, et al. NGM282 Improves Liver Fibrosis and Histology in 12 Weeks in Patients With Nonalcoholic Steatohepatitis. Hepatology. 2020;71(4):1198–212.

27. Lawitz EJ, Coste A, Poordad F, Alkhouri N, Loo N, McColgan BJ, et al. Acetyl-CoA Carboxylase Inhibitor GS-0976 for 12 Weeks Reduces Hepatic De Novo Lipogenesis and Steatosis in Patients With Nonalcoholic Steatohepatitis. Clin Gastroenterol Hepatol. 2018;

28. Harrison SA, Dennis A, Fiore MM, Kelly MD, Kelly CJ, Paredes AH, et al. Utility and variability of three non-invasive liver fibrosis imaging modalities to evaluate efficacy of {GR}-{MD}-02 in subjects with {NASH} and bridging fibrosis during a phase-2 randomized clinical trial. Huang J-F, editor. PLoS One [Internet]. 2018;13(9):e0203054. Available from: https://doi.org/10.1371/journal.pone.0203054https://dx.plos.org/10.1371/journal.pone.0203054

29. Imajo K, Tetlow LA, Dennis A, Shumbayawonda E, Mouchti S, Etc, et al. Quantitative multiparametric MRI can aid NASH diagnosis in a Japanese cohort. World J Gastroenterol. 2021;

30. Harrison SA, Gawrieh S, Roberts K, Lisanti CJ, Schwope RB, Cebe KM, et al. Prospective evaluation of the prevalence of non-alcoholic fatty liver disease and steatohepatitis in a large middle-aged US cohort. J Hepatol [Internet]. 2021;(May):1–8. Available from: http://dx.doi.org/10.1016/j.jhep.2021.02.034

31. McDonald N, Eddowes PJ, Hodson J, Semple SI, Davies NP, Kelly CJ, et al. Multiparametric magnetic resonance imaging for quantitation of liver disease: a two-centre cross-sectional observational study. Sci Rep. 2018;8(1):9189.

32. Siddiqui M, Grawenda A, Cadrain R, Collen R, Steinberg J, Luketic V, et al. The “IDEAL” method for fat quantification and iron-corrected T1 accurately measure the presence and severity of the individual histological features of nonalcoholic steatohepatitis (NASH). Hepatology. 2018 Oct;68(S1):1322 Abstract 2338.

33. Roca-Fernández A, Dennis A, Nicholls R, McGonigle J, Kelly M, Banerjee R, et al. Hepatic steatosis rather than underlying obesity confers a higher risk of testing positive and increases the risk of hospitalization for covid-19. Front Med Gastroenterol. 2020;accepted(March):1–8.

34. Jayaswal ANA, Levick C, Selvaraj EA, Dennis A, Booth JC, Collier J, et al. Prognostic value of multiparametric magnetic resonance imaging, transient elastography and blood-based fibrosis markers in patients with chronic liver disease. Liver Int. 2020;

35. Hanley JA, McNeil BJ. Maximum attainable discrimination and the utilization of radiologic examinations. J Chronic Dis. 1982;

36. Youden WJ. Index for rating diagnostic tests. Cancer. 1950;

37. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the Areas under Two or More Correlated Receiver Operating Characteristic Curves: A Nonparametric Approach. Biometrics. 1988;

38. Altman DG, Bland JM. Statistics Notes: Diagnostic tests 2: predictive values. BMJ. 1994 Jul;309(6947):102–102.

39. Tonev D, Shumbayawonda E, Tetlow L, Herdman L, French M, Rymell S, et al. The effect of multi-parametric magnetic resonance imaging in standard of care for nonalcoholic fatty liver disease: protocol for a randomized control trial. JMIR Res Protoc. 2020;9(10).

40. Schaapman JJ, Tushuizen ME, Coenraad MJ, Lamb HJ. Multiparametric MRI in Patients With Nonalcoholic Fatty Liver Disease. J Magn Reson Imaging. 2020;1–9.

41. Angulo P, Hui JM, Marchesini G, Bugianesi E, George J, Farrell GC, et al. The NAFLD fibrosis score: A noninvasive system that identifies liver fibrosis in patients with NAFLD. Hepatology. 2007;

42. Rowe I, Parker R. The diagnosis of nonalcoholic fatty liver disease should carry important prognostic information. Nat Rev Gastroenterol Hepatol. 2019;16(8):449–50.

43. Wildman-Tobriner B, Middleton MM, Moylan CA, Rossi S, Flores O, Chang ZA, et al. Association Between Magnetic Resonance Imaging–Proton Density Fat Fraction and Liver Histology Features in Patients With Nonalcoholic Fatty Liver Disease or Nonalcoholic Steatohepatitis. Gastroenterology [Internet]. 2018;155(5):1428-1435.e2. Available from: http://dx.doi.org/10.1053/j.gastro.2018.07.018

44. Newsome PN, Sasso M, Deeks JJ, Paredes A, Boursier J, Chan W-K, et al. FibroScan-AST (FAST) score for the non-invasive identification of patients with non-alcoholic steatohepatitis with significant activity and fibrosis: a prospective derivation and global validation study. lancet Gastroenterol Hepatol. 2020;5(4):362–73.

45. Staufer K, Halilbasic E, Spindelboeck W, Eilenberg M, Prager G, Stadlbauer V, et al. Evaluation and comparison of six noninvasive tests for prediction of significant or advanced fibrosis in

nonalcoholic fatty liver disease. United Eur Gastroenterol J. 2019;

46. Puri P, Spataro J, Jain S, Lemmons J, Paca E, Singh M, et al. FAST TRACKING THE FIBROSCAN® – AST (FAST) SCORE FOR HIGH RISK NASH PATIENTS: IMPLICATIONS FOR PRACTICE AT THE VETERANS HEALTH ADMINISTRATION. Hepatology. 2020 Nov;72(S1).

47. Harrison SA, Ratziu V, Boursier J, Francque S, Bedossa P, Majd Z, et al. A blood-based biomarker panel (NIS4) for non-invasive diagnosis of non-alcoholic steatohepatitis and liver fibrosis: a prospective derivation and global validation study. Lancet Gastroenterol Hepatol. 2020;1253(20):1–16.

48. Younossi ZM, Anstee QM, Wai-Sun Wong V, Trauner M, Lawitz EJ, Harrison SA, et al. The Association of Histologic and Noninvasive Tests With Adverse Clinical and Patient-Reported Outcomes in Patients With Advanced Fibrosis Due to Nonalcoholic Steatohepatitis. Gastroenterology. 2020;(February):1–12.

49. Noureddin N, Alkhouri N, Brown KA, Noureddin M. Driving NASH forward using the FAST score but obey the traffic lights. Hepatology. 2020;

50. Jung J, Loomba R, Imajo K, Madamba E, Gandhi S, Bettencourt R, et al. MRE combined with FIB-4 (MEFIB) index in detection of candidates for pharmacological treatment of NASH-related fibrosis. BMJ Gut. 2020;

51. Allen AM, Shah VH, Therneau TM, Venkatesh SK, Mounajjed T, Larson JJ, et al. Multiparametric Magnetic Resonance Elastography Improves the Detection of NASH Regression Following Bariatric Surgery. Hepatol Commun. 2020;4(2):185–92.

52. Daniels S, Leeming D, Eslam3 M, Hashem A, Nielsen M, Krag A, et al. ADAPT: An algorithm incorporating PRO-C3 accurately identifies patients with NAFLD and advanced fibrosis. Hepatology. 2019;69(3):1075–86.

53. Dennis A, Mouchti S, Kelly M, Fallowfield J, Hirschfield G, Pavlides M, et al. A composite biomarker using multiparametric magnetic resonance imaging and blood analytes accurately identifies patients with non-alcoholic steatohepatitis and significant fibrosis. Sci Rep [Internet]. 2020;10(1):1–11. Available from: https://doi.org/10.1038/s41598-020-71995-8

54. Vilar-Gomez E, Martinez-Perez Y, Calzadilla-Bertot L, Torres-Gonzalez A, Gra-Oramas B, Gonzalez-Fabian L, et al. Weight loss through lifestyle modification significantly reduces features of nonalcoholic steatohepatitis. Gastroenterology. 2015;

55. O'Hara J, Finnegan A, Dhillon H, Ruiz-Casas L, Pedra G, Franks B, et al. Cost of non-alcoholic

steatohepatitis in Europe and the USA: The GAIN study. JHEP Reports [Internet]. 2020;2(5):100142. Available from: https://doi.org/10.1016/j.jhepr.2020.100142

56. Schattenberg JM, Lazarus J V., Newsome PN, Serfaty L, Aghemo A, Augustin S, et al. Disease burden and economic impact of diagnosed non-alcoholic steatohepatitis in five European countries in 2018: A cost-of-illness analysis. Liver Int. 2021;41(6):1227–42.

57. Johansen P, Howard D, Bishop R, Moreno SI, Buchholtz K. Systematic Literature Review and Critical Appraisal of Health Economic Models Used in Cost-Effectiveness Analyses in Non-Alcoholic Steatohepatitis: Potential for Improvements. Pharmacoeconomics [Internet]. 2020;38(5):485–97. Available from: https://doi.org/10.1007/s40273-019-00881-7

58. Vali Y, Lee J, Schattenberg J, Romero-Gomez M, Tiniakos D, Bedossa P. Comparative diagnostic accuracy of blood-based biomarkers for diagnosing NASH vs. NAFL: phase 1 results of the LITMUS project. EASL Int Liver Congr Paris. 2021;June.

59. Eslam M, Ahmed A, Després JP, Jha V, Halford JCG, Wei Chieh JT, et al. Incorporating fatty liver disease in multidisciplinary care and novel clinical trial designs for patients with metabolic diseases. Lancet Gastroenterol Hepatol. 2021;6(9):743–53.

60. Blake L, Duarte R V., 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(9):1–8.

61. Eddowes PJPJ, McDonald N, Davies N, Semple SIKIKK, Kendall TJTJ, Hodson J, et al. Utility and cost evaluation of multiparametric magnetic resonance imaging for the assessment of non-alcoholic fatty liver disease. Aliment Pharmacol Ther [Internet]. 2018;47(5):631–44. Available from: http://doi.wiley.com/10.1111/apt.14469

62. Samur S, Carlon J, Chhatwal J. Comparative Cost-Effectiveness of Multiparametric Magentic Resonance Imaging for Detection of High-Risk Non-Alcoholic Steatohepatitis. AASLD Abstr. 2020;1–4.

63. Harrison SA, Ruane PJ, Freilich BL, Neff G, Patil R, Behling CA, et al. Efruxifermin in non-alcoholic steatohepatitis: a randomized, double-blind, placebo-controlled, phase 2a trial. Nat Med [Internet]. 2021;27(December 2019). Available from: http://dx.doi.org/10.1038/s41591-021-01425-3

Table 2: Descriptive statistics on full pooled individual participant data, as well as divided by those with NAS≥4&F≥2 versus those without. Significance difference represented a p<.05.

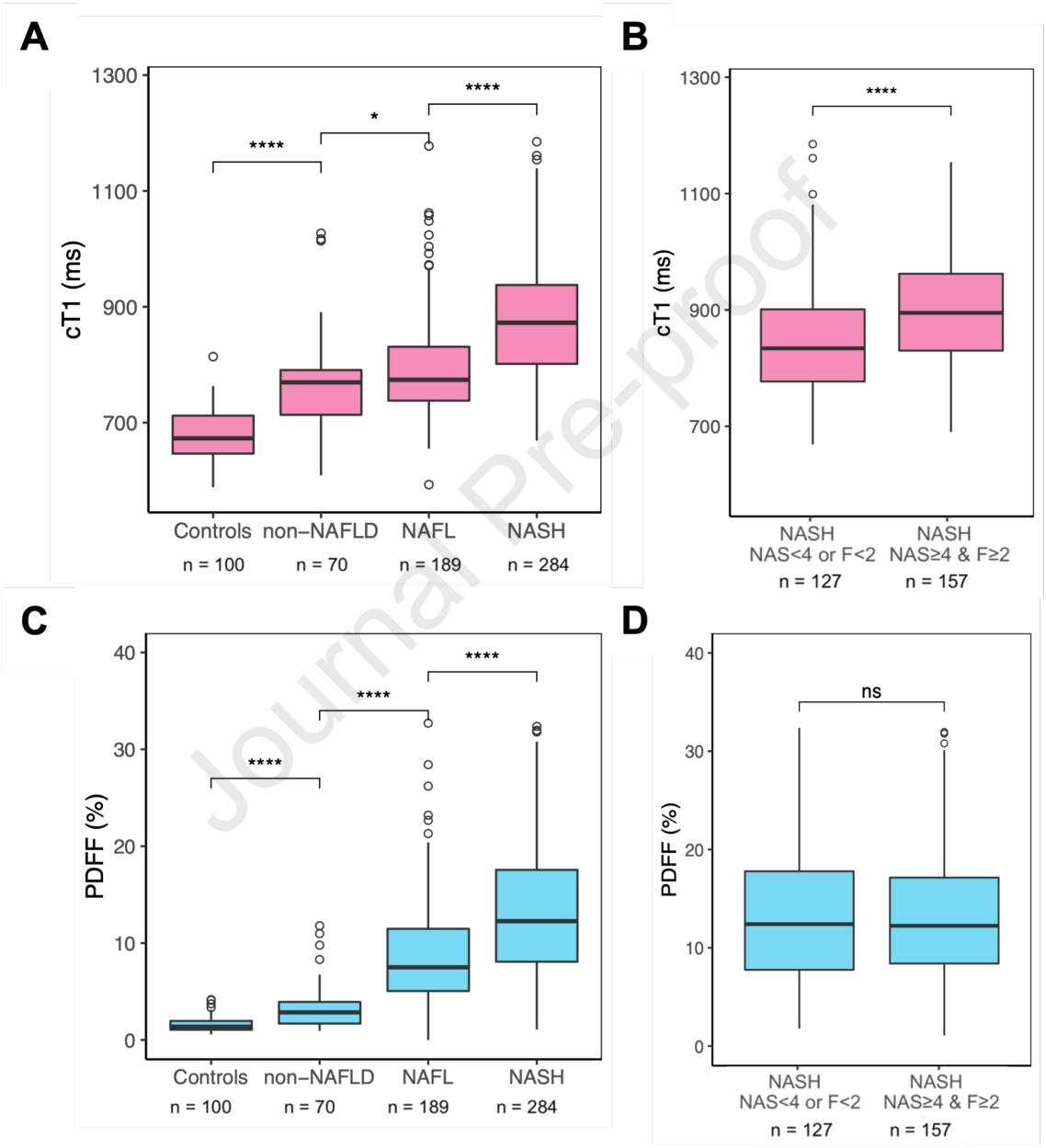
Descriptive Statistics:		Pooled data	NAS<4 or F<2	NAS≥4 & F≥2	p-value
	Total N (%)	543 (100)	127 (44.7)	157 (55.3)	
Age (years)	Median (IQR)	56 (13)	56 (12)	59 (17.5)	0.0323
	N/A (n)	44	12	6	
BMI (kg/m^2)	Median (IQR)	31 (7)	32 (8)	32 (7)	0.7488
	N/A (n)	21	3	1	
Sex	F, n (%)	220 (41.9)	62 (49.6)	66 (42.3)	0.2247
	M, n (%)	305 (58.1)	63 (50.4)	90 (57.7)	
	N/A (n)	18	2	1	
T2 Diabetes Mellitus	Yes, n (%)	173 (60)	36 (58)	86 (71)	0.1093
	N/A (n)	256	65	36	
Histology	Score/Grade	n (%)	n (%)	n (%)	
Fibrosis (Kleiner Brunt)	0	147 (27.1)	23 (18.1)	0 (0)	<0.0001
	1	152 (28)	75 (59.1)	0 (0)	
	2	88 (16.2)	9 (7.1)	56 (35.7)	
	3	101 (18.6)	12 (9.4)	72 (45.9)	
	4	55 (10.1)	8 (6.3)	29 (18.5)	
Ballooning	0	224 (41.3)	0 (0)	0 (0)	<0.0001
	1	237 (43.6)	114 (89.8)	93 (59.2)	
	2	82 (15.1)	13 (10.2)	64 (40.8)	
Lobular Inflammation	0	134 (24.7)	0 (0)	0 (0)	<0.0001
	1	283 (52.1)	107 (84.3)	61 (38.9)	
	2	116 (21.4)	20 (15.7)	86 (54.8)	
	3	10 (1.8)	0 (0)	10 (6.4)	
Steatosis	0	70 (12.9)	0 (0)	0 (0)	0.0145
	1	222 (40.9)	45 (35.4)	37 (23.6)	
	2	148 (27.3)	40 (31.5)	75 (47.8)	
	3	103 (19)	42 (33.1)	45 (28.7)	
NAS ≥4	n (%)	256 (47.1)	83 (65.4)	157 (100)	<0.0001
MRI liver fat (PDFF, %)	Median (IQR)	9.2 (9.2)	12.4 (10)	12.2 (8.7)	0.959
cT1 (ms)	Median (IQR)	812 (136)	834 (124)	895 (132)	<0.0001

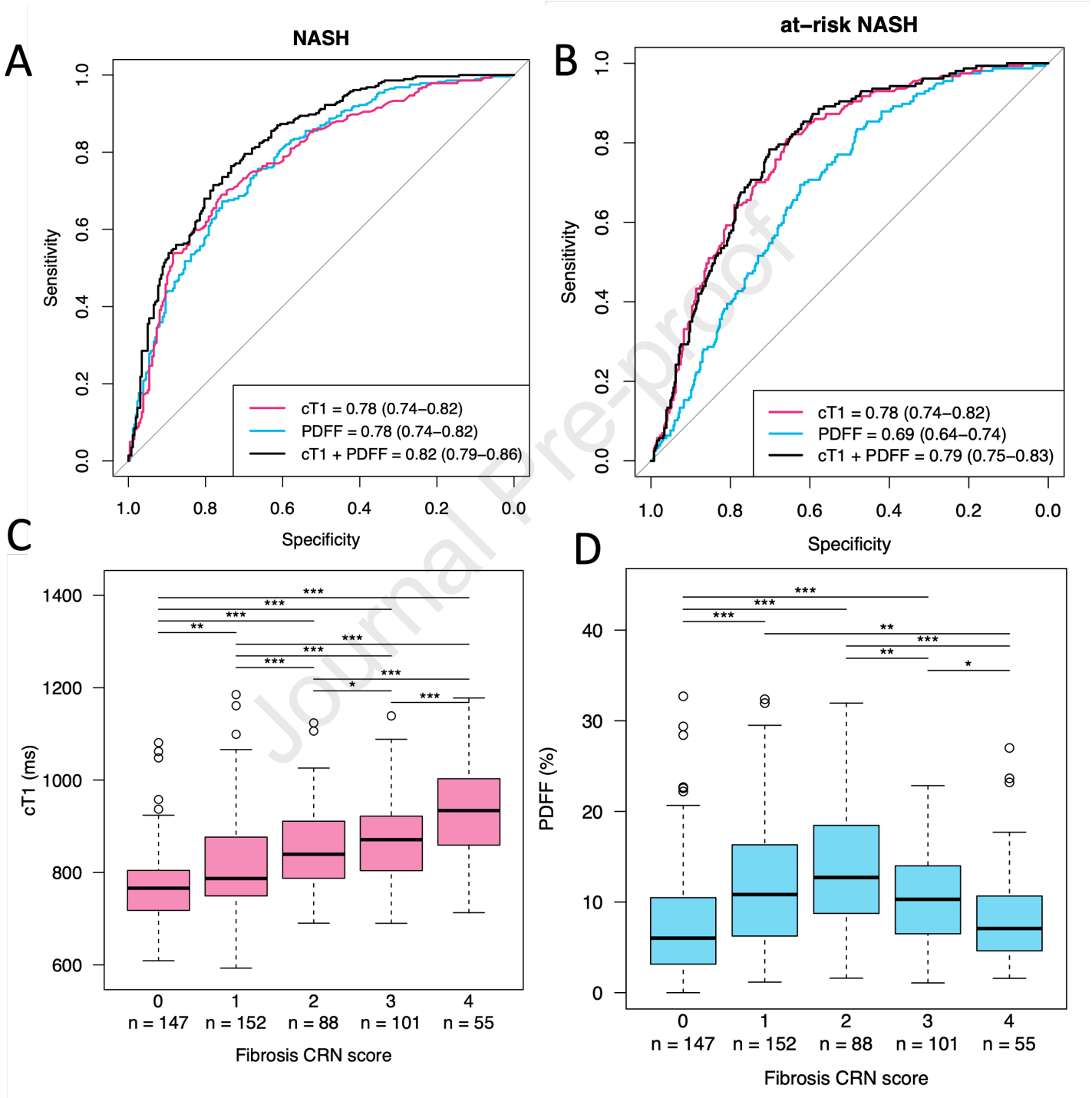
Table 2. Diagnostic accuracy of cT1 to identify patients with high-risk NASH at pre-specified thresholds.

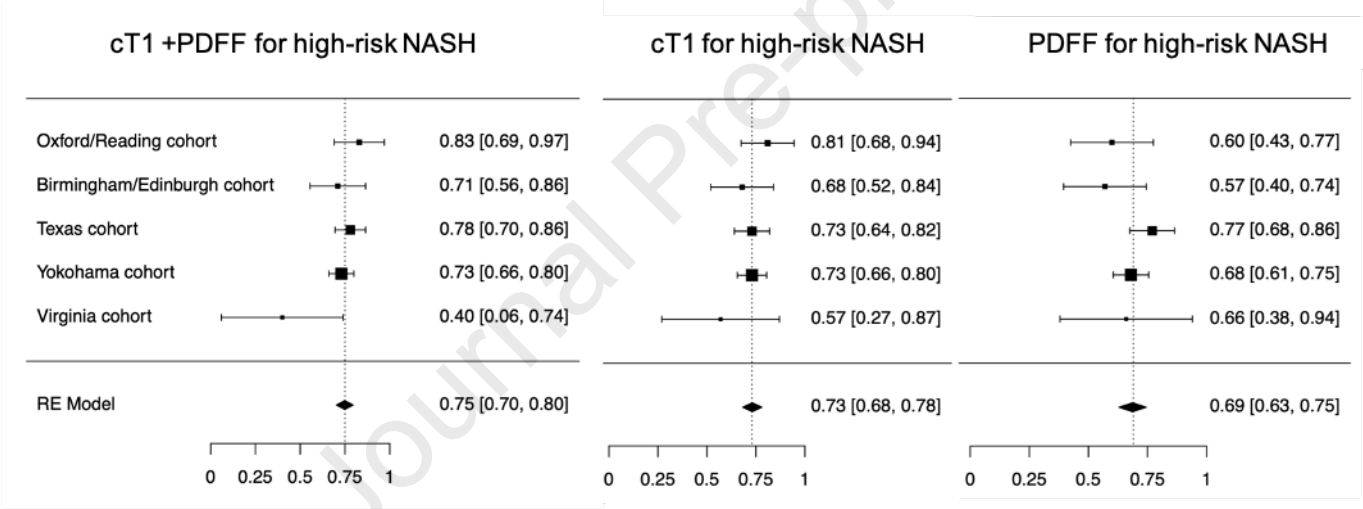
NAS≥4 & F≥2 (29% prev)	Threshold	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
cT1: AUROC = 0.78 [0.74-0.82]	≥800 ms	86	56	45	91
	≥825 ms	78	67	49	88
	≥875 ms	59	81	55	83
	≥900 ms	48	86	59	80
	≥925 ms	39	90	60	78

Table 3: Modelled positive and negative predictive values (PPV and NPV) for cT1 at simulated prevalence of high-risk NASH, based on performance in the pooled dataset (n=543).

Biomarker	Cut-off		Prevalence of high-risk NASH			
			10%	30%	50%	70%
cT1	≥825 ms	PPV (%)	21	50	70	85
	≥875 ms		26	57	76	88
	≥925 ms		30	63	80	90
cT1	≥825 ms	NPV (%)	96	88	75	57
	≥875 ms		95	82	66	46
	≥925 ms		93	77	60	39







What you need to know:

BACKGROUND: Non-invasive quantification of liver fat and fibro-inflammation using magnetic resonance imaging can identify patients with non-alcoholic steatohepatitis (NASH) and NASH with significant disease activity and fibrosis.

FINDINGS: MR liver fat (PDFF) and iron corrected T1 (cT1) showed high diagnostic performance for identification of NASH. cT1 was superior for NASH with significant disease activity and fibrosis

IMPLICATIONS FOR PATIENT CARE:

MR liver fat and cT1 are effective biomarkers for identifying those with NASH at greatest risk of disease progression and thus have the potential to provide accurate and non-invasive alternatives to liver biopsy in the clinical care pathway.