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Comparison of clinical prediction rules for ruling out cirrhosis in nonalcoholic fatty liver disease (NAFLD)

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SUPPORTING INFORMATION
Additional supporting information will be found online in the Supporting Information section.

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Summary

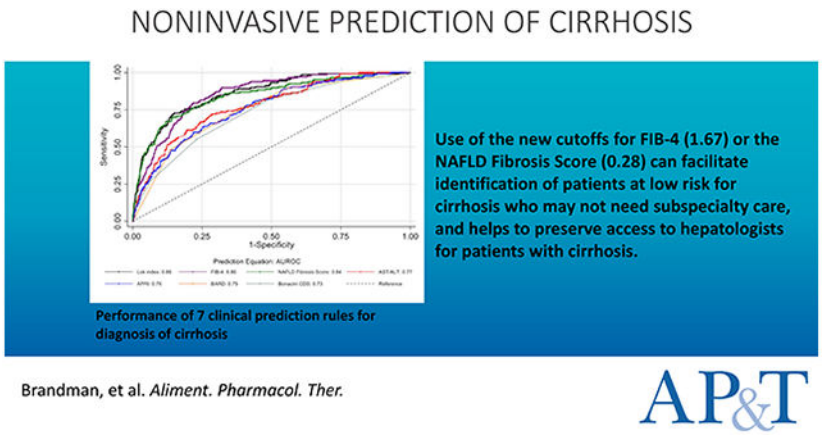
Background and Aims: Patients with nonalcoholic fatty liver disease (NAFLD) cirrhosis benefit from referral to subspecialty care. While several clinical prediction rules exist to identify advanced fibrosis, the cutoff for excluding cirrhosis due to NAFLD is unclear. This analysis compared clinical prediction rules for excluding biopsy-proven cirrhosis in NAFLD.

Methods: Adult patients were enrolled in the NASH Clinical Research Network (US) and the Newcastle Cohort (UK). Clinical and laboratory data were collected at enrolment, and a liver biopsy was taken within 1 year of enrolment. Optimal cutoffs for each score (eg, FIB-4) to exclude cirrhosis were derived from the US cohort, and sensitivity, specificity, positive predictive value, negative predictive value and AUROC were calculated. The cutoffs were evaluated in the UK cohort.

Results: 147/1483 (10%) patients in the US cohort had cirrhosis. All prediction rules had similarly high NPV (0.95–0.97). FIB-4 and NAFLD fibrosis scores were the most accurate in characterising patients as having cirrhosis (AUROC 0.84–0.86). 59/494 (12%) patients in the UK cohort had cirrhosis. Prediction rules had high NPV (0.92–0.96), and FIB-4 and NAFLD fibrosis score the most accurate in the prediction of cirrhosis in the UK cohort (AUROC 0.87–0.89).

Conclusions: This cross-sectional analysis of large, multicentre international datasets shows that current clinical prediction rules perform well in excluding cirrhosis with appropriately chosen cutoffs. These clinical prediction rules can be used in primary care to identify patients, particularly those who are white, female, and <65, unlikely to have cirrhosis so higher-risk patients maintain access to specialty care.

Graphical Abstract



1 | INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is an important public health problem, affecting an estimated 25%–30% of the world population,[1,2] with approximately 20% of patients having nonalcoholic steatohepatitis (NASH).[3] NAFLD can be progressive, particularly if NASH is present, with up to 30%–40% having progression of fibrosis and at risk for cirrhosis and its complications.[4–6] The increasing burden of NASH-associated cirrhosis is apparent, as it is the second leading indication for liver transplantation.[7] Fibrosis stage in NAFLD has been identified as the most important factor associated with mortality.[8–10] Identifying patients with cirrhosis due to NASH is critical so that appropriate surveillance for hepatocellular carcinoma (HCC) and clinical decompensation be performed. Given the NAFLD disease burden, triage of patients among primary care physicians and specialists is essential and simple, non-invasive tools to rule out cirrhosis in NAFLD patients are extremely useful. While noninvasive imaging studies such as ultrasound-based elastography and magnetic resonance elastography (MRE) have excellent ability to discriminate between cirrhosis and other stages of fibrosis with AUROC as high as ≥0.9,[11–13] several factors limit the ability to apply these tests to the large at-risk population: (1) the results of ultrasound-based elastography can be affected by obesity[14,15] or steatosis;[15] (2) testing requires available imaging technology and adequate experience to produce reliable results.[15] Liver biopsy, while considered the “gold standard” for diagnosis and staging of NAFLD, is fraught with problems when applying to the general population, due to cost, risk and potentially inadequate or misrepresentative specimens obtained.

Several clinical prediction rules to discriminate advanced fibrosis and cirrhosis (modified Brunt classification F3/4) from milder fibrosis (F0–2) have been published, including APRI, FIB-4 and NAFLD fibrosis score. Most of these rules were originally developed to assess for advanced fibrosis in non-NAFLD patients but have subsequently been well-validated for use in NAFLD patients.[16–19] Only the NAFLD Fibrosis Score and BARD scores were developed and validated for use in patients with NAFLD. The NAFLD fibrosis score has been demonstrated to be cost-effective in the risk stratification of patients with NAFLD in the primary care setting.[20] How well these tools separate non-cirrhotic (F0–3) vs. cirrhotic (F4) is also not well described. Given the myriad of clinical prediction tools available, a comprehensive evaluation of performance characteristics would be helpful to clinicians seeing patients with NAFLD.

Therefore, we aimed to evaluate seven clinical prediction rules in two large, well-defined, prospective clinical cohorts to determine appropriate cutoffs to rule out cirrhosis in NAFLD patients.

2 | METHODS

2.1 | Study design and participants: US Cohort

The current study on predictive clinical rules for cirrhosis was a cross-sectional analysis based primarily upon data collected prospectively from the large U.S. Multicenter NASH Clinical Research Network (CRN) cohort. Data from the enrolment visit from all participants in the NAFLD Database study and all participants enrolled up to the close

of the analysis database on November 2015 in NAFLD Database 2 study were included.[21] The details of the inclusion and exclusion criteria and study designs have previously been published.[21] Briefly, the NAFLD Database 2 study is an extension of the NAFLD Database 1 study and uses similar inclusion and exclusion criteria, except for requiring histological proof of NAFLD as an inclusion criterion.[22] The NASH CRN studies are sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, and all patients provided written informed consent for participation.

Information on demographic characteristics, medical history, clinical tests and liver biopsy results were collected at the baseline visit, as previously described.[21] All eligible adults met the following diagnostic criteria for NAFLD: (1) histologic diagnosis of NAFLD or histologic diagnosis of cryptogenic cirrhosis; (2) alcohol use history of <70 g/week for females or < 140 g/week for males; and (3) exclusion of liver disease of other aetiologies, including viral or autoimmune hepatitis, drug-induced liver disease and cholestatic or metabolic liver disease.

2.2 | Liver histology

All liver biopsy slides were stained with haematoxylin and eosin and Masson's trichrome, and were reviewed and scored centrally by the NASH CRN pathology committee as previously reported[23]; the review was performed blindly without knowledge of local pathology evaluation or clinical or laboratory characteristics of the patients.[23,24] The NAFLD activity score (NAS) was graded from 0 to 8 and is the sum of scores for steatosis (0–3), lobular inflammation (0–3) and hepatocellular ballooning (0–2). Definite NASH was deemed present as judged by the majority of the local NASH CRN pathologist and two additional NASH CRN pathologists.[24] Fibrosis stage was assessed according to the modified Brunt classification; 0 = no fibrosis, 1a = mild, zone 3 perisinusoidal fibrosis (requires trichrome), 1b = moderate, zone 3 perisinusoidal fibrosis (does not require trichrome), 1c = portal/periportal fibrosis, 2 = zone 3 perisinusoidal and periportal fibrosis, 3 = bridging fibrosis, 4 = cirrhosis.[23,24,25,26] Patients with stage F3 or F4 fibrosis were considered to have advanced fibrosis, and those with F4 were considered to have cirrhosis. All biopsies were taken within 1 year (NASH CRN database 1) or 90 days (NASH CRN database 2) of the enrolment visit.

2.3 | Study design and participants: UK Cohort

This study included consecutive patients with biopsy-proven NAFLD who attended the specialist fatty liver clinic at the Freeman Hospital, Newcastle-upon-Tyne, UK, enrolled prospectively. The clinical data were sourced ethically following receipt of informed consent from each patient and their research use was in accordance with the terms of the informed consents under an IRB/EC approved protocol. All data were obtained in a similar manner as for the US cohort. Liver biopsies were conducted as per routine clinical care for the investigation of abnormal liver function tests (raised ALT, AST or GGT) or to stage disease severity in patients with imaging evidence of fatty liver. Clinical and laboratory data were collected prospectively from the time of liver biopsy. Patients with evidence of other liver diseases (autoimmune hepatitis, viral hepatitis, drug-induced liver injury, haemochromatosis, cholestatic liver disease or Wilson's disease) were excluded. In addition, subjects consuming

excessive amounts of alcohol (alcohol intake >20 g/day for women; >30 g/day for men) at the time of biopsy or in the past were excluded. Patients with incomplete data to calculate all the non-invasive scores based on liver enzymes and clinical data were excluded.

Percutaneous liver biopsies were performed as per unit protocol and prepared in the same manner as in the US cohort within 90 days of enrolment, and were assessed by an experienced local hepatopathologist. Patients with liver biopsies specimens less than 15 mm in length were excluded. Histological scoring was performed according to the NASH Clinical Research Network criteria (CRN)[23] using the same criteria as the US cohort.

2.4 | Statistical analysis plan

Seven clinical prediction rules (AST:ALT ratio, AST to platelet ratio (APRI), BMI AST/ALT ratio diabetes (BARD) score, FIB-4 index, NAFLD fibrosis score, Bonacini Cirrhosis discriminant score (CDS), and Lok index) were calculated using previously published formulas (Table S1).[27–33] These scores have well-validated cutoffs to predict advanced fibrosis (bridging fibrosis or cirrhosis). In this study, new optimal cutpoints for diagnosis of cirrhosis in seven clinical prediction rules were identified using Youden's index as the metric to obtain the maximum sum of sensitivity and specificity, using the data from the US cohort. These cutoffs were then evaluated in the UK cohort. Each clinical prediction rule was evaluated for sensitivity, specificity, positive predictive value, negative predictive value and AUROC. The results adhere to the Standards for Reporting of Diagnostic Accuracy (STARD) for diagnostic tests, with the STARD checklist included as Table S2.

Data are presented as means with standard deviations or as percentages unless otherwise specified. Variables were compared in patients with cirrhosis to those without cirrhosis using chi-square test for categorical variables and *t*-test for continuous variables. The data analysis for this paper was generated using both SAS (SAS version 9.4, SAS Institute Inc.) and Stata software (StataCorp. 2017. Stata Statistical Software: Release 15.1; StataCorp LLC).

3 | RESULTS

3.1 | US cohort (NASH CRN cohort)

3.1.1 | Cohort characteristics—A total of 1483 patients met inclusion and exclusion criteria and formed the US cohort. Five hundred sixty-seven patients enroled in the NASH Database Study from July 2004 to February 2008 and 916 enrolled in the NASH Database 2 from July 2009 to November 2015. Cohort participants had a mean age of 50 years, were predominantly female (64%), and white (83%) (Table 1). Diabetes and hypertension were present in 37% and 57% of the cohort, respectively. Mean AST and ALT were 50 U/L (SD 35) and 68 U/L (SD 51), respectively. Most (65%) of patients had liver biopsy length of 15 mm or longer. Ten per cent ($N = 147$) of patients had cirrhosis on liver biopsy. Compared to patients without cirrhosis, those with cirrhosis were older (55 vs 49 years; $p < 0.0001$), more commonly white (93% vs 82%; $p < 0.0008$), had higher prevalence of diabetes and hypertension (66% vs 34%, $p < 0.0001$ and 67% vs 56%, $p = 0.008$, respectively), and higher BMI (36 vs 34 kg/m^2, $p = 0.004$). AST, AST/ALT ratio, INR were significantly

higher and platelet count lower (all $p < 0.01$) in patients with vs. without cirrhosis, whereas ALT was lower. Patients with cirrhosis had more ballooning, less steatosis and higher proportion with definite NASH than patients without cirrhosis (all $p < 0.0001$).

3.1.2 | Clinical prediction rule performance—The performance characteristics of the seven clinical prediction rules in identifying cirrhosis are presented in Table 2. Using the cutpoints derived from the use of the Youden index, sensitivity ranged from 64% to 82%, with FIB-4 and Bonacini CDS having the highest sensitivity at 80% and 82%, respectively. The NAFLD fibrosis score had the highest specificity (86%). All rules had low PPVs (≤35%), while NPVs were high (≥95%). The overall diagnostic accuracy to detect cirrhosis, using AUROC, was highest using FIB-4 (0.86), the Lok index (0.86) and NAFLD fibrosis score (0.84), as displayed in Figure 1. Performance of FIB-4 was significantly better than APRI, AST:ALT ratio, BARD and Bonacini (all $p < 0.001$). Neither the prediction cutpoints, nor the AUROCs and their associated p-values were substantially changed when each rule was assessed in patients with biopsy length ≥15 mm or ≥25 mm (Tables S3a and S3b).

Recognising that the use of the Youden index cutpoints may equally misclassify patients having or not having cirrhosis, we further analysed each clinical prediction rule to determine the optimal cutoff according to 90% sensitivity (“rule out” cutoff) and 90% specificity (“rule in” cutoff). Cutoffs derived from FIB-4 and NAFLD fibrosis score to identify cirrhosis were 1.28 and −1.59, respectively, for 90% sensitivity, and 2.35 and 0.58, respectively, for 90% specificity (Table S4). Using these cutoffs, performance was modelled according to different disease prevalence (1%, 10% and 25%). At 1% cirrhosis prevalence and 90% sensitivity, the NPV was >99% for all rules. When the cirrhosis prevalence was increased to 25%, the NPV remained high (≥93% for FIB-4 and NAFLD fibrosis score). The PPV when cirrhosis prevalence was 1% and specificity 90% was very low (≤7%) for all rules. When cirrhosis prevalence increased to 25%, the PPV increased to 63% and 68%, respectively (Table S5). Using the Youden-index derived FIB-4 cut-off of 1.67, the false-positive rate was lowest and the false-negative rate was highest when diagnosing cirrhosis vs. diagnosing other stages of fibrosis (Table S6).

3.2 | UK cohort (Newcastle cohort)

3.2.1 | Cohort characteristics—In the 494 patients included in the UK cohort, the mean age was 53 years, 57% were male and all were white. Diabetes was present in 57% of the cohort. Mean AST and ALT were 49 (SD 27) U/L and 71 (SD 45) U/L, respectively. Cirrhosis on biopsy was present in 59 (12%) of the patients in the UK cohort (Table 3). Similar to the US cohort, patients with cirrhosis were older (59 vs 53 years; $p < 0.001$), more frequently diabetic (84% vs 53%; $p < 0.001$), and had higher BMI (37 vs 35 kg/m^2; $p = 0.002$). Mean AST, AST/ALT ratio, INR and platelet count were significantly (all $p < 0.005$) higher in patients with cirrhosis compared to those without cirrhosis, whereas mean ALT was significantly lower ($p = 0.03$). Patients with cirrhosis had less ballooning, more steatosis and more lobular inflammation than patients without cirrhosis (all $p < 0.05$) but similar rates of definite NASH (41% with cirrhosis vs. 38% without cirrhosis).

3.2.2 | Clinical prediction rule performance—The clinical prediction rules were evaluated in the entire UK cohort, except for the Bonacini score and Lok index (n = 424 due to 70 patients not having INR available). Performance of the seven clinical prediction rules to diagnose cirrhosis in the UK cohort was similar to the performance in the US cohort (Table 4). Using the cutpoints derived from the Youden index analysis, APRI had the highest sensitivity to rule out cirrhosis (85%), FIB-4 still performed well, with the sensitivity of 78%. Specificity was highest for the Lok index (95%) and was 89% for the NAFLD fibrosis score. PPV was low in this cohort, though it had a wider range than the US cohort (19%–52%). NPV was high for all prediction rules, though slightly lower than the US cohort (≥92%). The overall diagnostic accuracy for detecting cirrhosis, using AUROC, was numerically the highest for the NAFLD fibrosis score (0.89) and FIB-4 (0.87).

4 | DISCUSSION

This study leverages data from two large multicentre, multinational studies, to evaluate the diagnostic performance of seven clinical prediction rules to rule out cirrhosis in patients with biopsy-confirmed NAFLD in well-characterised, predominantly white, <65-year-old patient cohorts that included mostly patients who were white, female and younger than 65. Among the seven different clinical prediction rules evaluated, FIB-4 and the NAFLD fibrosis score had excellent negative predictive value to exclude cirrhosis. The high sensitivity and NPV of both scores indicate that few patients would be misclassified as not having cirrhosis despite its presence on liver biopsy. These results also demonstrate that the previously well-validated cutoffs for ruling out advanced fibrosis perform well for ruling out cirrhosis in this patient population. We propose the use of new cutoffs for FIB-4 (1.67) or the NAFLD Fibrosis Score (0.28) to identify NAFLD patients with similar demographic characteristics who are unlikely to have cirrhosis have similar demographics as in our cohorts. This method facilitates the identification of patients at low risk for cirrhosis who may not need subspecialty care and helps to preserve access for patients with cirrhosis to hepatologists, with the aim of reducing liver-related morbidity and mortality. Because the cohort lacks racial and ethnic diversity within the US, caution should be used in applying these novel cutoffs in non-white patients. Earlier studies have demonstrated that higher cutoff values are likely appropriate for older patients,[34] so further validation of our novel cutoffs may be required prior to application in patients older than 65 to ensure appropriate sensitivity is preserved.

While prior studies have not specifically set out to identify those who may have cirrhosis, these studies have had similar results to ours with regard to the performance of clinical prediction rules in diagnosing advanced fibrosis. Our results are similar to what was observed in a meta-analysis of four studies that included a total of 1038 patients, where the NPV to rule out advanced fibrosis (F3–4) for FIB-4 and the NAFLD fibrosis scores were 0.9–0.91.[35] Moreover, our new FIB-4 and NAFLD fibrosis score cutoffs to rule out cirrhosis maintain a similarly high level of accuracy for identification of cirrhosis.[16] These results reaffirm the use of FIB-4 and NAFLD fibrosis score cutoffs to exclude the presence of cirrhosis in NAFLD patients and identify those who are at high risk but may need further testing to confirm the diagnosis.

Our use of the Youden index relied upon a high sensitivity for each clinical prediction rule (90%), with the goal of yielding robust NPV to rule out cirrhosis. Our methods yielded a single cutoff that may better inform primary care providers about which of their fatty liver patients are indeed at low risk for advanced fibrosis. This cutoff selection method also assumed the risk of classifying a patient as not having cirrhosis was the same as classifying a patient as having cirrhosis, which is not necessarily true clinically. While a false-negative test may eliminate opportunities to reduce liver-related morbidity and mortality through HCC and/or variceal surveillance,[36] a false positive may lead to additional unnecessary testing and cause undue anxiety to the patient. These risks have to be considered in the context of the populations where the tests are used. Since the prevalence of cirrhosis is low in the general population, the high negative predictive value of these new cutoffs is likely to represent true negatives. The low specificity and positive predictive value of these risk scores further underscore the need for additional approaches to confirm the presence of cirrhosis if patients are suspected to have cirrhosis on the basis of noninvasive tests. Use additional testing (eg, transient elastography, ELF, liver biopsy) will be necessary to confirm the presence of cirrhosis in patients with FIB-4 and NAFLD Fibrosis Score values above these cutoffs.

Although the specificity for the new cutoffs proposed for FIB-4 and NAFLD Fibrosis Score for cirrhosis in this current study is relatively low, the high sensitivity and NPV minimise the risk that patients will pay the price of misclassification into lower-risk groups. While we aimed to identify patients with cirrhosis, given the sub-optimal specificity and overlap of these new cutoffs for FIB-4 and NAFLD fibrosis scores with those previously established for advanced fibrosis (F3), it is likely that some patients with advanced fibrosis will be labelled as having cirrhosis. Given the high risk of liver-related events in patients with advanced fibrosis, this potential “misclassification” may result in appropriate linkage to subspecialty care. The other “misclassification” applies to the few patients with cirrhosis but are assessed as not having cirrhosis due to scores below the cutoffs. Future studies are needed to determine if repeatedly calculating FIB-4 scores and the NFS at routine follow-up visits will eventually identify those patients.

This study does have some limitations that must be acknowledged and may limit the generalisability of our findings. First, our cohort comprised a broad spectrum of NAFLD severity, which parallels that seen in the general NAFLD population. Even though the cohorts contain a relatively small number of patients with cirrhosis, it is likely that even this proportion is greater than that in the general population as both cohorts were compiled at highly specialised centres. If spectrum bias is present, this could affect the performance of the clinical prediction rules evaluated and their respective derived cutoffs. While the new cutoffs for cirrhosis for FIB-4 had excellent performance in the UK cohort, the lack of validation in more ethnically diverse cohorts is needed, particularly since the negative predictive value of FIB-4 will decrease in populations where the prevalence of cirrhosis is higher.[37,38] The gender of included patients was predominantly female, which may also affect the performance of FIB-4. Additionally, the cohorts used for this study had only a small minority of patients with age >65 years and thus the performance of these cutoffs could not be further assessed in the older population. Finally, our cross-sectional study

design does not account for variability in lab measurements over time. Further studies are needed to assess the trend in FIB-4 and its association with fibrosis progression.

It is impractical to subject the 25% of the US population at risk for NAFLD[1] to liver biopsy to accurately characterise disease severity, particularly since a very small proportion of this large group will actually have cirrhosis, yet it is important to identify them for closer monitoring. Moreover, clinical prediction rules that rely on complex formulas such as a previous score developed using the NASH CRN cohort[39] often do not gain widespread acceptance in routine clinical care. Application of simple clinical prediction rules with a single cutpoint may allow primary care providers to identify patients who may be at lower risk for having cirrhosis due to NAFLD on a large scale, thereby maintaining the capacity for higher-risk patients to be referred to gastroenterologists and hepatologists for further risk stratification. We have shown that simple methods utilising readily available clinical data accurately rule out cirrhosis in patients with NAFLD. These methods can be applied easily in the primary care setting to white, younger patients to avoid speciality referral for low-risk patients, though validation in populations who are older, non-white and male is needed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Funding information

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Declaration of personal interests:

Danielle Brandman: None for this project. Dr Brandman has received research support from Allergan, Conatus, and Grifols, and grant and research support from Gilead. She has served on an advisory board and consulted for Alnylam. Arun Sanyal: None for this project. Dr Sanyal is President of Sanyal Biotechnology and has stock options in Genfit, Akarna, Tiziana, Indalo, Durect and Galmed. He has served as a consultant to Astra Zeneca, Nitto Denko, Enyo, Ardelyx, Conatus, Nimbus, Amarin, Salix, Tobira, Takeda, Jannsen, Gilead, Terns, Birdrock, Merck, Valeant, Boehringer-Ingelheim, Lilly, Hemoshear, Zafgen, Novartis, Novo Nordisk, Pfizer, Exhalenz and Genfit. He has been an unpaid consultant to Intercept, Echosens, Immuron, Galectin, Fractyl, Syntlogic, Affimune, Chemomab, Zydus, Nordic Bioscience, Albireo, Prosciento, Surrozen and Bristol Myers Squibb. His institution has received grant support from Gilead, Salix, Tobira, Bristol Myers, Shire, Intercept, Merck, Astra Zeneca, Malinckrodt, Cumberland and Novartis. He receives royalties from Elsevier and UptoDate. Naga Chalasani: There are none for this paper. For full disclosure, Dr Chalasani has ongoing consulting activities (or had in the preceding 12 months) with NuSirt, Abbvie, Eli Lilly, Afimmune (DS Biopharma), Allergan (Tobira), Madrigal, Shire, Axovant, Coherus, Pronova (BASF) and Genentech. These consulting activities are generally in the areas of nonalcoholic fatty liver disease and drug hepatotoxicity. Dr Chalasani receives research grant support from Intercept, Lilly, Galectin Therapeutics and Cumberland where his institution receives the funding. Over the last decade, Dr Chalasani has served as a paid consultant to more than 35 pharmaceutical companies and these outside activities have regularly been disclosed to his institutional authorities. Cynthia Behling: Dr Behling is a consultant

for ICON and Covance. Brent A. Neuschwander-Tetri: None for this paper. Dr Tetri has consultant or advisor relationships with Allergan, Alnylam, Arrowhead, Axcella, Boehringer-Ingelheim, BMS, Durect, Enanta, Ferring, Fortress, Gelesis, Genfit, Gilead, HepGene, High Tide, HistoIndex, Intercept, Lipocine, Madrigal, Medimmune, Merck, Mundipharma, NGM, pH-Pharma, Siemens; he also has institutional research grants from Allergan, BMS, Cirius, Enanta, Genfit, Gilead, Intercept, Madrigal, NGM. Rohit Loomba: Dr Loomba serves as a consultant or advisory board member for Bird Rock Bio, Celgene, Enanta, GRI Bio, Madrigal, Metacrine, NGM, Receptos, Sanofi, Arrowhead Research, Galmed, NGM, GIR, Inc. and Metacrine, Inc. In addition, his institution has received grant support from Allergan, BMS, BI, Daiichi-Sankyo Inc., Galectin, Galmed, GE, Genfit, Gilead, Intercept, Janssen Inc, Madrigal, Merck, NGM, Pfizer, Prometheus, Siemens and Sirius. He is also co-founder of Liponexus Inc. Kris Kowdley: Dr Kowdley has consulted for Corcept, Gilead, Enanta, Intercept and Verlyx. His institution has received grant and research support from Allergan, Enanta, Galectin, Gilead, Immuron, Intercept, Prometheus and Zydus. Dr Kowdley is on the Advisory Board for Conatus and Gilead, and on the Speaker Bureau for Gillead and Intercept. Norah Terrault: Nothing to declare related to this work. Dr Terrault has received institutional grant and research support from Gilead and Allergan. No conflicts of interest: David Kleiner, James Tonascia, Ed Doo, Marie Boyle, Ricki Bettencourt, Cyrielle Caussy, Art McCullough. Stuart McPherson: Nothing to declare related to this work. SM has received consultancy fees, speakers' honoraria or research funding from AbbVie, Allergan, Bristol Myers Squibb, Cambwick, Gilead Sciences, Intercept, Merck Sharp Dohme and Sequana. Quentin Anstee: Nothing to declare related to this work. Q.M.A. is coordinator of the LITMUS IMI2 Consortium funded by the European Commission through grant agreement 777,377. Consultancy: 89Bio, Abbott Laboratories, Acuitas Medical, Allergan/Tobira, Altimmune, AstraZeneca, Axcella, Blade, BMS, BNN Cardio, Celgene, Cirius, CymaBay, EcoR1, E3Bio, Eli Lilly & Company Ltd., Galmed, Genentech, Genfit SA, Gilead, Grunthal, HistoIndex, Indalo, Imperial Innovations, Intercept Pharma Europe Ltd., Inventiva, IQVIA, Janssen, Madrigal, MedImmune, Metacrine, NewGene, NGMBio, North Sea Therapeutics, Novartis, Novo Nordisk A/S, Pfizer Ltd., Poxel, ProSciento, Raptor Pharma, Servier, Terns, Viking Therapeutics. Research Grant Funding: Abbvie, Allergan/Tobira, AstraZeneca, GlaxoSmithKline, Glympse Bio, Novartis Pharma AG, Pfizer Ltd., Vertex. Mark L. Van Natta: Nothing to declare. Manal F. Abdelmalek: Nothing to declare related to this work. Consultancy: 89Bio, Allergan/Tobira, BMS, Genfit SA, Intercept Pharma, Inventiva, Madrigal, NGMBio, Novartis, Novo Nordisk A/S, Promethera, TaiwanJ. Her institution has received grant and research support from Allergan/Tobira, Intercept, Gilead, Genfit, Galmed, Celgene, Madrigal, Poxel, Durect, Enanta, Inventiva, BMS, NGM Bio, NovoNordisk, Novartis, Viking, TARGET NASH, Progenity.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

APPENDIX 1

Members of the Nonalcoholic Steatohepatitis Clinical Research Network.

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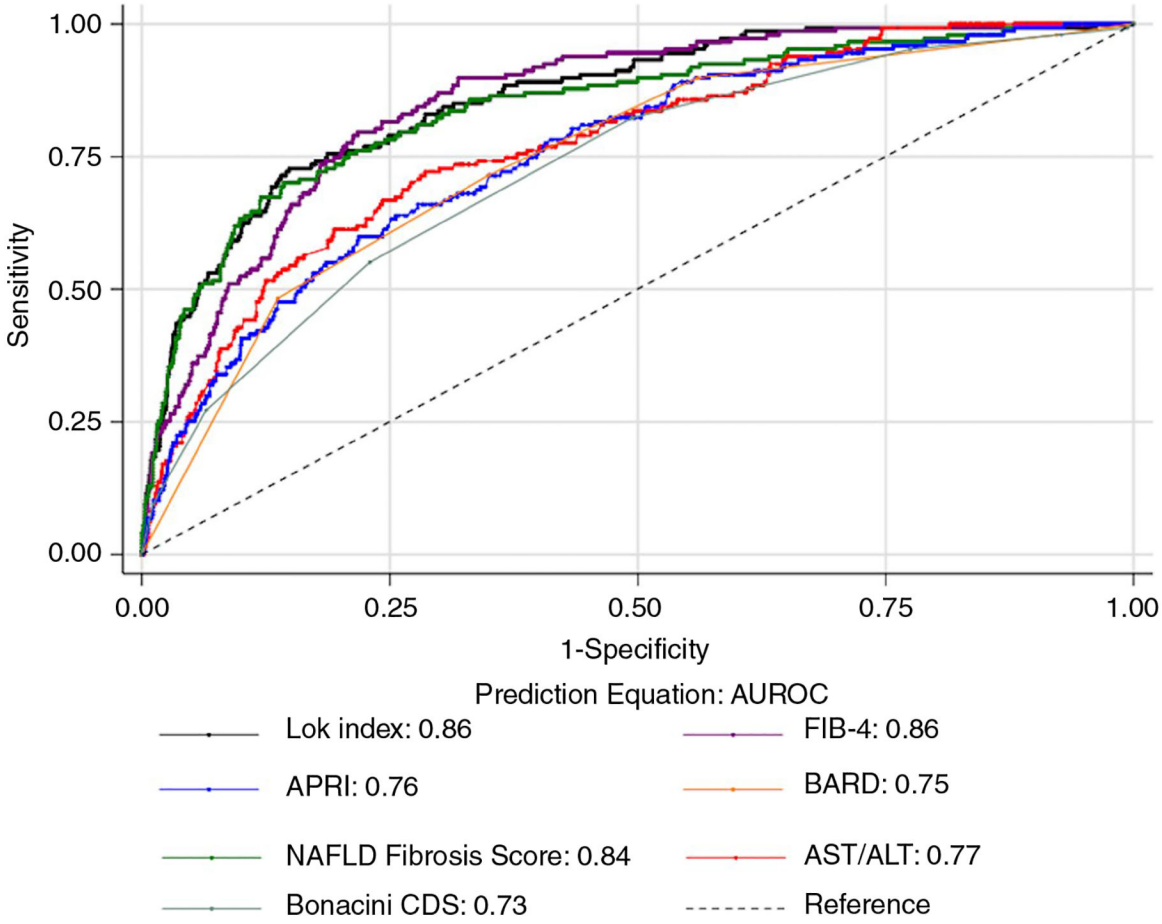

FIGURE 1.

Performance of seven clinical prediction rules for diagnosis of cirrhosis in the US cohort (US)

TABLE 1

Comparison of clinical and laboratory characteristics in patients with and without cirrhosis, US cohort (NASH CRN)

	Cirrhosis (*n* = 147)	**No cirrhosis (*n* = 1336)**	**Total (*n* = 1483)**	
	Mean (SD)/%	**Mean (SD)/%**	**Mean (SD)/%**	***p*-value**
Clinical and lab data				
Age, years	55 (10)	49 (12)	50 (12)	<0.0001
Sex, male (%)	33	36	36	NS
Race, white (%)	93	82	83	0.0008
Ethnicity, Hispanic (%)	6	12	11	0.04
Diabetes (%)	66	34	37	<0.0001
Hypertension (%)	67	56	57	0.008
Body mass index (kg/m^3)	36 (7)	34 (6)	34 (6)	0.004
AST (U/L)	56 (29)	49 (35)	50 (35)	0.01
ALT (U/L)	57 (39)	70 (52)	68 (51)	0.0003
AST:ALT ratio	1.1 (0.5)	0.8 (0.3)	0.8 (0.4)	<0.0001
International normalised ratio	1.14 (0.26)	1.01 (0.12)	1.02 (0.15)	<0.0001
Platelet count (1 K/mm^3)	164 (69)	248 (71)	239 (75)	<0.0001
Histology				
NAFLD activity score, 0–8	4.2 (1.6)	4.1 (1.8)	4.2 (1.8)	NS
Ballooning, 0–2	1.5 (0.7)	0.9 (0.9)	0.9 (0.9)	<0.0001
Lobular inflammation, 0–3	1.5 (0.7)	1.5 (0.7)	1.5 (0.7)	NS
Steatosis, 0–3	1.2 (0.8)	1.8 (0.8)	1.7 (0.9)	<0.0001
Definite NASH (%)	76	49	51	<0.0001
Fibrosis stage (%)				
Stage 0	0	32	29	<0.0001
Stage 1	0	29	26	
Stage 2	0	20	18	
Stage 3	0	20	18	
Stage 4	100	0	10	
Biopsy length (%)				
<15 mm	32	36	35	0.58

	Cirrhosis (*n* = 147)	No cirrhosis (*n* = 1336)	Total (*n* = 1483)	
	Mean (SD)/%	Mean (SD)/%	Mean (SD)/%	*p*-value
15–24 mm	39	39	39	
25+ mm	29	25	26	

TABLE 2

Performance characteristics of seven clinical prediction rules with cutoffs optimised for excluding cirrhosis in 1483 NAFLD patients with biopsy within 6 months of enrolment visit, US cohort (NASH CRN)

Prediction equation	Score cutoff[a]	Sensitivity	Specificity	PPV	NPV	AUROC
APRI score	0.54	0.64	0.74	0.22	0.95	0.76
AST:ALT ratio	0.88	0.72	0.71	0.23	0.96	0.77
BARD score	3	0.71	0.65	0.18	0.95	0.75
Bonacini cirrhosis discriminant score	5	0.82	0.51	0.16	0.96	0.73
FIB-4 score	1.67	0.80	0.78	0.29	0.97	0.86
Lok index	0.59	0.73	0.85	0.35	0.97	0.86
NAFLD Fibrosis Score	0.28	0.70	0.86	0.35	0.96	0.84

[a]As determined by the Youden index.

TABLE 3

Comparison of clinical and laboratory characteristics in patients with and without cirrhosis, UK cohort (Newcastle)

	Cirrhosis (*n* = 59)	**No cirrhosis (*n* = 435)**	**Total (*n* = 494)**	
	Mean (SD)/%	**Mean (SD)/%**	**Mean (SD)/%**	***p*-value**
Clinical and lab data				
Age (years)	59 (9)	52 (13)	53 (13)	<0.001
Sex, male (%)	63	48	50	0.004
Race, white (%)	100	100	100	–
Ethnicity, Hispanic (%)	0	0	0	–
Diabetes (%)	84	53	57	<0.001
Body mass index (kg/m^3)	37 (7)	35 (6)	35 (6)	0.002
AST (U/L)	58 (24)	48 (27)	49 (27)	<0.005
ALT (U/L)	59 (34)	73 (45)	71 (45)	0.03
AST:ALT ratio	1.1 (0.5)	0.7 (0.3)	0.8 (0.3)	<0.0001
International normalised ratio	1.14 (0.13)	1.06 (0.11)	1.07 (0.12)	<0.0001
Platelet count (1 K/mm^3)	172 (65)	248 (65)	238 (70)	<0.001
Histology				
NAFLD activity score, 0–8	5 (IQR 2–8)	4 (IQR 0–6)	—	<0.001
Ballooning, 0–2	1.7 (0.8)	1.95 (0.7)	—	0.042
Lobular inflammation, 0–3	1.34 (0.7)	0.8 (0.7)	—	<0.001
Steatosis, 0–3	1.48 (0.7)	1.07 (0.8)	—	<0.001
Definite NASH (%)	41	38	38	NS

TABLE 4

Performance characteristics of seven clinical prediction rules in 494[a] NAFLD patients with biopsy within 1 year of enrolment visit, UK cohort (Newcastle)

Prediction equation	Score cutoff[a]	Sensitivity	Specificity	PPV	NPV	AUROC
APRI score	0.54	0.85	0.49	0.19	0.96	0.79
AST:ALT ratio	0.88	0.61	0.77	0.27	0.94	0.77
BARD score	3	0.68	0.70	0.24	0.94	0.76
Bonacini cirrhosis discriminant score[b]	5	0.68	0.70	0.24	0.94	0.73
FIB-4	1.67	0.78	0.76	0.31	0.96	0.87
Lok index[b]	0.59	0.40	0.95	0.52	0.92	0.84
NAFLD Fibrosis Score	0.28	0.68	0.89	0.46	0.95	0.89

[a]As determined by the Youden index.

[b]Only 424 patients were analysed for the Bonacini score and Lok index.