Towards collaborative management of nonalcoholic fatty liver disease (TCM-NAFLD): a 'real-world' pathway for fibrosis risk assessment in primary care

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Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; ELF, Enhanced Liver Fibrosis test; FIB-4, Fibrosis-4 Index; HCC, hepatocellular carcinoma; HMC, hepatology management clinic; IFG, impaired fasting glucose; IQR, interquartile range; LSM, liver stiffness measurements; NAFLD, nonalcoholic fatty liver disease; NFS, nonalcoholic fatty liver disease (NAFLD) Fibrosis Score; PCP, primary care practitioner; SD, standard deviation; T2DM, type 2 diabetes mellitus.

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Abstract

Background: The optimal strategy to support primary care practitioners (PCPs) to assess fibrosis severity in nonalcoholic fatty liver disease (NAFLD) and thereby make appropriate management decisions remains unclear.

Aims: We aimed to examine the feasibility of using a 2-step pathway that combined simple scores (NAFLD Fibrosis Score and Fibrosis-4 Index) with transient elastography (FibroScan®) to streamline NAFLD referrals from a 'routine' primary care population to specialist hepatology management clinics (HMC).

Methods: The 2-step "Towards Collaborative Management of NAFLD" (TCM-NAFLD) fibrosis risk assessment pathway was implemented at two outer metropolitan primary healthcare practices in Brisbane. Patients aged ≥18 years with a new or established PCP-diagnosis of NAFLD were eligible for assessment. The pathway triaged patients at "high risk" of clinically significant fibrosis to HMC for specialist review, and "low risk" patients to receive ongoing management and longitudinal follow-up in primary care.

Results: A total of 162 patient assessments between Jun-2019 and Dec-2020 were included. Mean age was 58.7±11.7 years, 30.9% were male, 54.3% had type 2 diabetes or impaired fasting glucose, and mean body mass index was 34.2±6.9kg/m^2. 122 patients were considered "low risk" for clinically significant fibrosis, two patients had incomplete assessments, and 38 (23.5%) were triaged to HMC. Among 31

completed HMC assessments to date, 45.2% were considered to have clinically significant (or more advanced) fibrosis, representing 9.2% of 153 completed assessments.

Conclusion: Implementation of the 2-step TCM-NAFLD pathway streamlined hepatology referrals for NAFLD and may facilitate a more cost-effective and targeted use of specialist hepatology resources.

Key words: Nonalcoholic fatty liver disease; liver fibrosis; risk assessment; primary care; referral pathway; collaborative care

Introduction

Nonalcoholic fatty liver disease (NAFLD) is the most common chronic liver disorder seen in primary care[1], and recent Australian data predict a growing NAFLD-related disease burden over the next decade.[2] Despite its high prevalence of around 25% in the adult population,[3] only a small proportion of people with NAFLD (<5-10%) develop cirrhosis and related complications including hepatocellular carcinoma (HCC) over 10-20 years.[4,5] As the presence of advanced fibrosis (including bridging fibrosis (Brunt fibrosis stage F3) and cirrhosis (Brunt fibrosis stage F4)) is the most important determinant of adverse liver outcomes and overall mortality,[4-6] assessing fibrosis severity is necessary to make appropriate decisions about patient management.

Expert opinion recommends that people with NAFLD at "low risk" of advanced fibrosis can remain in primary care with a focus on managing cardiometabolic comorbidities, while those at "high risk" of advanced fibrosis require specialist referral and may benefit from surveillance for liver cancer and liver decompensation.[7] However, 'real-world' hepatology clinic data suggests the current approach to NAFLD referrals from primary care is inconsistent. Between 75%-90% of referred patients do not have advanced fibrosis[8,9] and most (88.5%) are referred for investigation of abnormal liver enzymes.[9] The reliance on abnormal liver enzymes to select cases for referral may fail to identify people with advanced fibrosis, as

aminotransferases are normal in many patients with NAFLD and the level of elevation does not reflect the severity of liver disease.[10]

The optimal strategy to support primary care practitioners (PCPs) to assess fibrosis severity in patients with NAFLD remains unclear. Clinical guidelines endorse the use of simple scores (NAFLD Fibrosis Score (NFS) and Fibrosis 4 Index (FIB-4)) for initial assessment of fibrosis.[11-13] These inexpensive tests can be calculated in primary care using readily available clinical and biochemical parameters. While the scores have high negative predictive values for excluding advanced fibrosis,[14] a substantial proportion of patients fall into an "indeterminate risk" category and require second-line assessment with ultrasound elastography such as FibroScan® or a commercial panel of serum markers such as the Enhanced Liver Fibrosis (ELF™) test. Few PCPs have direct access to FibroScan® or serum ELF test in Australia because the tests are not reimbursed. Therefore, these assessments are usually only obtained after referral to a hepatology centre, which contributes to potentially unnecessary referrals.

The purpose of this study was to implement a 2-step fibrosis risk assessment pathway in primary care and assess its utility for streamlining NAFLD referrals to hepatology management clinics (HMC). We specifically aimed to characterise patients with a PCP diagnosis of NAFLD referred to the pathway, and assess the prevalence of clinically significant fibrosis (equivalent to Brunt fibrosis stage ≥F2) in a 'routine' primary care population.

Methods

Liver fibrosis assessment in primary care

The 2-step "Towards Collaborative Management of NAFLD" (TCM-NAFLD) fibrosis risk assessment pathway (Figure 1) was adapted from the Camden and Islington NAFLD pathway[8] in collaboration with two primary healthcare practices in outer metropolitan Brisbane, Queensland. The practices comprised 20 and 11 PCPs, with a current practice population of 4372 and 4673 patients respectively. All PCPs in both practices were invited to refer patients aged ≥18 years with a new or established PCP-diagnosis of NAFLD to the TCM-NAFLD pathway. Local guidance defines NAFLD by demonstration of hepatic steatosis on liver ultrasound in the presence of metabolic risk factors and the exclusion of significant alcohol

consumption (≥20 g/day) or other chronic liver diseases (including a prior history of alcohol-related liver disease). However, NAFLD referrals without up-to-date liver imaging, documented alcohol intake, or screening tests for other liver diseases (e.g. hepatitis B or C, autoimmune hepatitis, haemochromatosis, drug-induced liver injury) were not refused, in order to emulate a 'real-world' scenario. A liver fellow and/or hepatology nurse who visited the practice every 1-2 weeks performed a liver fibrosis assessment according to the 2-step pathway. Informed written consent was obtained from each eligible patient, and the protocol was approved by the Metro South Health human research ethics committee (HREC/2019/QMS/49780).

2-step pathway

In step 1, overall risk stratification was performed using the NFS and FIB-4 scores. These scores were obtained using readily available online calculators hosted by MDCalc (https://www.mdcalc.com/fibrosis-4-fib-4-index-liver-fibrosis#evidence; https://www.mdcalc.com/nafld-non-alcoholic-fatty-liver-disease-fibrosis-score#evidence), as point-of-care risk stratification tools were not available in PCP practice software. At the time of this study, the online FIB-4 calculator applied an age-adjusted lower cutoff (<2.0) to exclude advanced fibrosis in patients aged ≥65 years,[15] whereas the NFS calculator did not. All patients aged ≤35 years were recommended to undergo alternative fibrosis assessment.

Patients were classified as having "low risk" of advanced fibrosis if both the NFS and FIB-4 scores were "low". These people were returned to the care of their referring PCP with a letter recommending ongoing management of NAFLD in primary care, and advice to monitor NFS and FIB-4 scores on an annual basis (or more frequently if indicated). For all patients with NAFLD, the letter to the PCP provided recommendations regarding ongoing assessment and management of cardiometabolic risk factors and lifestyle intervention with consideration of referral to a dietician, exercise physiologist and psychologist for assistance with weight management and increased physical activity.

Patients were classified as "high risk" if either score was "high". "High risk" patients were referred to a HMC at one of two nearby hospitals for further assessment.

"Indeterminate risk" was assigned if one or both scores were "indeterminate" but neither score was "high". These patients required a second step to assess fibrosis severity. Transient elastography was performed by a trained hepatology nurse after a 3-hour fast using FibroScan® technology (Echosens, Paris, France) with the standard M or XL probes in line with the manufacturer's instructions. Recommended FibroScan® operating procedures were followed along with adherence to criteria for definition of reliable liver stiffness measurements (LSMs) as follows: minimum of 10 valid measurements with a success rate of ≥60% and interquartile range (IQR) ≤30% of the final (median) result. The XL probe was used when the skin-capsule depth was ≥2.5 cm. Patients were classified as "low risk" of advanced fibrosis if valid LSM was less than 8.0 kPa.[16,17] A letter was written to the referring PCP recommending ongoing follow-up in primary care as described above, with advice to refer the patient for a repeat FibroScan® in 2-3 years. Patients with LSM ≥8.0 kPa were considered to have an increased likelihood of clinically significant fibrosis (≥F2) and were referred to HMC for further assessment.

Data collection

Demographic and clinical information were collected prospectively by the liver fellow and/or hepatology nurse at the time of fibrosis assessment using a structured questionnaire. Questionnaire items included whether the patient entered the NAFLD pathway based on an ultrasound finding of steatosis or abnormal liver enzymes, the presence of metabolic comorbidities (obesity, type 2 diabetes, hypertension, dyslipidaemia), other medical conditions, previously diagnosed liver disease, current and previous alcohol intake, and use of medications. Pathology data to calculate the NFS and FIB-4 scores were reviewed.

Patients with "high risk" simple scores or LSM ≥8.0 kPa underwent further clinical assessment in HMC that included anthropometric measurements, laboratory tests (routine biochemical, haematological, and serological assays), transient elastography (if required), liver imaging (computed tomography, magnetic resonance imaging, and/or ultrasound), and a liver biopsy if clinically indicated (for example to confirm or exclude NAFLD or advanced fibrosis in patients with discordant clinical data). The diagnosis of definite or probable advanced fibrosis (equivalent to Brunt fibrosis stage F3/4) was based on the composite

clinical judgement of the treating hepatologist using liver histology (if available), imaging, or a combination of noninvasive markers and clinical assessment.

Data analysis

The Shapiro-Wilk test was used to assess whether continuous variables significantly deviated from a normal distribution. Normally distributed data are presented as mean ± standard deviation (SD) and non-normal data are presented as median (IQR). Categorical data are summarised numerically and as proportions (%).

Differences between two groups were assessed using the independent-samples t-test, Mann-Whitney U test, or Pearson's chi-squared test (or Fisher's Exact test if ≥1 expected cell count was <5) for normally distributed, non-normal, and categorical data respectively. Differences between three or more groups were assessed using ANOVA, the Kruskal-Wallis test, or the Fisher-Freeman-Halton Exact test for normally distributed, non-normal, and categorical data respectively. Two-tailed p-values with alpha ≤0.050 were considered statistically significant. Data were analysed using IBM SPSS Statistics Version 27.

Results

Referrals and study population

Between June 2019 and December 2020, 220 patients with a primary care diagnosis of NAFLD were referred to the TCM-NAFLD pathway. Nineteen different PCPs within the two primary care practices referred patients to the study. Sixty of 220 (27.3%) referred patients were excluded as they were unable to be contacted (n=22), declined to participate (n=18), failed to attend initial assessment (n=6), or ineligible for other reasons (n=14; including interpreter unavailability, current alcohol excess, drug-induced liver injury, absence of steatosis on imaging, underage, or moved away from the health district). Two patients were reviewed twice following re-referral with new risk factors. A total of 162 patient assessments are included. One hundred and forty-three of these patients (88.3%) were referred with an ultrasound finding of steatosis, and 43 (26.5%) with abnormal liver enzymes.

Overall, the mean age of subjects upon entry to the TCM-NAFLD pathway was 58.7±11.7 years and 30.9% were male. The majority (72.8%) were Caucasian, with a mean body mass index (BMI) of 34.2±6.9 kg/m^2 and mean girth of 110.3±14.5 cm. The prevalence of type 2 diabetes mellitus (T2DM)/impaired fasting glucose (IFG) was 54.3%, and 17.3% of the cohort had class 3 obesity (BMI ≥40 kg/m^2).

Fibrosis risk assessment: step 1

"Low" NFS and FIB-4 scores were present in 56 (34.6%) and 131 (80.9%) of the cohort respectively. In 55 patients (34.0%), NFS and FIB-4 scores were concordant for "low risk" NAFLD. However, two of these patients were referred to HMC for clinical concerns (n=1 splenomegaly on imaging and n=1 on methotrexate therapy) and an additional eight patients were ≤35 years of age and advised to undergo second-line fibrosis assessment in primary care. "High" NFS or FIB-4 scores were present in 17 patients (10.5%) and these people were classified as having "high risk" NAFLD. Ninety patients (55.5%) had "indeterminate risk" NAFLD and required a second step to assess severity of fibrosis (Figure 2).

Selected demographic and clinical data according to "low", "indeterminate" or "high" risk stratification using individual and composite scores are summarised in Table 1. The data illustrate the impact of key variables within each algorithm.

Fibrosis risk assessment: step 2

Transient elastography was performed in 88 of 90 "indeterminate risk" patients (n=1 declined FibroScan® and n=1 awaiting FibroScan® assessment). LSM met quality criteria in 83 (94.3%) patients. Median LSM was 5.6 kPa (IQR 4.5-6.7 kPa) and required use of the XL probe in 77.1%. LSM <8.0 kPa, consistent with the absence of clinically significant fibrosis, was present in 73 (87.9%) patients. Most of these (n=69; 94.5%) remained in primary care and the remaining four were referred to HMC for other clinical concerns (n=2 on methotrexate therapy, n=1 with splenomegaly, and n=1 with 'free fluid' described on abdominal imaging). Compared to patients without clinically significant fibrosis, those with LSM ≥8.0 kPa had greater girth and higher serum ALT and AST (Table 2).

Hepatology management clinic assessment

A total of 38 patients (23.5%) were referred for HMC assessment (n=17 "high" NFS or FIB-4 score, n=10 LSM ≥8.0 kPa, n=5 unsuccessful or uninterpretable LSM, and n=6 with other clinical concerns). Six assessments had not been completed at the time of study closure and one patient who repeatedly failed to attend HMC assessment was discharged to primary care.

Transient elastography was performed in 16 patients with "high risk" simple scores. An elevated LSM (≥8.0 kPa) was present in five (31.3%). Liver biopsy was performed in one patient (Brunt fibrosis stage F3) which corresponded with their elevated LSM.

Among the 19 "indeterminate risk" patients referred for hepatology assessment, eight had a repeat FibroScan® in HMC (n=2 LSM <8.0kPa and n=6 LSM ≥8.0 kPa), seven were offered a liver biopsy (n=2 <F3 fibrosis, n=3 ≥F3 fibrosis, and n=2 refused) and six received a clinical decision based on their FibroScan® in primary care (n=2 LSM >20 kPa and n=4 LSM <8.0 kPa but referred for clinical concerns). Of 13 completed assessments, the majority (nine patients) were considered to have clinically significant fibrosis.

There were no significant differences between the five "high risk" and nine "indeterminate risk" patients who were diagnosed with clinically significant fibrosis, except for platelet count (194 ± 33 (10^9/L) vs 264 ± 35 (10^9/L) respectively, p=0.003) (Supplementary Table 1).

Overall TCM-NAFLD pathway

Overall, 153 of 162 patient assessments were completed. Fourteen patients (representing 9.2% of assessments from a 'routine' primary care population and 45.2% of completed HMC assessments) were considered to have clinically significant fibrosis (n=4; LSM ≥8.0-9.4 kPa), advanced fibrosis (n=4; LSM 9.5-12.9 kPa), or cirrhosis (n=6; LSM ≥13 kPa). All 14 patients were identified by an "indeterminate" or "high" NFS score. However, five patients (35.7%) scored "low" on the FIB-4 and may not have received further evaluation if composite scoring had not been used in step-1 of the TCM-NAFLD pathway. Four of 14 (28.6%) patients with clinically significant fibrosis (≥F2) had ALT and AST <40 IU/L at the time of fibrosis

assessment. The prevalence of clinically significant fibrosis was higher in people with T2DM/IFG than those without (15.9% vs. 1.4%; p=0.002).

Selected demographic and clinical data for all patients who received a FibroScan® (n=111) during the course of the study are summarised in Supplementary Table 2.

Discussion

Many PCPs do not routinely undertake an assessment of liver disease severity in their patients with NAFLD[9,18] and at present, there is limited data regarding how best to support fibrosis assessment in primary care. We examined the feasibility of using a 2-step fibrosis risk assessment pathway which combined simple scores with community-based transient elastography. In our unselected primary care cohort of patients with NAFLD, we found fibrosis assessment was attainable and streamlined referrals to local hepatology clinics.

Using our 2-step TCM-NAFLD pathway, we found that 139 of 153 (90.8%) completed patient assessments in a 'routine' primary care population were not considered to have clinically significant fibrosis. Most patients without clinically significant fibrosis (n=122; 87.8%) avoided referral to secondary care, and almost half of patients evaluated in HMC (45.2%) had at least clinically significant fibrosis (≥F2). Our findings support the results of a larger UK study (n=3,012) in which a primary care triage pathway (FIB-4 followed by the serum ELF™ test) reduced unnecessary NAFLD referrals by 81% and improved the detection of patients with advanced fibrosis 5-fold.[8] Although it's not yet known whether community-based NAFLD fibrosis assessment pathways reduce future adverse liver outcomes, modelling in the UK suggests the approach is cost efficient and improves resource utilisation.[8] Decreasing unnecessary referrals and investigations is also likely to have a favourable impact on the demand for secondary care hepatology services and healthcare costs.

Unlike the UK pathway, we used transient elastography as the second step in the TCM-NAFLD pathway to rule out advanced fibrosis when patients had an "indeterminate" NFS or FIB-4 score. The choice of test was determined by local availability and prior experience with outreach community FibroScan® programs for viral hepatitis.[19,20] Screening with transient elastography to detect significant fibrosis in the

general population and those with risk factors for liver disease has been shown to be cost-effective.[21] Several groups have now evaluated an integrated referral and management plan for liver disease,[22-25] although all but one of these pathways[24] required the patient to attend secondary care for assessment. In our study, access to community-based FibroScan® assessment allowed patients to be assessed in a timely manner, in a familiar, convenient environment, outside of the more costly and resource intensive hospital clinic. Further work is required to determine how a hepatology outreach service would translate "in the real world", outside of a research study. Future studies need to evaluate the scalability and cost-effectiveness of this approach in comparison to the use of serum fibrosis biomarkers, particularly in regional areas where access to ultrasound elastography may be impacted by geographic distance.

In our unselected primary care population, the overall prevalence of clinically significant fibrosis (≥F2) was 9.2% (F3/4 prevalence was 6.5%), consistent with previous population/community studies.[26-28] This is in contrast to our earlier study in diabetes clinics and at-risk populations in primary care,[17] in which the prevalence of clinically significant NAFLD fibrosis was 27.8%, reflecting the high prevalence of metabolic risk factors in patients with more advanced liver disease. In a large retrospective cohort study of patients with NAFLD (n>270,000) followed for 9 years, each additional metabolic trait increased the risk of cirrhosis and HCC.[29] Patients with coexisting diabetes, obesity, dyslipidaemia, and hypertension had a 2.6-fold higher risk of progression to cirrhosis and HCC (hazard ratio=2.6, 95% CI=2.3-2.9) compared to people with no metabolic traits.[29] Although the numbers in our current study are much smaller, there was a greater prevalence of clinically significant fibrosis in patients with T2DM/IFG compared to those without. Future studies should examine whether selecting patients with a higher burden of metabolic traits may allow a more targeted pragmatic approach to screening for NAFLD and advanced fibrosis, particularly in resource-constrained regions.

Despite local guidance on inclusion and exclusion criteria for the diagnosis of NAFLD, a small number of patients were referred for fibrosis assessment with current alcohol excess or drug-induced liver injury, or with clinical concerns that were outside the scope of the TCM-NAFLD pathway. In addition, people with "low risk" NAFLD were managed in primary care and we did not systematically evaluate whether other

liver diseases had been excluded. Although it is possible that some people with another liver disease or true advanced fibrosis may have been missed due to the lack of formal hepatology assessment, ongoing monitoring in primary care was advised to identify disease progression or false-negative fibrosis tests. Education and guidance to improve PCP awareness and familiarity with the diagnosis and management of liver disease will be essential in future strategies to implement community fibrosis assessment.[30]

A key strength of this study was its pragmatic 'real-world' design, which supports the applicability of findings to clinical practice and will facilitate translation of the pathway into 'routine' care. The TCM-NAFLD model fostered strong collaborative working relationships with PCPs within the local practice environment, which enabled communication regarding referrals, patient follow-up, collection of study data, and opportunities for targeted education and upskilling of PCPs. Nonetheless, this was a feasibility study without a 'usual care' comparator group. We were therefore unable to quantify the reduction in unnecessary referrals or the increase in appropriate referrals of patients with clinically significant fibrosis compared to standard of care. It is also unclear how many of the study patients would have been referred to HMC if the community fibrosis assessment pathway was not available.

Conclusion

The prevalence of clinically significant fibrosis in our 'routine' primary care cohort was low. Implementation of the 2-step TCM-NAFLD fibrosis risk assessment pathway streamlined hepatology referrals for NAFLD and may facilitate a more cost-effective and targeted use of specialist hepatology resources.

References

1. Armstrong MJ, Houlihan DD, Bentham L, Shaw JC, Cramb R, Olliff SL, et al. Presence and severity of non-alcoholic fatty liver disease in a large prospective primary care cohort. *J Hepatol* 2012; **56**: 234-40.

2. Adams LA, Roberts SK, Strasser SI, Mahady SE, Powell E, Estes C, et al. Nonalcoholic fatty liver disease burden: Australia, 2019-2030. J Gastroenterol Hepatol. 2020 Sep;35(9):1628-1635

3. 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**: 73-84.

4. Angulo P, Kleiner DE, Dam-Larsen S, Adams LA, Bjornsson ES, Charatcharoenwitthaya, P, et al. Liver fibrosis, but no other histologic features, is associated with long-term outcomes of patients with nonalcoholic fatty liver disease. *Gastroenterology* 2015; **149**: 389-97 e10.

5. Ekstedt M, Hagstrom H, Nasr P, Fredrikson M, Stal P, Kechagias S, Hultcrantz R. Fibrosis stage is the strongest predictor for disease-specific mortality in NAFLD after up to 33 years of follow-up. *Hepatology* 2015; **61**: 1547-54.

6. Taylor RS, Taylor RJ, Bayliss S, Hagstrom H, Nasr P, Schattenberg JM, et al. Association between fibrosis stage and outcomes of patients with nonalcoholic fatty liver disease: a systematic review and meta-analysis. *Gastroenterology* 2020; **158**: 1611-25 e12.

7. Newsome PN, Cramb R, Davison SM, Dillon JF, Foulerton M, Godfrey EM, et al. Guidelines on the management of abnormal liver blood tests. *Gut* 2018; **67**: 6-19.

8. Srivastava A, Gailer R, Tanwar S, Trembling P, Parkes J, Rodger A, et al. Prospective evaluation of a primary care referral pathway for patients with non-alcoholic fatty liver disease. *J Hepatol* 2019; **71**: 371-8.

9. Elangovan H, Rajagopaul S, Williams SM, Mckillen B, Britton L, McPhail S, et al. Nonalcoholic fatty liver disease: interface between primary care and hepatology clinics. *Hepatol Commun* 2020; **4**: 518-26.

10. Gawrieh S, Wilson LA, Cummings OW, Clark JM, Loomba R, Hameed B, et al. Histologic findings of advanced fibrosis and cirrhosis in patients with nonalcoholic fatty liver disease who have normal aminotransferase levels. *Am J Gastroenterol* 2019; **114**: 1626-35.

11. Arab JP, Dirchwolf M, Alvares-da-Silva MR, Barrera F, Benitez C, Castellanos-Fernandez M, et al. Latin American Association for the study of the liver (ALEH) practice guidance for the diagnosis and treatment of non-alcoholic fatty liver disease. *Ann Hepatol* 2020; **19**: 674-90.

12. Eslam M, Sarin SK, Wong VW, Fan JH, Kawaguchi T, Ahn SH, et al. The Asian Pacific Association for the Study of the Liver clinical practice guidelines for the diagnosis and management of metabolic associated fatty liver disease. *Hepatol Int* 2020; **14**: 889-919.

13. European Association for the Study of the Liver, European Association for the Study of Diabetes, European Association for the Study of Obesity. EASL-EASD-EASO clinical practice guidelines for the management of non-alcoholic fatty liver disease. *J Hepatol* 2016; **64**: 1388-402.

14. McPherson S, Stewart SF, Henderson E, Burt AD, Day CP. Simple non-invasive fibrosis scoring systems can reliably exclude advanced fibrosis in patients with non-alcoholic fatty liver disease. *Gut* 2010; **59**: 1265-9.

15. McPherson S, Hardy T, Dufour JF, Petta S, Romero-Gomez M, Allison M, et al. Age as a confounding factor for the accurate non-invasive diagnosis of advanced NAFLD fibrosis. *Am J Gastroenterol* 2017; **112**: 740-51.

16. Wong VW, Irles M, Wong GL, Shili S, Chan AW, Merrouche W, et al. Unified interpretation of liver stiffness measurement by M and XL probes in non-alcoholic fatty liver disease. *Gut* 2019; **68**: 2057-64.

17. Patel P, Hossain F, Horsfall LU, Banh X, Hayward KL, Williams S, et al. A pragmatic approach identifies a high rate of nonalcoholic fatty liver disease with advanced fibrosis in diabetes clinics and at-risk populations in primary care. *Hepatol Commun* 2018; **2**: 893-905.

18. Patel PJ, Banh X, Horsfall LU, Hayward KL, Hossain F, Johnson T, et al. Underappreciation of non-alcoholic fatty liver disease by primary care clinicians: limited awareness of surrogate markers of fibrosis. *Intern Med J* 2018; **48**: 144-51.

19. Brain D, Mitchell J, O'Beirne J. Cost-effectiveness analysis of an outreach model of hepatitis C virus (HCV) assessment to facilitate HCV treatment in primary care. *PLoS One* 2020; **15**: e0234577.

20. White L, Azzam A, Burrage L, Orme C, Kay B, Higgins S, et al. Facilitating treatment of HCV in primary care in regional Australia: closing the access gap. *Frontline Gastroenterol* 2019; **10**: 210-6.

21. Serra-Burriel M, Graupera I, Toran P, Thiele M, Roulot D, Wong VW, et al. Transient elastography for screening of liver fibrosis: cost-effectiveness analysis from six prospective cohorts in Europe and Asia. *J Hepatol* 2019; **71**: 1141-51.

22. Chalmers J, Wilkes E, Harris R, Kent L, Kinra S, Aithal GP, et al. The development and implementation of a commissioned pathway for the identification and stratification of liver disease in the community. *Frontline Gastroenterol* 2020; **11**: 86-92.

23. Davyduke T, Tandon P, Al-Karaghouli M, Abraldes JG, Ma MM. Impact of implementing a "FIB-4 First" strategy on a pathway for patients with NAFLD referred from primary care. *Hepatol Commun* 2019; **3**: 1322-33.

24. El-Gohary M, Moore M, Roderick P, Watkins E, Dash J, Reinson T, et al. Local care and treatment of liver disease (LOCATE) - a cluster-randomized feasibility study to discover, assess and manage early liver disease in primary care. *PLoS One* 2018; **13**: e0208798.

25. Moolla A, Motohashi K, Marjot T, Shard A, Ainsworth M, Gray A, et al. A multidisciplinary approach to the management of NAFLD is associated with improvement in markers of liver and cardio-metabolic health. *Frontline Gastroenterol* 2019; **10**: 337-46.

26. Koehler EM, Plompen EP, Schouten JN, Hansen BE, Darwish Murad S, Taimr P, et al. Presence of diabetes mellitus and steatosis is associated with liver stiffness in a general population: The Rotterdam study. *Hepatology* 2016; **63**: 138-47.

27. Roulot D, Costes JL, Buyck JF, Warzocha U, Gambier N, Czernichow S, et al. Transient elastography as a screening tool for liver fibrosis and cirrhosis in a community-based population aged over 45 years. *Gut* 2011; **60**: 977-84.

28. Wong VW, Chu WC, Wong GL, Chan RS, Chim AM, Ong A, et al. Prevalence of non-alcoholic fatty liver disease and advanced fibrosis in Hong Kong Chinese: a population study using proton-magnetic resonance spectroscopy and transient elastography. *Gut* 2012; **61**: 409-15.

29. Kanwal F, Kramer JR, Li L, Dai J, Natarajan Y, Yu X, et al. Effect of metabolic traits on the risk of cirrhosis and hepatocellular cancer in nonalcoholic fatty liver disease. *Hepatology* 2020; **71**: 808-19.

30. Bernardes CM, Ratnasekera IU, Kwon JH, Somasundaram S, Mitchell G, Shahid S, et al. Contemporary educational interventions for general practitioners (GPs) in primary care settings in Australia: a systematic literature review. *Front Public Health* 2019; **7**: 176.

Figure Legends

Figure 1. The TCM-NAFLD fibrosis risk assessment pathway.

† Age-adjusted FIB-4 lower cutoff (<2.0) was used in people aged ≥65 years and all patients ≤35 years were recommended to undergo alternative fibrosis assessment.

Abbreviations: FIB-4, Fibrois-4 Index; HCC, hepatocellular carcinoma; HMC, hepatology management clinic; LSM, liver stiffness measurements; NAFLD, nonalcoholic fatty liver disease; NFS, nonalcoholic fatty liver disease (NAFLD) fibrosis score; PCP, primary care practitioner.

Figure 2. The patient pathway following fibrosis risk assessment. At the time of study closure, one patient had yet to complete fibrosis assessment in primary care, six patients had yet to complete assessment in HMC, and two patients were returned to the care of their PCP (declined/failed to attend assessment).

† Age-adjusted FIB-4 lower cutoff (<2.0) was used in people aged ≥65 years and all patients ≤35 years were recommended to undergo alternative fibrosis assessment.

* Fibrosis assessment not completed.

Abbreviations: A/W, awaiting; D/C, discharged; FIB-4, Fibrosis-4 Index; FTA, failed to attend; HMC, hepatology management clinic; LSM, liver stiffness measurements; NAFLD, nonalcoholic fatty liver disease; NFS, nonalcoholic fatty liver disease (NAFLD) fibrosis score; PCP, primary care practitioner.

Tables

Table 1. Selected demographic and clinical data for the TCM-NAFLD pathway cohort, according to risk stratification using individual and composite NFS and FIB-4 scores

	NFS				FIB-4				Composite Risk			
	Low (n=56)	Ind (n=91)	High (n=15)	*P*	Low (n=131)	Ind (n=28)	High (n=3)	*P*	Low (n=55)	Ind (n=90)	High (n=17)	*P*
Age (years) †	53.5±12.1	60.9±10.5	65.1±10.7	**<0.001**	58.1±12.2	60.6±9.3	70.3±2.1	0.129	53.5±12.2	60.7±10.5	65.7±10.2	**<0.001**
Male ‡	17 (30.4%)	30 (33.0%)	3 (20.0%)	0.670	37 (28.2%)	12 (42.9%)	1 (33.3%)	0.237	16 (29.1%)	31 (34.4%)	3 (17.6%)	0.405
BMI (kg/m2) †	31.3±5.3	35.1±6.9	39.3±8.3	**<0.001**	34.3±6.9	33.9±7.5	31.3±3.4	0.737	31.4±5.4	35.1±6.9	38.3±8.3	**<0.001**
Girth (cm) † ¶	104.4±13.9	112.8±14.3	118.1±10.6	**0.001**	109.9±14.5	112.4±15.2	-	0.743	104.4±13.9	112.8±14.3	118.1±10.6	**0.001**
T2DM/IFG ‡	9 (16.1%)	64 (70.3%)	15 (100%)	**<0.001**	70 (53.4%)	16 (57.1%)	2 (66.7%)	0.933	9 (16.4%)	63 (70.0%)	16 (94.1%)	**<0.001**
Hypertension ‡	27 (48.2%)	62 (68.1%)	12 (80.0%)	**0.021**	81 (61.8%)	17 (60.7%)	3 (100%)	0.556	26 (47.3%)	61 (67.8%)	14 (82.4%)	**0.011**
Dyslipidaemia ‡	36 (64.3%)	64 (70.3%)	12 (80.0%)	0.508	93 (71.0%)	16 (57.1%)	3 (100%)	0.190	36 (65.5%)	62 (68.9%)	14 (82.4%)	0.446
ALT (IU/L) §	40 (29-56)	34 (25-48)	35 (20-47)	0.535	33 (24-47)	49 (36-62)	93 (59-104)	**<0.001**	39 (29-56)	35 (25-48)	35 (22-48)	0.937
AST (IU/L) §	26 (22-34)	27 (21-35)	23 (17-34)	0.124	24 (20-32)	37 (29-46)	62 (53-76)	**0.009**	26 (22-34)	27 (21-35)	23 (20-37)	0.178
Platelets (10^9/L) †	301±60	251±52	204±50	**<0.001**	278±57	204±42	203±43	**<0.001**	303±59	251±52	207±48	**<0.001**
Albumin (g/L) §	42 (40-43)	41 (39-42)	38 (36-40)	**<0.001**	41 (39-43)	41 (38-43)	40 (40-40)	0.377	42 (40-43)	41 (39-42)	38 (36-40)	**<0.001**

Data are presented as †mean±SD and analysed using ANOVA; ‡numerical proportions and analysed using the Fisher-Freeman-Halton Exact test; §median (IQR) and analysed using the Kruskal-Wallis test. ¶Girth data available for n=114 patients (n=42 composite 'low risk", n=58 composite "indeterminate risk", n=14 composite "high risk").

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; FIB-4, Fibrosis-4 Index; IFG, impaired fasting glucose; Ind, indeterminate; IQR, interquartile range; NFS, Nonalcoholic fatty liver disease (NAFLD) Fibrosis Score; SD, standard deviation; T2DM, type 2 diabetes mellitus.

Table 2. Selected demographic and clinical data for "indeterminate risk" patients according to step-2 risk stratification

	LSM <8.0 kPa (n=73)	LSM ≥8.0 kPa (n=10)	*P*
Age (years) †	61.6±10.2	57.5±10.5	0.239
Male ‡	26 (35.6%)	3 (30.0%)	1.000
BMI (kg/m2) †	34.5±6.7	37.3±6.7	0.219
Girth (cm) † ¶	111.0±13.1	122.1±15.2	**0.045**
T2DM/IFG ‡	48 (65.8%)	9 (90.0%)	0.160
Hypertension ‡	47 (64.4%)	8 (80.0%)	0.483
Dyslipidaemia ‡	50 (68.5%)	8 (80.0%)	0.716
ALT (IU/L) §	34 (23-47)	59 (36-79)	**0.002**
AST (IU/L) §	26 (21-34)	42 (28-70)	**0.009**
Platelets (10^9/L) †	247±52	268±36	0.228
Albumin (g/L) §	42 (39-42)	40 (39-42)	0.226

LSM not available for 7 "indeterminate risk" patients (n=5 LSM did not meet quality criteria, n=1 declined FibroScan®, and n=1 awaiting FibroScan® assessment in primary care). Data are presented as †mean±SD and analysed using ANOVA; ‡numerical proportions and analysed using the Fisher's Exact test; §median (IQR) and analysed using the Mann-Whitney U test. ¶Girth data available for 53 patients (n=46 LSM <8.0 kPa and n=7 LSM ≥8.0 kPa).

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; IFG, impaired fasting glucose; IQR, interquartile range; LSM, liver stiffness measurements; SD, standard deviation; T2DM, type 2 diabetes mellitus.