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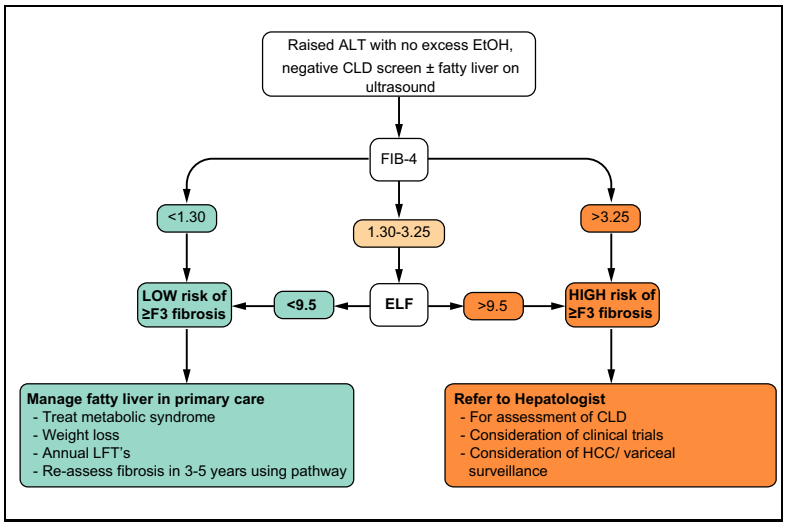
Prospective evaluation of a primary care referral pathway for patients with non-alcoholic fatty liver disease

Graphical abstract



Highlights

- Established blood tests can be used in primary care to stratify patients with fatty liver disease.
- A 2-step pathway (FIB-4 followed by ELF™ if required) reduced unnecessary referrals by 80%.
- This pathway also improved the detection of cases of advanced fibrosis 5-fold and cirrhosis 3-fold.
- This pathway can be used in primary care to identify patients who might benefit from referral to liver specialists.
- This should reduce unnecessary referrals while at the same time improving the detection of cirrhosis.

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Lay summary

Non-alcoholic fatty liver disease effects up to 30% of the population but only a minority of cases develop liver disease. Our study has shown that established blood tests can be used in primary care to stratify patients with fatty liver disease, leading to a reduction in unnecessary referrals by 80% and greatly improving the detection of cases of advanced fibrosis and cirrhosis.

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Prospective evaluation of a primary care referral pathway for patients with non-alcoholic fatty liver disease

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Background & Aims: The development of non-invasive liver fibrosis tests may enable earlier identification of patients with non-alcoholic fatty liver disease (NAFLD) requiring referral to secondary care. We developed and evaluated a pathway for the management of patients with NAFLD, aimed at improving the detection of cases of advanced fibrosis and cirrhosis, and avoiding unnecessary referrals.

Methods: This was a prospective longitudinal cohort study, with analyses performed before and after introduction of the pathway, and comparisons made to unexposed controls. We used a 2-step algorithm combining the use of Fibrosis-4 score followed by the ELF™ test if required.

Results: In total, 3,012 patients were analysed. Use of the pathway detected 5 times more cases of advanced fibrosis (Kleiner F3) and cirrhosis (odds ratio [OR] 5.18; 95% CI 2.97–9.04; p <0.0001), while reducing unnecessary referrals from primary care to secondary care by 81% (OR 0.193; 95% CI 0.111–0.337; p <0.0001). Although it was used for only 48% of referrals, significant benefits were observed in practices exposed to the pathway compared to those which were not, with unnecessary referrals falling by 77% (OR 0.23; 95% CI 0.658–0.082; p = 0.006) and a 4-fold improvement in detection of cases of advanced fibrosis and cirrhosis (OR 4.32; 95% CI 1.52–12.25; p = 0.006). Compared to referrals made before the introduction of the pathway, unnecessary referrals fell from 79/83 referrals (95.2%) to 107/152 (70.4%), representing an 88% reduction in unnecessary referrals when the pathway was followed (OR 0.12; 95% CI 0.042–0.349; p <0.0001).

Conclusions: The use of non-invasive blood tests for liver fibrosis improves the detection of advanced fibrosis and cirrhosis, while reducing unnecessary referrals in patients with NAFLD. This strategy improves resource use and benefits patients.

Lay summary: Non-alcoholic fatty liver disease effects up to 30% of the population but only a minority of cases develop liver disease. Our study has shown that established blood tests can be used in primary care to stratify patients with fatty liver disease, leading to a reduction in unnecessary referrals by 80% and greatly improving the detection of cases of advanced fibrosis and cirrhosis.

Introduction

Non-alcoholic fatty liver disease (NAFLD) is the commonest cause of deranged liver blood tests (LFTs) in primary care in Europe and North America,[1] with an estimated prevalence of 25–30% in the adult population.[2] Only a minority of people with NAFLD (5%) develop clinically significant liver disease,[2] but the burden is such that NAFLD is predicted to be the leading indication for liver transplantation within a decade.[3]

The majority of patients with NAFLD are followed up in the community by general practitioners (GPs). Liver fibrosis severity is the key determinant of liver-related outcomes in NAFLD.[4–6] However, identifying patients with significant fibrosis who might benefit from early specialist intervention is challenging. As clinical assessment is a poor discriminator of fibrosis, such patients progress silently until cirrhosis leads to complications. Accurate fibrosis assessment in primary care is limited by a reliance on LFTs, which correlate poorly with fibrosis[7,8] and limited access to discriminatory fibrosis tests. Thus, current management strategies are inefficient in identifying patients for specialist referral. Patients with mild disease are often referred for specialist review when the appropriate preventative interventions of lifestyle changes can be delivered effectively in primary

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care.[9,10] Conversely, patients with advanced fibrosis or cirrhosis who will benefit from specialist interventions including clinical trials and cirrhosis surveillance often remain undetected until they present with complications of cirrhosis, including hepatocellular carcinoma. This ineffective management contributes to the poor outcomes associated with liver disease and the increasing trends in NAFLD-related morbidity and mortality.

The evolution of non-invasive liver fibrosis tests has created the opportunity for GPs to use these tests in innovative pathways that permit earlier identification of patients with chronic liver disease and subsequent access to specialist care.[11] An example of this approach is outlined in the recent British Society for Gastroenterology guidance on the management of abnormal LFTs that recommends the use of non-invasive tests to stratify patients at risk of chronic liver disease.[12]

Whilst there is little evidence supporting the application of non-invasive tests in community settings, with only 1 study focusing on patients with NAFLD,[13] guidelines recommend a 2-tier approach to detect the presence of advanced fibrosis in NAFLD using either Fibrosis-4 (FIB-4) or NAFLD Fibrosis score, as an inexpensive first screen, in a combined cut-off approach with indeterminate scores retested using more sensitive and specific tests, enhanced liver fibrosis (ELF™) or FibroScan®, that are more costly.[14]

Through broad consultation, a care pathway for patients identified with NAFLD in primary care was developed using non-invasive fibrosis assessment (FIB-4 followed by ELF) to stratify patients to either remain in primary care or to be referred to secondary care. We present a prospective evaluation of the performance of the pathway 2 years after its introduction.

Materials and methods

Study setting and design

The Camden and Islington NAFLD Pathway (hereafter the "NAFLD pathway") was developed as a service innovation in conjunction with the primary care clinical commissioning groups (CCGs) of the London boroughs of Camden and Islington (C&I), between April 2013 and March 2014, before being introduced into practice. The NAFLD pathway working group met regularly to develop a pathway for the management of patients with NAFLD aiming to identify patients with advanced liver fibrosis (≥Kleiner F3), who might benefit from referral to secondary care for specialist hepatology review while identifying and managing patients with lesser degrees of fibrosis in primary care. The composition and aims of the working group including patient and public involvement are described in the supplementary information. The pathway evaluation was conducted between March 2014 and May 2016 with the aim of determining the impact of the pathway in reducing unnecessary referrals and increasing the detection and referral of patients with advanced fibrosis. The pathway was introduced into C&I CCGs representing 2 of the 25 CCGs making referrals to the liver specialist services at The Royal Free London NHS Foundation Trust, The Whittington Hospital NHS Trust and University College London Hospitals NHS Foundation Trust, accounting for 43% of the referrals in 2012–13. All practices within the 2 CCGs adopted the pathway, but individual GPs within C&I were at liberty to follow it or to use standard care for each referral. The evaluation was conducted as a longitudinal study in which C&I represented the CCGs exposed to the pathway and the remaining 23 CCGs represented the control CCGs.

The Camden and Islington NAFLD pathway

All individuals aged 18 and over attending their GP with a new or established diagnosis of NAFLD were eligible for entry. For purposes of the pathway, NAFLD was diagnosed in patients with steatosis on ultrasound, negative screens for other causes of liver disease and no alcohol excess (defined as >21 units of alcohol/week in males, >14 units/week in females).

The pathway consisted of a 2-step non-invasive test assessment, starting with the calculation of the FIB-4 score (Fig. 1). Patients with FIB-4 <1.30 were deemed to be at low risk of advanced fibrosis (<F3) and remained in primary care.[15] Primary care management consisted of treatment of cardiovascular risks and diabetes, annual LFTs, and re-assessment of the risk of advanced fibrosis after 3–5 years. Patients with FIB-4 >3.25 were deemed to be at high risk of advanced fibrosis and were recommended for referral to secondary care for specialist assessment. Patients with indeterminate FIB-4 values (≥1.30 and <3.25) had second tier testing with an ELF test. Patients with ELF scores <9.5 were recommended to remain in primary care while those with an ELF score ≥9.5 were recommended for referral to secondary care.[16,17]

Evaluation of standard care 2012–2013 prior to pathway introduction

A retrospective audit of referrals to secondary care by GPs was undertaken between 01/03/2012 and 28/02/2013 to determine the referrers' ability to identify patients with advanced fibrosis using standard care. The case records of all patients assigned a Read code and referred with a diagnosis of NAFLD were reviewed by hepatologists in the receiving hospital and evaluated for evidence of advanced fibrosis/cirrhosis (≥F3) based on a composite of history, physical examination, blood tests, imaging, FibroScan, and liver histology when available. FIB-4 scores were calculated and patients with FIB-4 <1.30 were deemed to have no evidence of liver fibrosis and thus referred inappropriately. Referrals originating from primary care practices within the C&I CCGs were analysed separately from those referred from other CCGs.

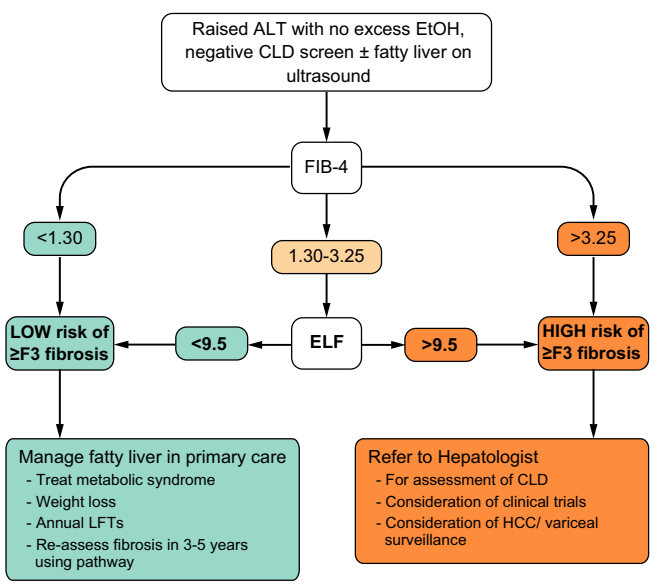

Fig. 1. The Camden and Islington NAFLD pathway. CLD, chronic liver disease; ELF, enhanced liver fibrosis; EtOH, ethanol; FIB-4, Fibrosis-4; HCC, hepatocellular carcinoma; LFTs, liver function tests; NAFLD, non-alcoholic fatty liver disease.

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Pathway evaluation

Following introduction of the NAFLD pathway, data were collected on the outcomes of NAFLD referrals for patients seen at the secondary care sites. The CCG of the referral origin and use of the NAFLD pathway or standard care were recorded. The primary care electronic patient record systems (EMISWeb, Egton Medical Information Systems) were interrogated centrally to obtain data on NAFLD diagnosis and use of the pathway to stratify patients for referral using Read codes in primary care. Secondary care electronic medical records were interrogated to extract data related to patient demographics, secondary care management, fibrosis staging and clinical events.

The diagnostic performance of the NAFLD pathway in detecting cases of advanced fibrosis was assessed against a reference standard composite clinical evaluation performed by expert hepatologists blinded to the use of the NAFLD pathway, as described above. All decisions were reviewed by the study team (AS and WMR) and any differences of opinion between the experts and the study team (<10% of cases) were resolved through discussion.

Secondary care evaluation of the patients consisted of more analyses and in most cases a FibroScan, performed independently of the use of the pathway. A subset of 35/152 patients, referred from C&I and deemed to have advanced fibrosis, underwent liver biopsy following clinical assessment. Biopsies were staged for fibrosis by a single histopathologist who was blinded to use of the pathway (Table S1).

The distribution of FIB-4 scores in patients assessed by C&I GPs before and after introduction of the pathway was compared to look for evidence of bias in patient selection.

Outcomes

The primary outcome was the reduction in the proportion of patients with NAFLD referred to secondary care who did not have evidence of advanced fibrosis based on clinical evaluation and were thus deemed to have been referred unnecessarily.

Secondary outcomes included:

- The number of cases and proportion of those referred who were deemed to have advanced fibrosis or cirrhosis after assessment by a liver specialist (true positive rate).
- Proportion of patients diagnosed with NAFLD avoiding referral after primary care stratification.
- Number of patients coded for NAFLD by GP before and after introduction of the pathway.

Sensitivity analyses were conducted to determine the impact of using age-specific cut-offs for FIB-4 to triage patients.[18] The impact of using alternative ELF cut-offs for detection of advanced fibrosis was investigated including the manufacturer's recommendation (ELF = 9.8) and the threshold recommended in recent NICE guidance on NAFLD (ELF = 10.51).[19]

In order to determine the effectiveness of the pathway compared to standard care, the outcomes of patients referred using the NAFLD pathway were compared to those of patients referred from C&I prior to introduction of the pathway; and to those of patients referred using standard care from C&I and from other CCGs during the evaluation period following introduction of the pathway.

In order to determine the effectiveness of the introduction of the pathway to all general practices across the 2 CCGs of C&I, outcomes for all patients referred from C&I, irrespective of the use of the NAFLD pathway, were compared to those of patients referred from all other CCGs where the pathway was not introduced during the evaluation period.

Statistical analyses

Statistical analyses were performed using SPSS (version 22, SPSS Inc., Chicago, IL, USA). The odds ratios (ORs) for differences in outcomes for patients managed in accordance with the pathway and those managed using standard care were calculated, along with 95% CIs and chi-square tests for statistical significance using Medcalc statistical software (MedCalc Software 2018).

Ethical approval

The Royal Free London NHS Foundation Trust Research and Development Department judged this study to be an evaluation of a service improvement innovation. Therefore, this study was registered for audit (EDGE ID:122031) but not subject to review by an independent ethics committee, and individual patient consent was not sought. All activities were performed in accordance with the guidelines of the Helsinki Declaration.

Results

Participants

Between 01/03/2014 and 31/05/2016 in C&I CCGs, 3,012 patients were coded as having NAFLD, with an equal distribution in the numbers entered into the NAFLD pathway and standard care (Table 1). Seventy-two per cent of eligible practices (52/72) used the NAFLD pathway to stratify a proportion of their patients. Patients entered into the NAFLD pathway were older (54.4 years *vs.* 51.5, p <0.001), had a higher prevalence of treated type 2 diabetes (27.6% *vs.* 21.0%, p <0.001) and hypertension (41.7% *vs.* 33.0%, p <0.001), and less dyslipidaemia (13.5% *vs.* 14.6%, p <0.001) than patients managed by standard care. There were no significant differences in Q-Risk2 score, glycated haemoglobin, aminotransferases, platelet counts or high-density lipoprotein. The distribution of calculated FIB-4 scores in 695 cases for which the data were available was identical between the patients managed using the NAFLD pathway and those managed using standard care <1.30: 513/695 (73.8%); 1.30–3.25: 162/695 (23.3%); >3.25: 20/695 (2.9%).

Stratification of patients with NAFLD in primary care using the NAFLD pathway

Between 2012–13 and 2014–16 the number of patients assigned Read codes in the electronic patient records per annum by GPs in C&I increased from 601/year to 1,506/year, representing a 2.5-fold increase. The number of cases of NAFLD referred from C&I GPs nearly doubled from 83 in 2012–13 to 329 in 2014–16 (164.5/year). However, considering the increased coding, the proportion of NAFLD coded patients referred to secondary care from all C&I GPs fell from 13.8% (83/601) to 10.9% (165/1,506).

Comparison of the distribution of FIB-4 scores of patients referred for NAFLD by C&I GPs before and after the introduction of the NAFLD pathway revealed no evidence of bias in patient selection (Table S2).

Over 2 years, 1,452 patients were risk-stratified for the presence of advanced fibrosis using FIB-4 (Fig. 2). FIB-4 score <1.30 was calculated in 1,022 patients (71.3%), whilst 43 patients (3.0%) had FIB-4 >3.25. The remaining 387 patients had an indeterminate FIB-4 score (1.30–3.25) and proceeded to an ELF test. Of these, 155 (40.0%) had ELF <9.5, and 232 (60.0%) had ELF >9.5.

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Table 1. Patient demographics.

	Standard care	Pathway patients	*p* value	Camden and Islington pathway split by FIB-4			
				FIB-4 <1.30	FIB-4 1.30–3.25	FIB-4 >3.25	*p* value (<1.30 vs. >1.30)
	n = 1,560	n = 1,452		1,022 (71.3%)	387 (25.7%)	43 (3.0%)	
FIB-4 range	–	0.20–15.61		0.20–1.29	1.30–3.24	3.30–15.6	–
Age, years	51.5 ± 14.1	54.4 ± 13.7	<0.001	50.5 ± 12.8	63.4 ± 11.2	64.2 ± 11.9	<0.001
Male, n(%)	570 (50.5%)	788 (54.3%)	n.s.	560 (54.7%)	204 (71.1%)	24 (55.8%)	n.s.
BMI (kg/m^2) mean ± SD (n)	30.5 ± 7.1 (1,082)	30.4 ± 5.9 (1,238)	n.s.	30.4 ± 5.6	30.7 ± 6.3	27.3 ± 5.7	n.s.
T2DM, n(%)	237/1,126 (21.0%)	344/1245 (27.63)	<0.001	190/846 (22.5%)	141/364 (38.7%)	13/35 (37.1%)	<0.001
HbA1c, mmol/mol (mean ± SD)	4,212.8 (585)	42.5 ± 13.35 (1,059)	n.s.	42.3 ± 13.6 (769)	43.4 ± 13.4 (267)	41.4 ± 15.2 (23)	n.s.
Hypertension, n(%)	371/ 1,124 (33.0%)	521/1,248 (41.7%)	<0.001	266/ 849 (31.3%)	234/364 (64.2%)	21/35 (60.0%)	<0.001
Hyperlipidaemia, n(%)	95/650 (14.6%)	168/1,248 (13.5%)	<0.001	96/ 849 (11.3%)	64/364 (7.5%)	8/35 (22.8%)	<0.001
Total cholesterol, mmol/L (mean ± SD)	4.9 ± 1.1 (602)	4.8 ± 1.1 (1,084)	0.03	4.8 ± 1.1 (792)	4.6 ± 1.2 (267)	4.8 ± 1.1 (25)	0.02
HDL, mmol/L (mean ± SD)	1.3 ± 0.4 (602)	1.3 ± 0.4 (1,084)	n.s.	1.3 ± 0.4 (792)	1.4 ± 0.4 (267)	1.3 ± 0.4 (25)	0.006
IHD, n (%)	49/1,127 (3.9%)	84/1,248 (6.7%)	<0.001	30/849 (3.5%)	48/364 (5.6%)	6/35 (17.1%)	n.s.
Q-risk,% (n)	12.1 ± 10.7 (501)	13.6 ± 11.3 (900)	n.s.	11.9 ± 10.7 (670)	18.6 ± 12.1 (211)	16.1 ± 9.9 (19)	<0.001
ALT, IU/L (mean ± SD)	43.0 ± 36.5 (1,096)	45.1 ± 36.5 (1,254)	n.s.	45.3 ± 29.5	42.8 ± 27.4	59.5 ± 39.2	n.s.
AST, IU/L (mean ± SD)	33.7 ± 22.1 (704)	33.7 ± 22.6 (1,206)	n.s.	29.4 ± 17.3	37.8 ± 23.9	70.2 ± 52.1	<0.001
Bilirubin, mmol/L (mean ± SD)	8.9 ± 5.9 (1,094)	8.9 ± 5.7 (1,250)	n.s.	8.6 ± 5.2	9.2 ± 5.1	14.2 ± 13.3	0.02
Albumin, g/L (mean ± SD)	45.3 ± 5.9 (1,101)	45.3 ± 3.1 (1,249)	n.s.	45.7 ± 2.7	44.8 ± 3.6	42.4 ± 6.4	<0.001
Ferritin, ng/ml (mean ± SD)	190.1 ± 231.6 (436)	190.21 ± 227.5 (753)	n.s.	172.1 ± 186.6	202.8 ± 220.3	468.2 ± 612.9	0.001
INR (mean ± SD)	1.1 ± 0.5 (245)	1.2 ± 0.6 (266)	n.s.	1.1 ± 0.48	1.3 ± 0.7	1.3 ± 0.5	n.s.
Platelets, 10^9/L (mean ± SD)	260.4 ± 70.1 (1,092)	255.1 ± 65.8 (1,254)	n.s.	271.4 ± 61.5	226.4 ± 56.6	159.0 ± 65.8	<0.001

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; FIB-4, Fibrosis-4 score; HbA1c, glycated haemoglobin; HDL, high density lipoprotein; IHD, ischaemic heart disease; INR, international normalized ratio; T2DM, type II diabetes mellitus. *p* values were calculated using t-test for normally distributed variables and Chi squared tests for categorical variables.

In total, 1,177 patients were stratified as being at low risk of advanced fibrosis (81.1%) and remained in the primary care setting. The remaining 275 patients (18.9%) were recommended for referral to a specialist for further investigation. The GPs referred 152 of these 275 patients (55.3%) for specialist investigation within the follow-up period (Fig. 3). To interrogate the reasons for non-referral, 3 surgeries were audited including 32 of the non-referrals. In this sub-group, reasons for non-referral included: patient already under the care of a hepatologist (n = 4), inappropriate for pathway due to alcohol excess (n = 2), comorbidity precluding need for specialist review (n = 1), continued monitoring in primary care (n = 3) awaiting outpatient appointment at time of evaluation (n = 2), and lost to follow-up (n = 2). Reasons were not recorded for 18 patients. Process evaluation revealed that 37/152 (24.3%) referrals had normal LFTs, and therefore should not have been on the pathway. Of the patients referred to secondary care using the NAFLD pathway, hepatologists judged that 29.6% had advanced fibrosis and 14.5% had cirrhosis compared to 4.8% and 3.6%, respectively, prior to introduction of the NAFLD pathway. Advanced fibrosis or cirrhosis was identified by liver biopsy (n = 14, 31.1%), FibroScan (n = 25, 55.6%) or radiological features of cirrhosis (n = 6, 13.3%). Of the 45 patients with advanced fibrosis or cirrhosis, 7 patients were referred due to FIB-4 alone (of whom 6 were cirrhotic) and 38 due to the combination of FIB-4 and ELF (Fig. 4).

Referrals made using the NAFLD pathway compared to standard care during the evaluation period

Comparisons were made between referrals from C&I GPs using the pathway to GPs in C&I using standard care; and to GPs using standard care in other CCGs where the pathway had not been discussed or introduced (Tables 2 and 3). The NAFLD pathway was 5 times better at selecting cases of advanced fibrosis and cirrhosis than standard care. When compared to standard care referrals from C&I, use of the pathway improved detection of advanced fibrosis and cirrhosis 4.9-fold (OR 4.90; 95% CI 2.56–9.36; p <0.0001) and when compared to referrals made by GPs outside C&I using standard care the pathway improved detection 5.2-fold (OR 5.18; 95% CI 2.97–9.04; p <0.0001). This equates to an 81% reduction in unnecessary referrals from primary care (OR 0.193; 95% CI 0.111–0.337; p <0.0001) when the pathway was used.

Hepatologists diagnosed more cases of cirrhosis amongst patients referred using the NAFLD pathway compared to those referred by C&I GPs using standard care (22/152 [14.5%] compared to 10/177 [5.6%]). This equates to nearly a 3-fold improvement in the detection of cases of cirrhosis (OR 2.83; 95% CI 1.29–6.18; p = 0.009). The number of referrals required to detect 1 case of advanced fibrosis was 3.4 using the pathway compared to 12.6 using standard care.

Comparison of the NAFLD pathway with standard care provided by other CCGs during the evaluation period revealed similar results to those observed when comparing the pathway and standard care used by GPs within C&I (see Table 3 and supplementary information).

Referrals made from Camden and Islington before and after introduction of the NAFLD pathway

Due to the increased awareness of NAFLD in 2014–16 compared to 2012–13, rates of referral to secondary care were analysed proportionate to the number of contemporaneously coded

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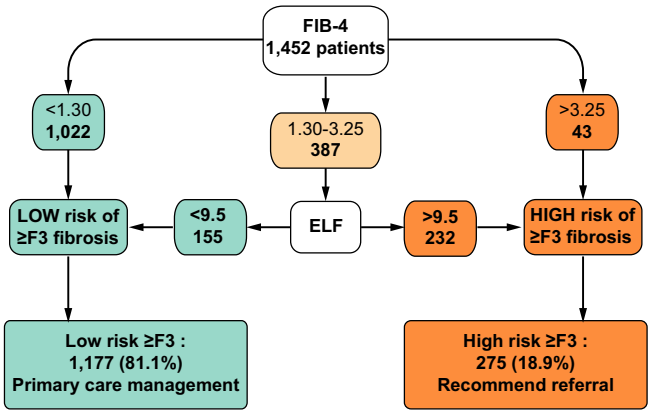

Fig. 2. Primary care risk stratification using the Camden and Islington NAFLD pathway 2014–2016. ELF, enhanced liver fibrosis; FIB-4, Fibrosis-4; NAFLD, non-alcoholic fatty liver disease.

NAFLD cases, rather than comparing the absolute numbers of cases referred and detected per year.

In the year prior to pathway introduction, 79/83 (95.2%) referrals made to secondary care were deemed unnecessary. Following introduction of the NAFLD pathway over a period of 2 years, the number of unnecessary referrals fell to 107/152 (70.4%) representing an 88% reduction when the pathway was followed (OR 0.12; 95% CI 0.042–0.349; p <0.0001) (Tables 2,3). The improvement in selection of cases of advanced fibrosis led to an increase in the number of cases of cirrhosis detected from 3/83 (3.6%) to 22/152 (14.5%), a 74% improvement (OR 0.259; 95% CI 0.075–0.892; p = 0.0323) representing 8 additional cases of cirrhosis per year.

There were no statistically significant differences in the outcomes for patients managed using standard care before or after introduction of the pathway suggesting that there was no Hawthorne or bystander effect[20] from diffusion of the benefits of the pathway to patients managed using standard care.

The impact of using age-adjusted FIB-4 thresholds

Subsequent to the design and implementation of the NAFLD pathway the influence of age on FIB-4 was investigated, leading to a recommendation to adjust the threshold of FIB-4 score in people aged over 65.[18] While adopting this higher threshold would have reduced the number of unnecessary referrals to secondary care by 29 from 122 to 93, (23% reduction), this would result in the loss of 12 cases with advanced fibrosis of which 4 had cirrhosis (Table 2).

Modelling of the impact of other ELF thresholds

The effect of using the ELF threshold proposed by NICE (10.51)[19] and the manufacturers of ELF (9.8)[21] rather than the threshold selected by the NAFLD pathway working group was investigated in the referral population (Table 4). Employing a threshold of 9.8 would have avoided 11 (7.2%) unnecessary referrals but with a concomitant loss of 3 (6.7%) cases of advanced fibrosis. Use of an ELF threshold of 10.51 would reduce the number of inappropriate referrals by 34 (22%), at a cost of missing 10 cases of advanced fibrosis (22%) comprising 7 cases of F3 fibrosis and 3 cases of cirrhosis.

Discussion

In this study, we report the results of a prospective, pragmatic, real world pathway to triage patients with NAFLD in primary care using non-invasive fibrosis tests based on their risk of advanced fibrosis. This represents the largest reported primary care cohort of patients with NAFLD to date. The NAFLD pathway reduced the proportion of unnecessary referrals of NAFLD cases while at the same time improving the detection of advanced fibrosis and cirrhosis. When the NAFLD pathway was followed, it resulted in a reduction in unnecessary referrals by 81%, a 5-fold increase in the referral of cases of advanced fibrosis and cirrhosis and a 3-fold improvement in the detection of cases of cirrhosis.

Prior to introduction of the pathway, the vast majority of referrals made to secondary care hepatologists could have been

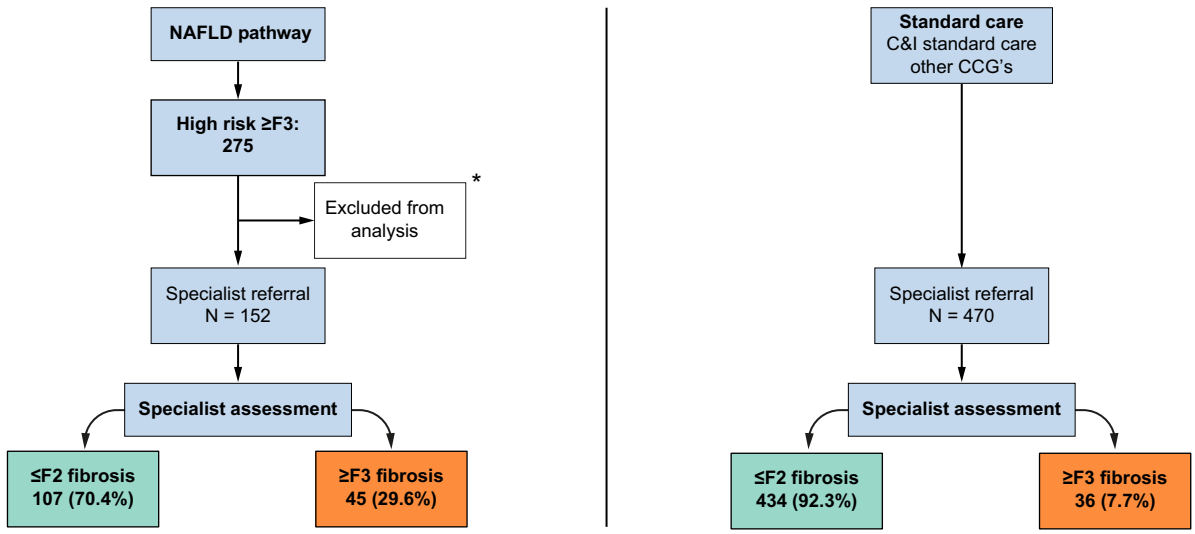

Fig. 3. Liver specialists' evaluation of referrals to secondary care of NAFLD cases in the evaluation period 2014–2016. CCG, clinical commissioning group; NAFLD, non-alcoholic fatty liver disease.

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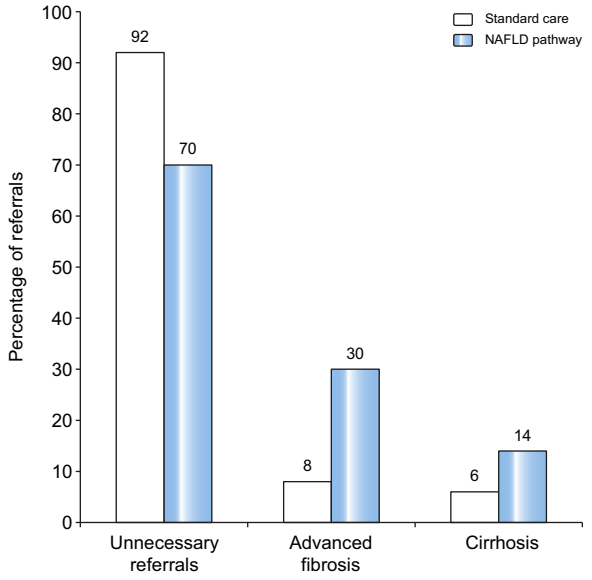

Fig. 4. Evaluation of patients referred to secondary care from Camden and Islington 2014–2016. NAFLD, non-alcoholic fatty liver disease.

managed in primary care. We believe that this pattern of referral is common for NAFLD. Reducing inappropriate referrals represents an opportunity to reduce unnecessary investigations, inconvenience and even harm for patients, pressure on secondary care services and costs for the healthcare system. The NAFLD pathway processed 1,452 patients in 2 years demonstrating the ability to function at scale and manage the rising prevalence of NAFLD.

Compared to other studies in the general population, this is the first that specifically focused on patients with established NAFLD and also provided a comprehensive algorithm for referral to secondary care. Other studies in primary cared screened patients with risk factors for NAFLD or alcohol-related liver disease or general population cohorts based on specific age cut-offs.[22] Moreover, most such studies have failed to report on the outcome of positive screening results, *i.e.* on the proportion of patients who truly had advanced fibrosis or cirrhosis.

The NAFLD pathway working group elected to use blood tests to stratify liver fibrosis severity rather than transient elastography that has been used in other successful pathways.[23] Blood tests have the advantages that they are easily incorporated into routine investigations in primary care, require no specialist equipment, training or operation and have a lower diagnostic failure rate compared to elastography-based methods including FibroScan, which has failure rates of between 5–15%, especially in NAFLD.[24] Application of the first stage "simple" and inexpensive test, FIB-4, allowed us to prevent referral of 70.3% of cases of NAFLD detected in primary care who did not have evidence of advanced fibrosis. However, use of FIB-4 alone only permitted the selection of just 3.0% of cases for referral to secondary care with high probability of cirrhosis. Addition of the "direct biomarker" ELF test was only required in 26.7% of cases in the pathway, but the additional use of ELF avoided inappropriate referral for 40.1% of those with indeterminate FIB-4 results. It is therefore important to underline that over two-thirds of patients with NAFLD can be reassured with the use of readily available inexpensive tests.

Following introduction of the pathway, only 19% of cases of NAFLD diagnosed in primary care were deemed suitable for

Table 4. Impact of using different ELF™ thresholds for patient stratification.

	ELF ≥9.8		ELF ≥10.51	
Relative to ELF ≥9.5	**n**	**%**	**n**	**%**
Referrals avoided	11	7.2	34	22.4
Missed cases of F3/F4 fibrosis	3	6.7	10	22.2
Missed cases of cirrhosis		0	3	13.6

ELF, enhanced liver fibrosis.

Table 2. Clinical estimates of liver fibrosis for patients diagnosed with NAFLD before and after introduction of the Camden and Islington NAFLD pathway.

	2012–2013			2014–2016						Age adjusted FIB–4
	C&I	Other CCGs	All CCGs	C&I pathway	C&I standard care	All C&I	Other CCGstandard care	All standard care	All CCGs	C&I path FIB-4 >2.0
n =	83	109	192	152	177	329	293	470	622	93
<F3	79	100	179	107	163	270	271	434	541	60
<F3%	95.2	91.7	93.2	70.4	92.1	82.1	92.5	92.3	87	64.5
F3&F4	4	9	13	45	14	59	22	36	81	33
F3&F4%	4.8	8.3	6.8	29.6	7.9	17.9	7.5	7.7	13	35.5
F4	3	4	7	22	10	32	15	25	47	18
F4%	3.6	3.7	3.6	14.5	5.6	9.7	5.1	5.3	7.5	19.4

C&I, Camden and Islington; CCG, clinical commissioning group; FIB-4, Fibrosis-4 score; NAFLD, non-alcoholic fatty liver disease.

Table 3. Impact of implementation of the Camden and Islington NAFLD pathway.

Intervention	Comparator	Referrals avoided			Advanced fibrosis/cirrhosis detection			Cirrhosis detection		
		Proportion (%)	95% CI	*p* value	OR	95% CI	*p* value	OR	95% CI	*p* value
C&I pathway	C&I before	88	75–96	0.0001	8.30	2.87–24.05	0.0001	4.51	1.31–15.56	0.017
C&I pathway	C&I standard care	80	61–89	<0.0001	4.90	2.56–9.36	<0.0001	2.83	1.29–6.18	0.0092
C&I pathway	Other CCGs	81	66–89	<0.0001	5.18	2.97–9.04	<0.0001	3.14	1.57–6.24	0.0011
All of C&I	Other CCGs	77	35–92	0.006	4.32	1.52–12.25	0.006	2.87	0.86–9.62	0.0871

C&I, Camden and Islington; CCG, clinical commissioning group; NAFLD, non-alcoholic fatty liver disease; OR, odds ratio. Odds Ratios were calculated for the "Intervention" groups compared to the listed "Comparator" groups.

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referral to secondary care. Although not appropriate to compare this proportion with referral practice prior to the pathway introduction, it is noteworthy that using the same criteria, 93% of patients referred to secondary care prior to the pathway introduction were judged to have been unnecessary.

The beneficial effects of the pathway were restricted to cases that followed the pathway. During the evaluation period, despite evidence of improved awareness of NAFLD, suggested by increased coding of NAFLD, there was no evidence of improvement in case detection or any reduction in unnecessary referrals when standard care was followed rather than the pathway. This demonstrates the value of use of the pathway but also shows that there was no diffusion of the pathway benefits to patients managed with standard care or any significant change in "standard" practice due to emerging awareness of NAFLD during the evaluation period.

Only 48% of referrals from C&I were made using the NAFLD pathway. Despite this, introduction of the pathway produced significant improvements in referral practice even when referrals made using standard care were included in the analysis. This demonstrates the success of the service improvement delivered in the context of routine clinical care despite moderate adoption and suggests that the results are generalizable. More widespread use of the NAFLD pathway could result in even greater improvements in efficiency and the detection of cases of advanced fibrosis. This might be achieved with more extensive efforts to disseminate the pathway and insistence that the pathway should be adopted for all NAFLD referrals.

Use of an age-adjusted FIB-4 threshold or of a higher ELF threshold according to the manufacturer's or the NICE recommendations would have improved the positive predictive value of the NAFLD pathway for detection of advanced fibrosis at the expense of an increased number of false negative cases. We believe that the use of such thresholds is not justified in this context as the reduction in referral numbers carries significant risks of missing cases that would benefit from specialist care and would be difficult to implement in primary care. Individual healthcare commissioners may decide to prioritize the detection of advanced fibrosis and long-term cost effectiveness over shorter term cost savings associated with avoiding referral of patients with lesser degrees of fibrosis.

Prior to introduction of the NAFLD pathway, funders expressed concern that the pathway might lead to a marked increase in referrals to secondary care leading to greater costs. Despite an increase in the diagnosis of NAFLD between 2012–2016 denoted by the increase in the coding of patients for NAFLD, use of the pathway resulted in a 3% reduction in the proportion of NAFLD cases that were referred to secondary care per year whether or not the pathway was followed, with only a modest increase in the total number of patients referred.

The strengths of this study include the prospective collection of real-world data, the size of the cohort, which is the largest primary UK cohort with regards to NAFLD, and the engagement of appropriate stakeholders in the pathway design.

The limitations mostly stem from the nature of the implementation design, which was designed to evaluate a health service innovation. It was not possible to conduct a randomized controlled trial because of the commitment to adopt the pathway once it was discussed with GPs and public health clinicians who formed the opinion that there was sufficient evidence to implement the pathway without a trial. This view was subsequently endorsed by NICE in the NAFLD Guidance[24].

The NAFLD pathway evaluation lacked a hard outcome measure of liver fibrosis and rather used the composite clinical judgement of an expert clinician blinded to the pathway use. The secondary care evaluation of the included patients thus reflects real-world practice, with an inevitable degree of selection bias in the patients undergoing liver biopsy.

Similarly, the lack of formal evaluation of the prevalence of fibrosis amongst patients allocated to remain in primary care prevented assessment of the "false negative" rate for the pathway allocation. However longer term follow-up for clinical outcomes and more detailed health economic analyses will reveal the clinical impact of stratification and the true cost effectiveness of the pathway. Patient and service provider acceptance is being gathered and will be reported in due course.

Conclusions

The C&I NAFLD pathway improved the selection of patients with advanced fibrosis and cirrhosis for referral to secondary care, reducing unnecessary referrals. This in turn delivers improvements in the detection of serious liver damage, better use of healthcare resources and immediate cost savings. The reduction in referrals to secondary care reduces strain on services that are confronting a rising prevalence of obesity and NAFLD as well as improving patient experiences by avoiding unnecessary clinic appointments and investigations. This is the first study to incorporate the British Society for Gastroenterology guidance on the management of NAFLD and validates the recommendation to use FIB-4 and ELF for 2-stage stratification. The NAFLD pathway is highly generalizable, as GPs will have access to both FIB-4 and ELF tests through most biochemistry laboratories.

It remains to be seen if the use of the NAFLD pathway delivers benefits in terms of a reduction in the incidence and complications of NAFLD cirrhosis.

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Conflict of interest

WMR is an inventor of the ELF test but receives no related royalties. WMR, JP and AS have received speakers' fees from Siemens Healthineers. The other authors declare no competing interests.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

AS data collection, study design, primary authorship; RG data collection, study design; ST study concept, critical revision of manuscript for important intellectual content; PT study concept, critical revision of manuscript for important intellectual content; JP data analysis, critical revision of manuscript for important intellectual content; AR critical revision of manuscript for important intellectual content; DS data collection;

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DT study concept, critical revision of manuscript for important intellectual content; KS study concept, critical revision of manuscript for important intellectual content; SM study concept, critical revision of manuscript for important intellectual content; EAT study concept and design, critical revision of manuscript for important intellectual content; WR study concept and design, critical revision of manuscript for important intellectual content. All authors approved the final version of the manuscript before submission.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2019.03.033.

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