Research Article

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Presence and severity of non-alcoholic fatty liver disease in a large prospective primary care cohort

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Background & Aims: Non-alcoholic fatty liver disease (NAFLD) is a common cause of abnormal LFTs in primary care, but there are no data defining its contribution nor reporting the range of NAFLD severity in this setting. This study seeks to calculate the range of disease severity of NAFLD in a primary care setting.

Methods: Adult patients with incidental abnormal LFTs, in the absence of a previous history, or current symptoms/signs of liver disease were prospectively recruited from eight primary care practices in Birmingham. NAFLD was diagnosed as fatty liver on ultrasound, negative serological liver aetiology screen, and alcohol consumption $\leqslant$30 and $\leqslant$20 g/day in males and females, respectively. The NAFLD Fibrosis Score (NFS) was calculated to determine the presence or absence of advanced liver fibrosis in subjects identified with NAFLD.

Results: Data from 1118 adult patients were analysed. The cause of abnormal LFTs was identified in 55% (614/1118) of subjects, with NAFLD (26.4%; 295/1118) and alcohol excess (25.3%; 282/1118) accounting for the majority. A high NFS (>0.676) suggesting the presence of advanced liver fibrosis was found in 7.6% of NAFLD subjects, whereas 57.2% of NAFLD patients had a low NFS (<−1.455) allowing advanced fibrosis to be confidently excluded.

Conclusions: NAFLD is the commonest cause of incidental LFT abnormalities in primary care (26.4%), of whom 7.6% have advanced fibrosis as calculated by the NFS. This study is the first of its kind to highlight the burden of NAFLD in primary care and provide data on disease severity in this setting.

Keywords: Primary care; Non-alcoholic fatty liver; Fibrosis; Liver function test.
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Abbreviations: (A)LFT, (abnormal) liver function tests; UHB, University Hospital Birmingham; PCP, primary care practitioner; UK, United Kingdom; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; HCC, hepatocellular carcinoma; BALLETS, Birmingham and Lambeth Liver Evaluation Testing Strategies; USS, ultrasound; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; GGT, gamma-glutamyl transferase; A-1AD, alpha 1 antitrypsin deficiency; HBV, viral hepatitis B; HCV, viral hepatitis C; AIH, autoimmune hepatitis; PSC, primary sclerosing cholangitis; PBC, primary biliary cirrhosis; BMI, body mass index; NFS, NAFLD Fibrosis Score; IFG, impaired fasting glucose; NPV, negative predictive value; PPV, positive predictive value; MW, Mann, Whitney *U* test; IQR, interquartile range.

Introduction

The incidence of liver disease is rising throughout the world and now accounts for 1.5% of deaths in the UK (www.statistics.gov.uk). In parallel with this, there has been a year on year rise in the number of liver function test (LFT) profiles carried out in UK primary care practices (from 62,300 to 109,619/year between 2002 and 2010; University Hospital Birmingham (UHB) laboratories audit, UK). Primary care practitioners (PCPs) are thus commonly faced with the scenario of abnormal liver function tests (ALFT) in patients in whom there are no clinical risks, signs or symptoms of liver disease. Non-alcoholic fatty liver disease (NAFLD) is now recognized as the most common cause of hepatic dysfunction in general population [1,2], however, this is yet to be confirmed in primary care practice. Furthermore, because of the indolent asymptomatic nature of NAFLD, identifying those with advanced disease in whom specific interventions may be required remains a clinical challenge in primary care.

The prevalence of NAFLD has risen markedly to 14–34% of the general-population in Europe [2,3], Asia [4], and America [5] in recent years. Whilst patients with simple NAFLD are believed to have benign disease, there is now clear evidence that those who have progressed to non-alcoholic steatohepatitis (NASH) and fibrosis are at a much higher risk of developing hepatocellular carcinoma (HCC), liver failure, and death [6,7]. The majority of data describing the severity of liver fibrosis in NAFLD arises from selected populations in secondary referral centres [7–13]. In a large UK prospective study, Skelly *et al.*

demonstrated that 18% (23/120) of biopsy confirmed NASH patients had significant fibrosis after presenting to their secondary care centre with unexplained ALFTs [12]. This and other such studies [9,10] included patients in whom the decision to refer had been made on clinical grounds by PCPs/consultant colleagues and were then rigorously screened in liver clinics for other disease aetiologies prior to proceeding to liver biopsy. These studies are, therefore, influenced by ascertainment bias and may overestimate the severity of NAFLD emerging from primary care.

It is currently expected with the alarming growth of obesity and type 2 diabetes that the burden of NAFLD on primary care and liver services will continue to rise in the UK [14]. To date, no studies have determined the underlying disease severity of NAFLD in primary care. PCPs remain at the forefront of identifying the patients with advanced NAFLD who require further evaluation, closer surveillance for complications (and interventions where appropriate) and stricter lifestyle modifications. By investigating a large UK primary care sample of patients with incidental ALFTs and absent clinical features of liver disease, this study is the first of its kind to determine the presence and disease severity of silent NAFLD in a primary care setting.

Materials and methods

Study population

Birmingham and Lambeth Liver Evaluation Testing Strategies (BALLETS) is a prospective study of patients with an incidental finding of ALFTs in primary care funded by NIHR Health Technology Assessment program (http://www.hta.ac.uk/1459). Patients were prospectively recruited from primary care practices from Birmingham and Lambeth areas, between 2006 and 2008. The primary aim of the BALLETS study was to assess the clinical utility of ALFTs in patients in whom liver disease was not suspected clinically by the PCP. St. Thomas' Hospital Research Ethics Committee approved the study and all study participants gave signed informed consent to be included.

This current cross-sectional sub-study utilizes baseline data from patients enrolled in the BALLETS study from the eight primary care practices within the Birmingham region only. PCPs from participating practices reviewed all new incidental ALFT results arising from their practices in patients in whom the clinical suspicion of underlying liver disease was absent or low. Patients over eighteen years old were eligible for the sub-study if one or more LFT analyte was abnormal and there was no previous documented history of liver disease, intravenous drug use and/or alcohol-related health problems. Current signs or symptoms suggestive of liver disease, pregnancy, and a diagnosis of disseminated malignancy were also considered exclusion criteria. Eligible patients who consented for the study completed an interview during which current illnesses, past medical history, alcohol consumption, socio-demographic details, and drug history were recorded. Reasons for the original LFTs being ordered by the PCP were also recorded. Patient's height, weight, and waist circumference were measured. All patients had a repeat set of LFTs and a full serological liver aetiology screen (viral, genetic and autoimmune) at the study visit. An abdominal ultrasound scan (USS) was obtained in the fasted state using an ultrasound machine (TITAN® Sonosite) operated by one of five (10–30 years experience) abdominal sonographers. All scans were recorded on tape and 50 of these were selected at random and validated by a consultant radiologist (Olliff S).

PCPs were sent a consolidated report of all study investigations. The study team recommended to the PCP the need for a hepatology referral to the tertiary liver clinic (UHB) in the event of one of the following: (1) positive serological liver aetiology screen; (2) sonographic features of cirrhosis (coarse echotexture, irregular contour), space occupying liver lesion(s) or biliary duct dilatation. All liver clinic letters were retrospectively reviewed (until 1st May 2010) to identify which of these diagnoses were followed up and confirmed by a liver specialist (Supplementary Table 1).

Data definitions

The sub-study LFT profile consisted of alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), gamma-glutamyltransferase (GGT), total bilirubin, and albumin measurements. Seven of the eight Birmingham practices sent samples to a central laboratory at UHB, whilst the remaining practice sent samples to the laboratory of Russells Hall Hospital. Initial LFTs requested by the PCP were used as a criterion for study entry, whereas the repeat LFTs undertaken at the study visit were performed to increase the likelihood of a complete panel of the six analytes listed and to avoid analyte selection bias that may have occurred in the primary care practice. The analytes were classified as normal or abnormal based on reference ranges specific to each of the two individual laboratories, which are compliant with International Quality Control Standards (Supplementary Table 2). The full blood liver aetiology screen consisted of viral hepatitis B (HBV) surface antigen, viral hepatitis C (HCV) antibody, caeruloplasmin, iron and transferrin saturation, alpha-1 anti-tryspin, anti-smooth muscle, and anti-mitochondrial antibodies.

Body mass index (BMI) was defined as weight in kilograms divided by the square of the height in metres (kg/m^2). Obesity was defined as BMI $\geqslant$30 kg/m^2. Alcohol intake was reported as standard units (1 U = 10 g alcohol) of alcohol consumed on average per week in the 6 months prior to recruitment. Mild (female 1–7 U, male 1–11 U/week) and moderate (female 8–14 U, male 12–21 U/week) alcohol consumption were defined as drinking within the current UK health guidelines (female $\leqslant$14, male $\leqslant$21 U/week; British Medical Association 1995). At-risk alcohol consumption was defined as exceeding these guidelines.

For the purposes of this sub-study, type 2 diabetes was defined in patients with a documented history of the disease or a recorded drug history of anti-diabetic medication. Hypertension was defined as a past medical history of the disease or a current recorded drug history of two or more anti-hypertensive medications.

The diagnosis of NAFLD was based on the following criteria: (1) sonographic diagnosis of fatty liver, defined as diffusely increased liver echogenicity (>right renal parenchyma) with vascular blurring; (2) a negative history of alcohol consumption exceeding current UK health guidelines; and (3) exclusion of liver disease of other aetiology including drug-induced, autoimmune, viral hepatitis, cholestatic, metabolic and genetic liver disease.

NAFLD Fibrosis Score

The NAFLD Fibrosis Score (NFS) [8] is a simple non-invasive scoring system designed to identify or exclude advanced fibrosis (classified as Kleiner stages F3 and F4 [15]) in patients with an established diagnosis of NAFLD on imaging. The NFS was developed and validated by Angulo *et al.* [8] in over 700 liver biopsy-proven patients with NAFLD and is routinely used in liver clinics to select those at risk of disease progression and HCC. The NFS utilizes a number of simple clinical and laboratory independent predictors of advanced liver fibrosis: NFS = $-1.675 + 0.037 \times$ age (years) $+ 0.094 \times$ BMI (kg/m^2) $+ 1.13 \times$ IFG/diabetes (yes = 1, no = 0) $+ 0.99 \times$ AST/ALT ratio $- 0.013 \times$ platelet count ($\times 10^9$/L) $- 0.66 \times$ albumin (g/dl) [8]. The low cut-off score (<$-$1.455) has a negative predictive value (NPV) of 88–93% and the high cut-off score (>+0.676) has a positive predictive value (PPV) of 79–90% for the presence of advanced fibrosis in NAFLD in secondary care populations [8,16]. The NFS was calculated retrospectively using the web-based calculator (http://NAFLDscore.com).

As the original BALLETS study protocol did not incorporate a platelet count, retrospective data collection of the electronic haematology laboratory archive at the UHB enabled platelet counts within 6 months of patient enrolment to be recorded. To avoid false positive or false negative NFS, the scoring system was not applied to participants with a past medical history of platelet disorders, on myelosuppressive medications or an active systemic-inflammatory disease.

Statistical analysis

Descriptive statistics were applied to characterize the whole study cohort and the identified NAFLD group. Continuous clinical and laboratory variables are reported as medians and interquartile ranges (IQR) as all variables had a non-parametric distribution on D'Agostino and Pearson Omnibus Normality testing (GraphPad Prism 5). Categorical variables are reported as numbers and percentages. Due to a variation in normal reference ranges between the two laboratories utilized for the initial PCP LFT samples, blood results from Russell Hall Hospital (n = 89 patients) were standardised to the central laboratory reference ranges at UHB using the proportion of the upper (or lower with albumin) limit of normal.

Results

A total of 1118 primary care patients were included. The PCPs reason for the LFT requests are shown in Table 1. The majority (38%; 424/1118) of these resulted from routine chronic disease check-ups. In 4.5% (50/1118) of cases no reason was recorded. Liver aetiology screen and ultrasound were successfully completed in 98% (1101/1118) of patients at the study visit. There was a 100% agreement between the consultant radiologist and the study sonographers in reporting the presence or absence of fatty liver on USS in 50 randomly selected cases. Study demographics and characteristics are summarised in Table 2.

Table 1. The 10 most commonly recorded reasons for why the LFT's were undertaken by the PCP. Values are percentages (numbers). Percentages include all values (n = 1118). Other reasons accounted for 20.9% (234).

Documented reason	Percentage (n)
Diabetes review	18.0 (201)
Non-specific routine bloods	15.2 (171)
Hypertensive disease review	11.4 (128)
Gastrointestinal symptoms (excluding liver-specific)	10.0 (112)
Generalised fatigue or tiredness	6.2 (69)
Cardiovascular disease review	4.7 (53)
Medications review (non-specific)	4.5 (50)
Hyperlipidaemia disease review	3.8 (42)
Neurological symptoms (inc. confusion)	2.7 (31)
Musculoskeletal symptoms (i.e. joint pain)	2.4 (27)

Causes of ALFTs

The cause of ALFTs was identified in 54.9% (614/1118) of cases (Table 3). Detailed testing for viral, genetic, and autoimmune causes yielded 33 diagnoses (3.0%). NAFLD was identified as the commonest cause of ALFTS accounting for 26.4% of all cases, exceeding alcohol excess (25.3%). The demographics and metabolic parameters of the identified NAFLD group are summarised in Table 2. There were no reported cases of cirrhotic appearances or ascites on USS in the NAFLD cohort. Splenomegaly ($\geqslant$13 cm) was reported in 7.8% (23/295) of NAFLD cases, albeit only marginally enlarged (median 13.6 cm, IQR 13.2–14.0). Two or more ALFT analytes were present in 40.7% of NAFLD subjects (120/295), with the remainder having a single analyte abnormality (59.3%; 175/295) on PCP sampling. GGT was the most common LFT abnormality in the NAFLD cohort (75.7%; 197/260), with a median value 1.6 times the upper limit of normal (Fig. 1). Median time difference between bloods ordered by the PCP and the study visit was 30 days (IQR 18–51).

At-risk alcohol consumption was reported in 25.3% (282/1118). The majority of at-risk alcohol consumers were male (73.4%; 126/282) and drank a significant greater amount of alcohol (units per week) than females (median 42 (IQR 30–56) versus 29 (IQR 21–46), Mann–Whitney U test = $p < 0.001$). An echo-bright fatty liver was identified with USS in 44.7% (126/282) of

Table 2. Demographics and characteristics of study participants (left) and those identified with NAFLD (right).

Characteristics	Total (n = 1118)	NAFLD (n = 295)
Median (IQR) age (years)	60 (48-70)	58 (49-66.7)
Gender		
Male	56 (628)	56.6 (167)
Female	44 (490)	43.4 (128)
Ethnicity (%)		
White	83.9 (938)	84.1 (248)
African-Caribbean	3.9 (44)	2.0 (6)
Asian/Arabic	8.1 (90)	9.8 (29)
Mixed/other	1.3 (15)	1.7 (5)
Unknown	2.8 (31)	2.4 (7)
Alcohol consumption cut-offs		
Abstinence	42.5 (475)	56.9 (168)
Mild	20.8 (232)	28.1 (83)
Moderate	10.5 (117)	14.9 (44)
At-risk	26.3 (294)	0 (0)
Metabolic Phenotypes		
Type 2 diabetes	23.5 (263)	38.6 (116)
Hypertensive Disease	43.2 (483)	45.4 (134)
Obesity	40.7 (455)	60.3 (179)
Median (IQR) measured BMI (Kg/m^2)	28.7 (25.3-33.1)	31.5 (28.1-35.8)
Median (IQR) waist circumference (cm)		
Male	103 (95-112)	107 (101-115)
Female	96 (85-109)	107 (96-115)

Values are percentages (numbers) unless stated otherwise. Percentages do not include missing values.

Table 3. Causes of incidental ALFT. Percentages include all values (total n = 1118). LFT analyte (inclusive of normal and abnormal values) from study visit are expressed as medians (IQR).

Cause	Percentage (n)	GGT [U/L]	ALT [U/L]	AST [U/L]	ALP [U/L]	Bili [μmol/L]	Alb [g/L]
NAFLD	26.4 (295)	59 (41-88)	38 (27-54)	30 (23-40)	206 (167-266)	9 (6-12)	45 (43-47)
At-risk alcohol intake							
Non-Fatty liver	14.0 (156)	69 (46-115)	30 (22-44)	28 (22-35)	190 (159-238)	10 (7-13)	46 (44-48)
Fatty liver	11.3 (126)	81 (52-148)	46 (33-65)	36 (28-49)	178 (150-218)	9 (8-13)	47 (45-49)
PBC	0.81 (9)	99 (45-186)	15 (20-31)	27 (25-36)	396 (337-463)	7 (6-13)	43 (42-45)
HBV	0.72 (8)	53 (32-418)	92 (49-156)	62 (26-97)	184 (147-242)	8 (5-15)	46 (43-52)
Haemochromatosis							
Homozygote [C282Y or H63D]	0.54 (6)	73 (31-166)	59 (43-79)	39 (32-56)	202 (158-382)	8 (5-23)	46 (45-48)
Comp. heterozygote [C282Y + H63D]	0.36 (4)	56 (25-458)	51 (54-149)	25 (42-238)	121 (75-135)	12 (5-21)	51 (45-53)
Other (inc. cancer, drug, abscess)	0.36 (4)	85 (27-179)	29 (17-58)	31 (18-44)	273 (191-368)	12 (7-18)	44 (39-48)
HCV*	0.17 (2)	x (34, 452)	x (151, -)	x (101, 70)	x (514, 214)	x (8, 8)	x (48, 47)
PSC*	0.17 (2)	x (-, 600)	x (51, 212)	x (33, 124)	x (176, 990)	x (12, 10)	x (47, 46)
A1AD*	0.17 (2)	x (59, 62)	x (41, 50)	x (24, 25)	x (161, 138)	x (11, 12)	x (48, 50)
Unexplained group	45.1 (504)	56 (33-91)	26 (19-38)	26 (22-33)	202 (162-274)	9 (6-13)	45 (43-47)

*True analyte values are listed in brackets if n <4. (*x*) represents missing value or median.

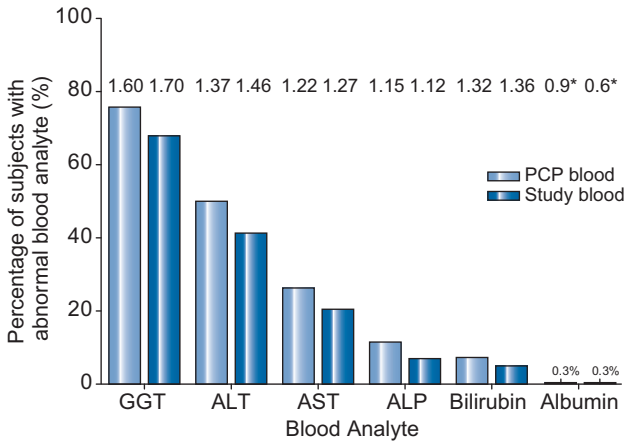

Fig. 1. Frequency and extent of LFT abnormalities in the identified NAFLD cohort. Percentages do not include missing values. The extent of the LFT abnormality is expressed as a proportion of the upper (or lower*) limit of normal (median values reported above bars).

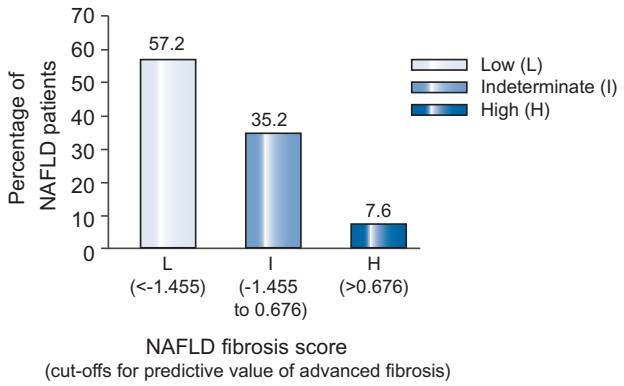

Fig. 2. NAFLD Fibrosis Scores in patients that met the diagnostic criteria for NAFLD. Percentages do not include missing values.

subjects who consumed at-risk levels of alcohol. The majority of excess drinkers (87%; 110/126) had a BMI greater than 25 kg/m^2. USS identified cirrhotic appearances in two cases (one with splenomegaly; 15 cm) of at-risk alcohol consumption. The diagnosis of compensated alcohol-induced cirrhosis was confirmed by tertiary liver specialists.

No cause for LFT abnormality was identified in the remainder of study subjects (45.1%; 504/1118). Liver disease could not be ruled out in 8.1% (41/504) of unexplained cases due to incomplete liver aetiology screen (n = 10), USS (n = 7) and absence of referral to liver specialist/patient non-attendance after a positive liver aetiology screen test (bile duct dilatation, n = 1; transferrin saturation >50%, n = 6; low caeruloplasmin, n = 17). LFTs normalised between PCP and study visit sampling (median 30 days, IQR 18–63) in 19.9% (92/463) of unexplained cases with a completed USS and liver aetiology screen. Metabolic risk factors in the unexplained ALFT group included obesity (30.5%, 154/504), diabetes (19.0%, 96/504) and hypertension (41.3%, 208/504). Of note, 18.5% (95/504) had co-existing obesity with either diabetes and/or hypertensive disease.

Disease severity in the cohort of patients with NAFLD

To calculate the severity of NAFLD in this cohort we retrospectively applied the NFS. The score was calculated in 236 of the

295 patients who met the diagnostic criteria for NAFLD (Fig. 2). The NFS was not calculated in the remaining 59 patients with NAFLD as a result of incomplete records of blood platelets (n = 50), BMI (n = 5) and AST/ALT ratio (n = 4). A high NFS (>+0.676) was found in 7.6% (18/236) of patients with NAFLD, suggesting the presence of underlying advanced liver fibrosis (Stages F3/F4 on Kleiner classification [15]). Advanced fibrosis was predicted to be absent in the majority of NAFLD subjects with a low NFS (<−1.455) being calculated in 57.2% (135/236). The presence of advanced fibrosis, however, could not be confidently excluded in 35.2% (83/236) of the NAFLD patients who scored an indeterminate value with the NFS (−1.455 to +0.676).

Discussion

This large primary care study highlights that NAFLD accounts for over 25% of incidental ALFTs in primary care consultations, in which the consulting PCP's suspicion of underlying liver disease is low or absent. In contrast, only 3.0% of all study patients had a specific viral (HBV/HCV), genetic, or autoimmune disease identified on thorough study testing. Application of a simple, non-invasive scoring system suggests that undetected advanced liver fibrosis is present in 7.6% and absent in 57.2% of the NAFLD patients. Incidental ALFTs were most commonly encountered during routine chronic disease reviews (38% cases), including diabetes, hypertension, and cardiovascular disease. This study is the first of its kind to report the severity of NAFLD in patients with incidental ALFTs in primary care.

Our study evaluated a PCP-based population with ALFTs rather than a population volunteered from the general community. Nonetheless, the frequency of NAFLD (26%) identified in our study is within the wide range (14–34%) previously reported in general population studies carried out in Italy [2], Spain [3], Asia [4], and America [5]. The variation in reported frequencies may be influenced by ethnic diversity [5,17] and differences in study methodologies. These include variable alcohol thresholds that define NAFLD, lack of consistency in screening for other disease aetiologies, and variation in risk stratification for liver disease at study enrolment. All the studies nevertheless confirm the strong association between NAFLD and components of the metabolic syndrome [4,18], the prevalence of which has increased rapidly worldwide [14]. The high proportion of patients with diabetes (38.6%), obesity (60.3%) and hypertension (45.4%) in the NAFLD group in our study is in keeping with population-based studies [2].

The suspected proportion of advanced fibrosis within our NAFLD cohort is 7.6%. Additionally, from experiences in hospital care [8,16,19], we predict that a sub-set of the 35.2% of patients with an indeterminate NFS may also have advanced fibrosis. There are currently no data on the severity of NAFLD in primary care. The most relevant studies that best reflect low-risk populations are restricted to biopsy findings in living-related liver donors, in which the prevalence of NASH (± fibrosis) ranges from 1.1% in Japan [20] to 18.5% in the US [21]. The latter figure is likely to be an overestimate due to the lack of detail on alcohol consumption and full liver aetiology screening in liver donors. Secondary/tertiary centre studies of variable size (range118–733) and Caucasian predominance have reported that 11–27% of patients with biopsy-proven NAFLD and elevated aminotransferases have advanced (stages 3/4) fibrosis [7,13,19,22,23]. The higher rates of advanced fibrosis reported in these liver specialist centres are likely to be due to referral/sampling bias.

Our study has several unique strengths. First, this is the largest prospective cohort of primary care patients with clinically unsuspected liver disease and incidental ALFTs to be reported. Second, this is the first study to apply the non-invasive NFS to identify patients with advanced NAFLD fibrosis in primary care that are most in need of intensive lifestyle modifications and surveillance for liver-related complications (e.g. HCC detection). Third, the detailed assessment of the liver aetiology screen (alcohol/drug data, serology, genetics, and USS imaging) undertaken and high completion rate (98%) has meant that a cause for ALFT was identified in the majority of cases (55%). Previous large-scale population-based retrospective analyses of ALFTs have been limited by the absence of USS [1] and the lack of information on alcohol and measured anthropometry [24] to accurately describe the presence of NAFLD. The high rate of liver disease identification in our patient sample that PCPs perceived as a low risk group may also be explained by the fact that GGT, which has the highest reported sensitivity for liver disease above other LFTS [24], was the commonest LFT abnormality. The finding of an elevated GGT in more than 70% of the NAFLD group as opposed to ALT (51.0%) and AST (26.2%) has not previously been reported in adult NAFLD patients. This finding has also been reported in paediatric NAFLD [25].

One limitation of this study is that the application of the NFS was validated against liver biopsy in NAFLD patients attending hospital [8,16,19], and so it is possible that the severity of NAFLD may be over-estimated in our primary care cohort. However, our NAFLD cohort has very similar patient characteristics (Caucasian, obese, middle-aged, with ALFTs) to those reported by Angulo *et al.* [8], and in many countries the distinction between primary and secondary care is not as clear. The NFS was chosen over other non-invasive systems [23,26,27] that detect advanced fibrosis for the purpose of our study as it is an easily applicable tool (web-based calculator) that has the best reported PPV in secondary care [16], entails minimal extra cost to GPs (i.e. platelet sampling) and incorporates blood and clinical parameters that are routinely available in primary care. We were not able to validate the NFS against other non-invasive modalities [26–28] as these had not been developed nor sufficiently studied by the time our study had started. Moreover, there are issues about how to validate such modalities in primary care, as it is unlikely and also unethical that liver biopsies would ever be performed in such a large sample of patients or in this setting. NFS is limited to predicting the presence or absence of advanced fibrosis only, and does not distinguish between benign steatosis alone (non-NASH) and the inflammatory process of steatohepatitis (NASH). Previous studies have highlighted that NAFLD patients with NASH (independent of fibrosis) have a higher risk of death from liver disease and to a greater extent cardiovascular disease than those with non-NASH [7,29]. At present, however, non-invasive tools do not exist in primary care to identify individuals with NASH ± early fibrosis.

Despite a thorough non-invasive aetiology screen and detailed alcohol history, 45% had unexplained ALFTs in our cohort. However, as we targeted the more problematic patients in primary care that have incidental ALFTs in the absence of a clinical suspicion of underlying liver disease, this is not a surprise. Furthermore, unlike previous general population studies [1,2] that only

utilised ALT, AST, and/or GGT, our study recruited patients with a wider spectrum of LFT analytes to reflect common practice in primary care. It is, therefore, possible that some of the unexplained ALFTs represent transient (viral) illness, Gilbert's syndrome, under (self-) reported use of alcohol/over-counter medications or non-liver related disease (i.e. bone, muscle) [1]. The finding that 20% of the unexplained group normalised LFTs within an average of 30 days of re-testing supports this hypothesis. Although USS is the most readily available imaging tool available in primary care, the fact that 18% of the 'unexplained' group had co-existing obesity with diabetes and/or hypertension raises the possibility that reliance on ultrasound alone will miss a proportion of cases of NAFLD. The difficulty in detecting the presence of fatty liver with USS is well reported in the morbidly obese and when the degree of fat infiltration is less than 33% of the hepatic content [30]. Furthermore, biopsy reports have shown that fat content is lost towards the more advanced stages of NAFLD, with the resultant fibrotic tissue being undetectable on USS [30]. The lack of markers of insulin sensitivity and lipid profile in the study meant we were unable to non-invasively quantify hepatic fat [31], and hence potentially determine the numbers of undetected NAFLD on USS within the 'unexplained' group.

Our findings have important clinical and public health implications. This study raises awareness that NAFLD accounts for a significant proportion of incidental ALFTS commonly encountered by PCPs, in the absence of a clinical suspicion of liver disease. We have identified a potential sub-set of NAFLD patients with advanced fibrosis (7.6%) that require early assessment and management in secondary care. We would advocate a certain degree of reassurance with regard to the absence of underlying advanced fibrosis/cirrhosis and an impetus for regular metabolic disease risk assessment and lifestyle modifications in patients with a low NFS (57.2%). In the absence of validated scoring systems, patients at present with an indeterminate NFS require closer surveillance in primary care with referral to secondary care as deemed appropriate by the PCP.

In conclusion, we provide novel information on the severity of NAFLD in a primary care setting, as well as guidance on the triaging of such patients for further investigation and management.

Conflict of interest

The authors who have taken part in this study declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

Authors contribution

M.J.A., D.D.H., P.N.N. and R.J.L. contributed to the design of the sub-study. M.J.A. and D.D.H. analysed the data and M.J.A. wrote the first draft of the manuscript. M.J.A., D.D.H., P.N.N., R.J.L., and J.M.N. contributed to the redrafting of the manuscript and the final submitted version. MJA is the guarantor, had full access to the data in the sub-study, and takes full responsibility for the integrity of the data and the accuracy of the data analysis. R.J.L., J.M.N., P.G., S.P.O., R.C. were investigators for the original BALLETS study. L.B. was the lead research nurse responsible for the data collection in the Birmingham study arm of the original BALLETS study. J.C.S. contributed to the biochemical and genetic laboratory sample processing.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.jhep.2011.03.020.

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