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Non-alcoholic fatty liver disease

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Non-alcoholic fatty liver disease (NAFLD) is now more common than alcoholic liver disease owing to the rapid rise in the prevalence of obesity,¹ and NAFLD is the most common cause of abnormal liver function tests.² Its prevalence worldwide is thought to be approximately 20% in the general population and up to 70% in patients with type 2 diabetes mellitus.³ The first recognisable stage of NAFLD is hepatic steatosis, when fat content exceeds 5% of liver volume. Simple steatosis is usually benign in terms of risk of progression to more advanced liver disease, but given its high prevalence it none the less represents an important cause of cirrhosis.⁴ Notably, NAFLD is strongly associated with insulin resistance and hyperglycaemia and it is therefore closely linked to type 2 diabetes. Non-alcoholic steatohepatitis (NASH), the next stage of NAFLD, develops when hepatic inflammation ensues, and its prevalence in the general population is estimated at 3-5%;³ people with NASH are at much higher risk of clinically significant and progressive liver fibrosis, cirrhosis, and hepatocellular carcinoma.⁴⁻⁵ Relevant clinical questions include how to evaluate abnormal liver function test results, whether it is important to identify NAFLD, how to pragmatically identify patients who may have NASH, and who to refer for specialist evaluation. In this article we outline how NAFLD may be recognised in primary care, we suggest when further investigations are needed, and we show why NAFLD should be a strong driver for sustainable weight loss to reduce metabolic and, potentially, hepatic risks.

Who gets NAFLD?

Obesity is a major risk factor for the development of NAFLD. The increase in obesity is therefore the main driver for the greater prevalence of NAFLD in the community. There is a strong link between NAFLD and type 2 diabetes, even beyond adiposity.⁶ Male sex and a family history of type 2 diabetes

SOURCES AND SELECTION CRITERIA

We sought relevant studies from the Cochrane Database of Systematic Reviews, Medline, and Embase, with particular emphasis on systematic reviews, randomised controlled trials, and meta-analyses of trials. Search terms included “non-alcoholic fatty liver disease” and “non-alcoholic steatohepatitis”. Studies were limited to those in adults and written in English.

are also associated with a greater risk of NAFLD and NASH at any given body mass index,⁷ and preliminary evidence suggests greater liver fat content in certain ethnicities that are also known to be at increased risk of type 2 diabetes.⁸ Preliminary evidence suggests a genetic predisposition to hepatic accumulation of fat in some people through the PNP3A gene.⁹ Such people may not necessarily display the usual metabolic associations with NAFLD, but genetic screening for PNP3A is not currently recommended.³ Strictly speaking, NAFLD should only be diagnosed in people who consume no or only modest amounts of alcohol (daily intake <20 g (2.5 units) in women and <30 g (3.75 units) in men), although the clinical reality is that in many people both obesity and alcohol will contribute to their level of liver fat and risk of progressive liver disease.¹⁰ Uncommon causes of fatty liver also should be considered (drugs including amiodarone, diltiazem, steroids, synthetic oestrogens, tamoxifen, and highly active antiretroviral therapy; refeeding syndrome and total parenteral nutrition; severe weight loss after jejunioileal or gastric bypass; lipodystrophy and other rare disorders) by taking an appropriate medical history.

When should NAFLD be suspected and how is it diagnosed?

It is important to stress that many patients with NAFLD will be overweight or obese, asymptomatic, and have normal liver function test results. As NAFLD may have a benign asymptomatic course and because there is a lack of definitive evidence about effective interventions, there is currently no compelling reason to screen for the condition in an untargeted fashion. NAFLD is typically first suspected when the results of liver function tests, measured as part of routine testing (for example, health checks), are moderately abnormal. The usual observed biochemical pattern in hepatic steatosis due to NAFLD is of increased levels of transaminases, with alanine aminotransferase (ALT) levels exceeding those of aspartate aminotransferase (AST). This classical pattern is particularly useful in differentiating between hepatic steatosis from NAFLD and alcoholic liver injury, with the latter normally associated with a high AST:ALT ratio. With the progression of hepatic steatosis to NASH and associated hepatic fibrosis, however, AST levels increase with a resultant rise in the AST:ALT ratio.¹¹ γ glutamyltransferase (GGT) may also be modestly increased along with the NAFLD pattern for transaminases. Both ALT and GGT have been shown in cross sectional studies to be modestly associated with the

SUMMARY POINTS

Non-alcoholic fatty liver disease (NAFLD) represents a spectrum of liver disease with key stages consisting of hepatic steatosis (NAFL), steatohepatitis (NASH), fibrosis, and eventual cirrhosis

NAFLD affects more than 20% of populations worldwide and most patients with type 2 diabetes mellitus

The risk of progressive liver disease in the earliest stage of NAFLD, hepatic steatosis, is low but patients with NASH are at far higher risk, and hepatic steatosis due to NAFLD is also a major risk factor for the development of type 2 diabetes

Most patients with NAFLD are asymptomatic and the disease is typically suspected based on raised alanine aminotransferase (ALT) levels together with other clinical and biochemical features, or an incidental finding during abdominal ultrasonography

Owing to the slow progression of NAFLD, randomised clinical trials have been unable to identify drugs that conclusively reduce progression to cirrhosis, but sustained weight loss has been shown to improve liver function test results and liver histology and thus lifestyle improvement remains the key intervention

There is no convincing evidence that NAFLD independently increases a patient's cardiovascular risk but there is also no reason to withhold statins in patients with NAFLD who are at high cardiovascular risk unless transaminase levels are more than three times the upper limit of normal

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- ▶ Obstructive sleep apnoea (BMJ 2014;348:g3745)

presence of fatty liver on ultrasonography and with liver fat content as measured by magnetic resonance imaging spectroscopy,¹² whereas AST is not related. Another common way in which NAFLD is identified is by incidental finding of increased hepatic echogenicity on abdominal ultrasonography, when carried out for other reasons such as right upper quadrant abdominal pain. However, ultrasonography has poor sensitivity for diagnosing NAFLD, and many patients with important steatosis on biopsy are not recognised by such imaging,¹³ underlining the imperfect nature of both biochemistry and imaging for identifying NAFLD.

Common forms of presentation of NAFLD

Case 1 (box 1) shows one of the common presentations of NAFLD in which liver function tests have been checked. Although some uncertainty about alcohol intake is often present, this patient’s pattern of an increased ALT level with AST levels less than those for ALT along with other characteristics linked to insulin resistance or higher risk of type 2 diabetes—namely, high body mass index, high triglyceride level, low high density lipoprotein cholesterol level, and high or high normal HbA_{1c} level—strongly suggests the presence of NAFLD, specifically hepatic steatosis. The question of whether ultrasonography of the liver is required to confirm the suspicion is discussed below.

In case 2 (box 2), fatty liver has been identified on abdominal ultrasonography and the clinician must distinguish between NAFLD and alcoholic liver disease. In this case, the patient is adamant about abstinence from alcohol. The clinician had recently checked the patient’s liver function test results and both transaminases were within the normal reference interval, with the ALT level higher than that of AST. Notably, higher ALT and GGT levels within the normal range are associated with a greater risk of type 2 diabetes.¹⁴ Further supportive evidence for the presence of NAFLD in this patient includes the related finding of hypertriglyceridaemia together with a family history of type 2 diabetes, although no formal glycaemia testing had been performed for this patient. Although overweight, the patient was not obese.

How is NAFLD distinguished from alcoholic liver disease?

Hepatic steatosis due to alcohol excess is often associated with an AST:ALT ratio >1.5, unlike non-alcoholic fatty liver disease. Alcohol excess also commonly results in an increased high density lipoprotein cholesterol together with triglyceride levels, which can vary between being normal and vastly increased, even in the same patient, depending on the timing

Box 1 | Typical scenario for identified NAFLD

Case 1

Mr A is seen for cardiovascular risk screening:

- Age 43, body mass index 31 kg/m², 14 units of alcohol per week
- Cholesterol 6.2 mmol/L, triglyceride 3.5 mmol/L, high density lipoprotein cholesterol 0.9 mmol/L
- ALT 62 U/L, AST 38 U/L (normal <50 U/L)
- Blood pressure: systolic 145 mm Hg, diastolic 88 mm Hg
- HbA_{1c} 44 mmol/mol

ALT=alanine aminotransferase; AST=aspartate aminotransferase.

of blood sampling in relation to alcohol intake. This pattern of biochemistry is less consistent with insulin resistance and NAFLD. Some other features can help to distinguish one from the other (table). People may have mixed patterns of biochemistry and both obesity and alcohol related risk factors.

How should suspected or confirmed NAFLD be managed?

Several points require consideration in deciding how to treat patients with NAFLD (figure).

Depending on how NAFLD is first suspected, whether based on abnormal transaminase levels (with AST levels less than those of ALT) or an incidental finding on ultrasonography, additional evidence is often helpful. Details of previous lipid profiles, type 2 diabetes in patients and their families, past results for fasting glucose or HbA_{1c}, alcohol intake, and current weight provide incremental information to help in the diagnosis of NAFLD. Where such information is not available or where lipid profiles or screening tests for type 2 diabetes have not been done in recent years, this medical history should be obtained and the necessary blood tests performed. The patient should be provided with lifestyle advice to aid sustained weight loss and reduce alcohol intake.

Repeating liver function tests in 3-6 months in those with NAFLD on ultrasonography gives patients time to implement lifestyle changes, at which point they can be reassessed by the clinician. Similar or improved results (a reduction in ALT or other metabolic parameters such as body weight, triglyceride, HbA_{1c}) should drive ongoing improvements to lifestyle, whereas deterioration in results can be approached as described below. Screening for type 2 diabetes is particularly important given the close relation between NAFLD and dysglycaemia, as it provides the opportunity to not only potentially identify undiagnosed type 2 diabetes¹⁵ but to also identify those at increased risk, as defined in recent guidelines from the National Institute for Health and Care Excellence.¹⁶

Box 2 | Typical scenario for suspected NAFLD

Case 2

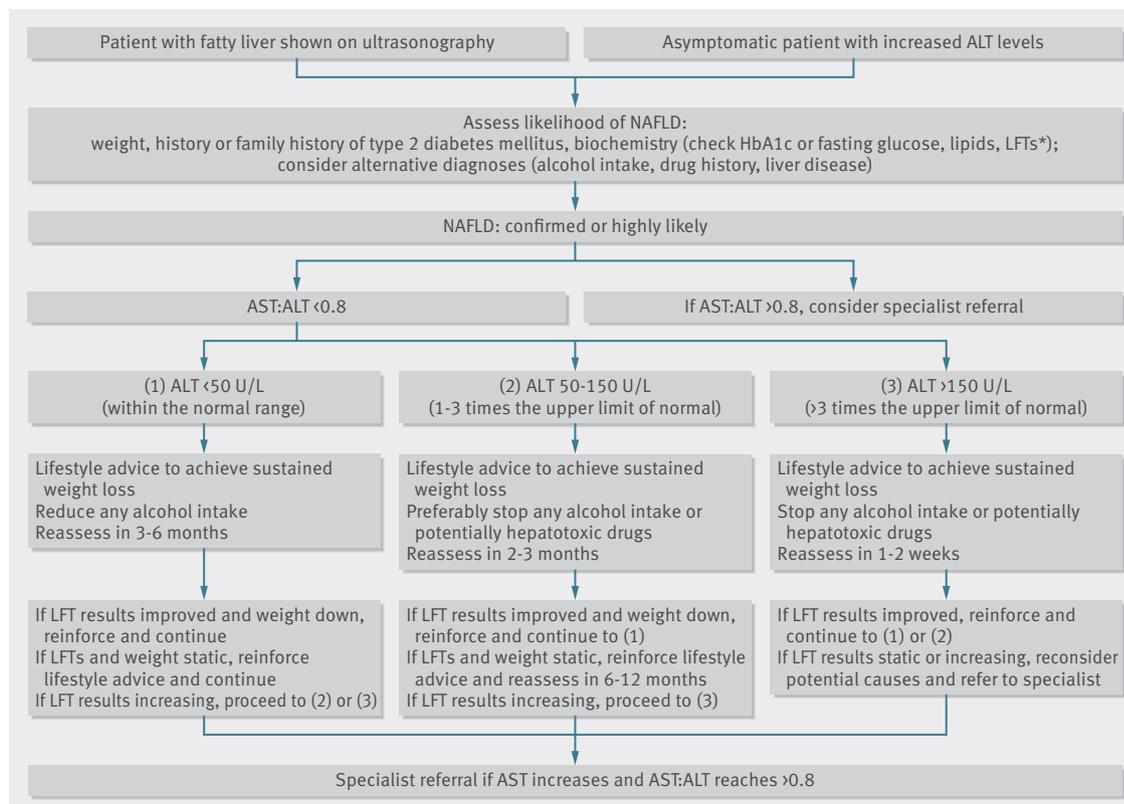
Mrs B is referred for abdominal ultrasonography because of abdominal discomfort:

- Age 56, body mass index 28 kg/m², no alcohol
- Ultrasound findings: increased hepatic echogenicity in keeping with fatty liver
- Family history of type 2 diabetes
- ALT 38 U/L, AST 25 U/L
- Cholesterol 5.2 mmol/L, triglyceride 4.1 mmol/L, high density lipoprotein cholesterol 1.2 mmol/L
- No glycaemia testing ever performed

ALT=alanine aminotransferase; AST=aspartate aminotransferase.

Typical features of non-alcoholic fatty liver disease (NAFLD) and alcoholic liver disease		
Characteristics	NAFLD	Alcoholic liver disease
Body weight	Increased	Variable
Fasting plasma glucose or HbA _{1c}	Increased	Normal
Reported daily alcohol intake	<20 g for women, <30 g for men	>20 g for women, >30 g for men
ALT	Increased or normal	Increased or normal
AST	Normal	Increased
AST:ALT ratio	<0.8 (>0.8 with more advanced disease)	>1.5
GGT	Increased or normal	Considerably increased
Triglycerides	Increased	Variable, may be considerably increased
HDL cholesterol	Low	Increased
Mean corpuscular volume	Normal	Increased

ALT=alanine aminotransferase; AST=aspartate aminotransferase; GGT=γ glutamyltransferase; HDL=high density lipoprotein.



Proposed algorithm for diagnosis and initial management of suspected or confirmed non-alcoholic fatty liver disease (NAFLD) in primary care. ALT=alanine aminotransferase; LFTs=liver function tests; AST=aspartate aminotransferase. *Some biochemistry laboratories only measure one of the transaminases and in such cases it will be necessary to request both ALT and AST tests in relevant patients

Hepatic steatosis due to NAFLD is a risk factor for both type 2 diabetes and NASH, and its occurrence should form a major incentive for improvements to lifestyle.

Where the liver function test results are mildly or moderately raised (transaminases 50-150 U/L (1 to 3 times the upper limit of normal) with AST levels less than those of ALT) and the available information (based on body weight, lipids, HbA_{1c} or glucose, family history of type 2 diabetes, alcohol intake) suggests NAFLD, patients should also be asked to return for repeat liver function tests in 2-3 months, having been advised to reduce any alcohol intake or preferably discontinue it and to pursue lifestyle improvements to sustainably reduce weight. Noticeable increases in transaminases (>150 U/L (>3 times the upper limit of normal) with AST levels less than those of ALT) or the additional increase of alkaline phosphatase (ALP) should heighten awareness of the possibility of other causes and of the potential for progressive liver disease, whether due to NAFLD or another cause. These patients should be seen again within a few weeks for repeat testing and consideration of specialist referral.

Published recommendations for the management of abnormal transaminase levels exist, and this review is not intended to be a comprehensive guide to investigating all abnormal liver function test results. On the basis of the available clinical information, it is important to consider other liver conditions that are treatable or that may have important consequences for family screening such as chronic viral hepatitis, autoimmune liver disease, haemochromatosis, or drug induced liver injury. With the increasing prevalence of obesity it is inevitable that other liver diseases will be present among those

with risk factors for NAFLD. This clinical overlap is sometimes compounded by the presence of mild to moderately raised ferritin and immunoglobulin (predominantly IgA) levels in NAFLD, both of which may reflect on the stage of liver damage in NAFLD without evidence of primary iron overload or autoimmune disease.^{17 18} Coexisting hepatic steatosis is itself a cofactor for the progression of other primary liver diseases.

Although only a few patients with abnormal liver function test results will have serious liver disease requiring immediate treatment, studies have shown that most abnormal results remain so on repeat testing. Therefore appropriate investigation and treatment can be planned when these are first identified.¹⁹

Is ultrasonography needed if NAFLD is strongly suspected?

In most patients with mildly abnormal transaminase levels plus a suggestive biochemical and risk factor profile in keeping with hepatic steatosis due to NAFLD, many clinicians pursue the diagnosis by means of liver ultrasonography. Proponents suggest a low threshold for ultrasonography scans for screening patients with suspected NAFLD.²⁰ However, ultrasonography has several notable limitations: the variability between sonographers; the technical difficulties of scanning obese patients in a robust and reproducible way; the inability to distinguish NASH, which is far more likely to progress to advanced liver disease, from simple steatosis; the lack of an agreed grading system; the huge number of patients potentially requiring ultrasonography, which would overwhelm local services; and the lack of additional treatment options based on the scan result.^{21 22} In our opinion the

additional benefit of routinely requesting liver ultrasonography to diagnose NAFLD in patients with suggestive phenotypic and biochemical features and no features of other liver disease or more advanced liver disease is therefore unproved and highly questionable.

Weight loss and lifestyle improvements are the key goal in NAFLD

Because of the low incidence of progressive liver disease in early NAFLD and the duration required for advanced liver disease to occur, randomised trials of lifestyle improvements and various drugs have necessarily been limited to changes in surrogate markers as their primary outcomes. Therefore, as yet there is no conclusive evidence for any particular treatment approach, and cost effective and non-invasive surrogates that robustly track with later development of cirrhosis are much sought after. For most patients with presumed or confirmed NAFLD, the key is to offer lifestyle advice that can lead to sustained weight loss. A recent systematic review of 23 studies evaluating the effect of diet or physical activity in adult populations with NAFLD showed that these lifestyle modifications consistently reduced liver fat and improved glucose control and insulin sensitivity.²³ Limited data suggest that lifestyle interventions may also yield benefits for liver histology. Should glycaemia testing confirm type 2 diabetes or show that a patient is at high risk of its development, then lifestyle advice is recognised to be critical to the management of these patients as per universal guidance for the disease,²⁴ and here it may have a dual benefit. General advice on healthy eating and increasing levels of physical activity can be delivered in primary care, or specialist settings where required. Patients can also be encouraged to attend a commercial weight loss programme of their choice. Recent evidence from a randomised trial shows that commercial weight loss programmes perform potentially better than advice given by the National Health Service in achieving weight loss.²⁵ Should ALT and GGT levels decline along with weight reduction, these encouraging results should be shared with patients as further incentive to sustain their lifestyle improvements. Numerous trials of drug treatments, such as metformin, pioglitazone, vitamin E, and statins have failed to deliver conclusive evidence of reductions in clinically

TIPS FOR NON-SPECIALISTS

In patients with raised alanine aminotransferase (ALT) or γ glutamyltransferase (GGT) levels or with hepatic steatosis noted on ultrasonography, non-alcoholic fatty liver disease (NAFLD) should be suspected in those with risk factors (increased body weight, raised fasting glucose or HbA1c, modestly raised triglycerides, low high density lipoprotein cholesterol, and AST:ALT ratio <0.8) and with daily alcohol intake <20 g in women and <30 g in men

Patients with or suspected of having NAFLD should be screened for type 2 diabetes and, in the absence of type 2 diabetes, patients with NAFLD should be given preventive advice whether or not they fall into the high diabetes risk category

Cardiovascular risk in NAFLD should be calculated using the usual risk scores

There should be no hesitation in recommending statins for patients with NAFLD who are at increased cardiovascular risk unless their transaminase levels are more than three times the upper limit of normal

Routine liver ultrasonography is not required in most patients with suspected NAFLD

Patients with suspected or confirmed NAFLD should be given lifestyle advice on sustainable weight reduction and, because obesity and alcohol may act synergistically to promote liver disease, a reduction in alcohol intake should also be strongly advised

Referral to a gastroenterologist should be considered in patients with features of NAFLD, in whom other significant liver disease has been excluded and whose AST:ALT ratio reaches >0.8 owing to increasing AST levels

significantly progression of liver disease, although some studies have yielded improvements in surrogate markers.²⁶

Does NAFLD indicate that patients are at increased cardiovascular risk?

Undoubtedly NAFLD is often accompanied by classical cardiovascular risk factors including, but not limited to, type 2 diabetes and low levels of high density lipoprotein cholesterol. This has driven a plethora of observational studies linking markers of NAFLD (including ALT and GGT, fatty liver on ultrasonography, steatosis on liver histology) to cardiovascular surrogate markers and cardiovascular outcomes.²⁷ While some studies have found associations between these NAFLD surrogates and cardiovascular risk, many have been limited by inadequate adjustment for established cardiovascular risk factors.²⁸ Crucially, for NAFLD to be considered as a truly important and independent risk factor, it will need to show clinically meaningful improvements in cardiovascular risk prediction when added to calculators that already include these established risk factors.²⁹ No such evidence yet exists. Importantly, our suggested approach for evaluating the likelihood of NAFLD provides much of the information needed to calculate cardiovascular risk using established risk calculators. Therefore, current evidence suggests that cardiovascular risk should be calculated using the usual available tools without consideration of the presence or absence of NAFLD.

What if patients are already using a statin or require a statin based on cardiovascular risk?

Given that many patients with NAFLD will have risk factors for cardiovascular disease, many will already be taking

ADDITIONAL EDUCATIONAL RESOURCES

Resources for healthcare professionals

British Society of Gastroenterology

(www.bsg.org.uk/clinical/commissioning-report/nash-and-non-alcoholic-fatty-liver-disease.html)

—a source of information for clinicians on background, current practice, and recommended practice for NAFLD in the United Kingdom

American Association for the Study of Liver Diseases, American College of Gastroenterology, and the American Gastroenterological Association

(<http://gi.org/clinical-guidelines/clinical-guidelines-sortable-list/>)

—a comprehensive American guideline on all aspects of NAFLD

Resources for patients

National Health Service

(www.nhs.uk/conditions/fatty-liver-disease/pages/introduction.aspx)

—comprehensive source of information for patients on NAFLD, its stages, and sensible lifestyle modifications

American College of Gastroenterology (<http://patients.gi.org/topics/fatty-liver-disease-naflD/>)

—a source of patient information on the causes, risk factors, investigation, and treatment of NAFLD

All the websites are free to access and do not require registration

QUESTIONS FOR FUTURE RESEARCH

Are there non-invasive surrogates for progression to advanced liver disease (fibrosis, cirrhosis) that can be robustly applied in future trials in non-alcoholic fatty liver disease (NAFLD)?

What simple algorithms can be developed that effectively predict the presence of or progression to progressive liver disease?

Is NAFLD an independent predictor of cardiovascular disease after established risk factors have been fully accounted for?

a statin or may require statin treatment because of their increased cardiovascular risk. Statin treatment, including high potency statin treatment, is safe in the presence of NAFLD and should not be avoided because of mild to moderately raised transaminase levels (up to three times the upper limit of normal).³⁰ Indeed, preliminary evidence from the Greek Atorvastatin and Coronary Heart Disease Evaluation study suggests that those with increased transaminase levels (up to three times the upper limit of normal) may derive an even greater cardiovascular benefit from statins.³¹ Robust evidence for the safety of statins in those with NAFLD and transaminases over three times the upper limit of normal is lacking and statin treatment is probably best avoided in such people unless recommended after specialist hepatology review. In those with moderately abnormal liver function test results (<150 U/L (<3 times the upper limit of normal)) at the time of starting statins, it is prudent to redo the tests one or two months after the start of statin treatment.

When should patients with confirmed or suspected NAFLD be referred to a gastroenterologist?

Given the high prevalence of NAFLD coupled with the low risk of progressive liver disease in most people with simple steatosis, only those considered to be at high risk of progressive liver disease should be referred to secondary care for further evaluation. Several risk scores have been developed for the assessment of NAFLD severity.³²⁻³³ The NAFLD fibrosis score seems to be the most accurate in comparative studies, but it is not readily calculable and a large proportion of patients have indeterminate results. A simpler score, FIB-4, seems to be of similar accuracy but it still requires clinicians to carry out some form of electronic calculation. The simplest instrument is the BARD score, which places a heavy weighting on the AST:ALT ratio, with a value >0.8 considered to be associated with advanced fibrosis. Indeed an AST:ALT ratio

>0.8 on its own has been found to perform well as an indicator of more severe liver disease.³³ In this study, the AST:ALT ratio provided the best negative predictive value for advanced fibrosis and also demonstrated good diagnostic accuracy with a C statistic of 0.83 which was comparable to or better than results for more complex scores, where C statistics ranged from 0.67 to 0.86.

In practical terms, patients with features of NAFLD in whom other major liver disease has been excluded and whose AST:ALT ratio is increasing to >0.8 as a result of a rising AST level should be considered at risk of progressive liver disease and referred for further evaluation. In addition, we would suggest that patients with ALT or AST levels more than three times the upper limit of normal or with abnormal ALP levels should be considered for specialist referral. Development of other clinical or laboratory features of advanced liver disease or portal hypertension, such as the appearance of spider naevi or unexplained thrombocytopenia, would warrant specialist referral.

Liver ultrasonography and assessment of the severity of NAFLD using more specific severity scoring, serological assessment of fibrosis, or measurement of liver stiffness (transient elastography or acoustic radiation force imaging), can be performed in a secondary care setting. Liver biopsy may be required to clarify the severity of the underlying liver disease but even this “definitive” investigation is subject to considerable variability.³⁴ Recognition of those patients with more advanced liver disease or at risk of progressive liver damage allows appropriate monitoring; in particular patients with cirrhosis can be entered into surveillance programmes for hepatocellular carcinoma and the presence of oesophago-gastric varices.

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References are in the version on bmj.com.

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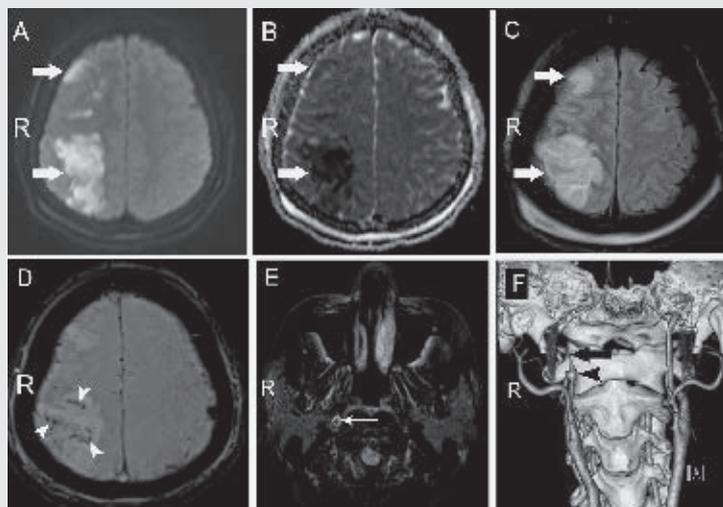


Fig 2

PICTURE QUIZ

Focal neurological deficits after trauma

- 1 Brain diffusion weighted magnetic resonance imaging (DWI) (fig 2A) and the corresponding apparent diffusion coefficient (ADC) map (fig 2B) and fluid attenuated inversion recovery sequence (fig 2C) susceptibility weighted MRI (fig 2D) show acute ischaemic infarcts in the right frontoparietal region with petechial haemorrhage (fig 2C). In addition, there is right cervical internal carotid artery dissection (fig 2D-1F) with pseudoaneurysm (fig 2F).
- 2 Traumatic right cervical carotid artery dissection resulting in acute ischaemic infarction in the corresponding arterial distribution.
- 3 Maintenance of airway, breathing, and circulation; prevention of hypotension, swallow assessment and care, prophylaxis for deep venous thrombosis; gentle physiotherapy; bowel, bladder, and skin care; and antithrombotic treatment for three to six months for secondary prevention of ischaemic stroke.

STATISTICAL QUESTION What are randomised consent designs?

The randomised consent design used in the above trial is best described as a single consent one (answer b).