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Dr Margaret G Keane
BSc(Hons) MBBS MRCP
Clinical Research Fellow in Gastroenterology and Hepatology

Ms Cindy Lai
BSc
Fourth year medical student

Dr Stephen P Pereira
BSc(Hons) PhD FRCP
Reader in Hepatology and Gastroenterology UCL Institute for Liver and Digestive Health, University College London, London, UK

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AUTHORS
Dr Margaret G Keane
BSc(Hons) MBBS MRCP
Clinical Research Fellow in Gastroenterology and Hepatology

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Dr Stephen P Pereira
BSc(Hons) PhD FRCP
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UCL Institute for Liver and Digestive Health, University College London, London, UK

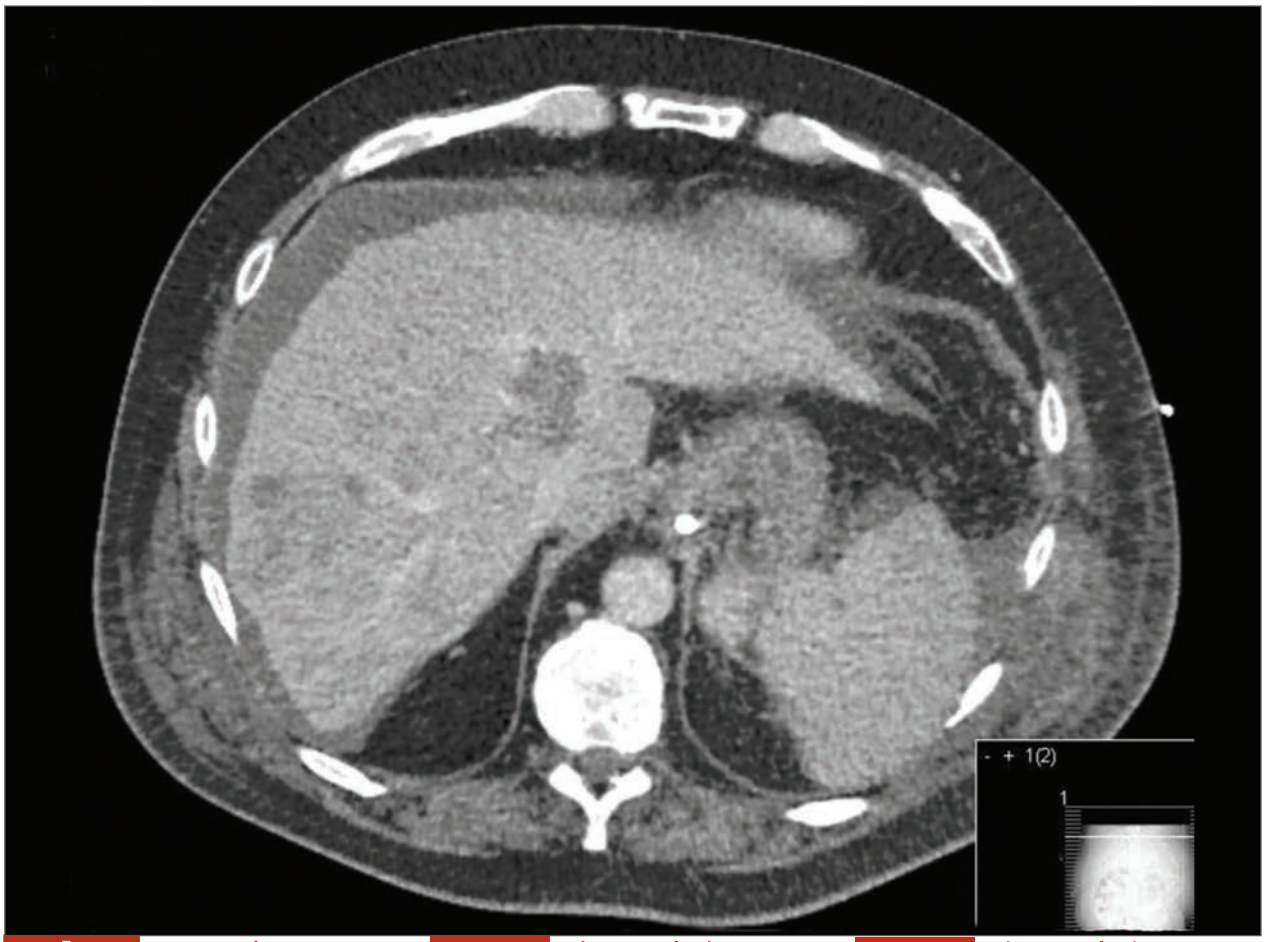


FIGURE 1
CT scan of a patient with a cirrhotic liver containing a multifocal hepatocellular carcinoma

What are the causes of cirrhosis?

CIRRHOSIS IS A CONDITION THAT ARISES AS A RESULT OF CHRONIC LIVER DAMAGE, TYPICALLY OVER many years. It is characterised by fibrosis and nodularity of the liver parenchyma. Cirrhosis interferes with the normal functions of the liver, reducing its ability to produce proteins (reduced hepatic synthetic function), which in turn can lead to coagulopathy, low serum albumin and raised bilirubin levels.

Chronic liver disease affects 30,000 people in the UK with 7,000 new diagnoses made each year. Incidence is rising steeply, between 1992 and 2001 there was a 45% increase in the incidence of cirrhosis in the UK.[1] This was primarily attributed to increasing levels of alcohol consumption and obesity.[2]

Mortality from cirrhosis is also rising; between 1993 and 2000 the British Society of Gastroenterology (BSG) reported that mortality from cirrhosis doubled to a rate of 12.7 per 100,000 population in 2000. In 2010, there were 5,631 deaths from the complications of liver cirrhosis. During this period, mortality from cirrhosis in women also increased steeply (a 46% increase in Scotland and 44% increase in England and Wales).[3]

The prevalence of cirrhosis is also more common in the most deprived populations in England and Wales. This is thought to be due to a higher prevalence of risk factors for cirrhosis in this cohort (excess alcohol consumption, obesity, chronic viral hepatitis). The greatest inequalities were in those aged 25-44 years, with relative risks of 4.73 (95% CI:4.00-5.59) and 4.24 (95% CI:3.50-5.13) for men and women respectively, when »

How should patients be investigated?

How should patients be monitored?

comparing the most to the least deprived quintiles. Urban areas had higher alcohol-related mortality rates than rural areas.[2,4]

COMMON CAUSES OF CHRONIC LIVER DISEASE

The causes of chronic liver disease in adults are wide ranging. Common causes include alcohol, non-alcoholic fatty liver disease and chronic viral hepatitis (B and C). Less common causes include autoimmune liver diseases e.g. autoimmune hepatitis, primary biliary cirrhosis or primary sclerosing cholangitis, genetic conditions e.g. α–1 antitrypsin disease and Wilson's disease, secondary biliary cirrhosis, Budd–Chiari syndrome or veno-occlusive disease, prolonged exposure to certain toxins or drugs e.g. amiodarone, isoniazid, methotrexate, and chronic right-sided heart failure, see table 1, left.

Table 1

Causes of cirrhosis in adults[37]

Common

- Excess alcohol consumption
- Hepatitis B (± delta)
- Hepatitis C
- Non-alcoholic fatty liver disease

Less common

- Autoimmune hepatitis
- Primary biliary cirrhosis
- Secondary biliary cirrhosis
- Primary sclerosing cholangitis
- Haemochromatosis
- Wilson's disease
- Alpha-1–antitrypsin deficiency
- Cystic fibrosis
- Drugs: methotrexate, isoniazid and amiodarone
- Right-sided heart failure, tricuspid regurgitation, pericarditis
- Veno-occlusive disease: Budd-Chiari syndrome

PRESENTATION

Nearly half of patients with cirrhosis are asymptomatic.[5] As a result the condition may only be discovered incidentally as a result of abnormalities in liver function tests or imaging of the abdomen, performed for other reasons.

Alternatively patients may present with signs and symptoms of the complications of cirrhosis e.g. jaundice, ascites, variceal bleeding, hepatic encephalopathy or hepatocellular carcinoma (see below) or non-specific symptoms of chronic disease e.g. fatigue or weight loss.

Detecting patients with cirrhosis in primary care usually relies on identifying common risk factors that are associated with the development of cirrhosis. In the UK, the most common risk factors include excess alcohol consumption and obesity.[2] Worldwide, most cases of cirrhosis are caused by chronic viral hepatitis (B or C).[6]

'Liver function tests correlate poorly with the presence of liver fibrosis or cirrhosis'

There is marked geographical variation in the frequency of risk factors for cirrhosis in the UK. The NHS Atlas of Variation in Healthcare for People with Liver Disease found that the highest rates of hospital admission for end-stage liver disease caused by chronic hepatitis C virus were in central London and the North West of England. Admissions for alcohol-related liver disease were also most common in the North West.[7]

Assessment

Currently, there are no standard criteria for the investigation of patients with suspected cirrhosis and significant variation exists between different clinical commissioning

Table 2

Common non-invasive serum markers of fibrosis

Serum marker panels of fibrosis	Test components	Conditions in which test has been applied	Sensitivity (> F2)	Specificity (> F2)
Enhanced liver fibrosis (ELF) test[39,40]	Hyaluronic acid, N-terminal propeptide of type III collagen, tissue inhibitors of matrix metalloproteinase-1	HCV, HBV ALD, NAFLD PBC	87-90%	27-77%
FIBROSpect II[14]	Hyaluronic acid, tissue inhibitors of matrix metalloproteinase-1, alpha 2-macroglobulin	HCV NAFLD	70–83%	66–79%
FibroTest/FibroSure[41]	γ2-macroglobulin, γ2-globulin, γ-globulin, apolipoprotein A1, γ glutamyl transferase, total bilirubin	HCV	75%	85%
Fib-4[42]	(Age x AST)/((platelet count) x $(ALT)^{1/2}$)	NAFLD, HCV ± HIV	70%	97%
Serum hyaluronic acid level, serum AST and albumin level (SHASTA) index[15]	Hyaluronic acid, AST, albumin	HCV HIV+HCV	100%	52%
Aspartate aminotransferase to platelet ratio index (APRI)[43]	(AST elevation/platelet count) x 100	HCV, HCV+HIV NAFLD	76%	72%
NAFLD fibrosis score[44,45]	Age, body mass index, blood glucose levels, aminotransferase levels, platelet count, and albumin	NAFLD	77%	71%
Hepascore[46]	Age, gender, bilirubin, GGT, hyaluronic acid, γ2-macroglobulin	HCV ALD	63%	89%
BARD score[47]	BMI, AST:ALT ratio, type 2 diabetes	NAFLD	85%	67%

Key: HCV = hepatitis C virus; HBV = hepatitis B virus; ALD = alcoholic liver disease; NAFLD = non-alcoholic fatty liver disease; PBC = primary biliary cirrhosis; HIV = human immunodeficiency virus; F2 = fibrosis ± septal growth of most portal areas on liver biopsy (see table 5, p18)

Table 3

Laboratory test findings for some of the common causes of cirrhosis

Aetiology	Laboratory test findings	Specific treatments
Alcohol	AST:ALT >2 Raised γGT Raised MCV	Abstinence
Non-alcoholic fatty liver disease	Low HDL cholesterol Raised glucose Raised triglycerides	Low calorie diet, diet and exercise
Hepatitis B	HBsAg (+ve) HBV-DNA (+ve)	Antivirals
Hepatitis C	Anti-HCV HCV-RNA (+ve)	Antivirals
Autoimmune hepatitis	ANA (+ve) ASMA (+ve)	Prednisolone, azathioprine
Primary biliary cirrhosis	Cholestatic LFTs AMA (+ve)	Ursodeoxycholic acid
Primary sclerosing cholangitis	Cholestatic LFTs	
Haemochromatosis	Raised ferritin Transferring saturation index (> 45%) Raised liver iron content HFE gene mutation	Phlebotomy, deferoxamine
Wilson's disease	Low ceruloplasmin Low serum copper Raised 24-hour urine copper excretion	Penicillamine, zinc

groups and individual practices.[8] Guidelines are currently being developed for primary care to standardise the investigation of patients with suspected cirrhosis and to define criteria for referral to secondary care.[9] Guidelines will also attempt to standardise methods used in secondary care to diagnose and assess the severity of cirrhosis and to define referral criteria to tertiary care e.g. for assessment for liver transplant.[9]

If a patient is suspected of having cirrhosis, most GPs will arrange for blood tests and an ultrasound of the liver to be performed.

Blood tests

Abnormal liver function tests (LFTs) are a common finding in primary care. However, they can be elevated for many reasons and correlate poorly with the presence of liver fibrosis or cirrhosis e.g. alanine amino transaminase (ALT) is only elevated in 1–4% of asymptomatic patients with cirrhosis.[10]

In 2001, a national audit of the management of patients with abnormal LFTs (twice the upper limit of normal reference range) in UK primary care was performed:

- 62% of patients had an identifiable diagnosis requiring hospital intervention or follow-up
- 18% of patients were not appropriately followed up
- 11% had undetected major liver disease which would have benefitted from specialist review.[8]

Ultrasound

Ultrasound is an excellent first-line investigation in patients with suspected liver disease. It can detect more than 90% of gallstones.[11] It can also differentiate between solid and cystic lesions within the liver parenchyma. IV contrast (microbubble agents) and/or Doppler can further improve overall sensitivity. Ultrasound also has a high sensitivity (91%) and specificity (94%) for the detection of cirrhosis.[12]

Table 4

Child-Pugh score

Score	1	2	3
Bilirubin (mg/dl)	< 2	2-3	>3
Prothrombin time (INR)	< 4s (< 1.7)	4-6s (1.7–2.3)	> 6s (> 2.3)
Albumin (g/dl)	> 3.5	2.8–3.5	< 2.8
Ascites	Absent	Mild	Severe
Encephalopathy	Absent	Mild	Severe

The Child-Pugh score ranks the severity of cirrhosis into three classes. A score of ≤6 defines the patient as class A, 7 to 9 as class B, and ≥10 as class C. Class A is associated with a 3-year survival of 73%, Class B 59% and Class C 46%[38]

Non-invasive markers of cirrhosis

The gold standard test for the diagnosis of cirrhosis remains a liver biopsy, however this is only available in secondary care and is associated with complications such as sub-capsular haemorrhage in up to 1% of cases. Non-invasive serum markers of cirrhosis are currently being investigated as an alternative method of stratifying referrals to secondary care, see table 2, p16.

'Ultrasound has a high sensitivity and specificity for the detection of cirrhosis'

Currently, if any combination of these initial investigations is suggestive of chronic liver disease, referral to secondary care is advised. The referral should be arranged urgently if the patient displays signs of decompensation e.g. variceal bleeding, jaundice, significant ascites, hepatic encephalopathy.

For patients with stable disease awaiting a routine appointment, many GPs will begin to investigate the cause of the liver disease by sending a non-invasive liver screen in addition to the investigations above, as this may inform specific treatment, see table 3, above.

GRADING THE SEVERITY OF CHRONIC LIVER DISEASE

Severity of chronic liver disease can be assessed clinically or pathologically. Staging of liver fibrosis is an important predictor of prognosis and is necessary to guide management.

Clinical scoring systems

Commonly used scores include the Child-Pugh score, see table 4, left, or the Model for End Stage Liver Disease (MELD) score (www.mdcalc.com/meld-score-model-for-end-stage-liver-disease-12-and-older/)

Biopsy

A liver biopsy remains the gold standard investigation for diagnosis »

Table 5

Histological assessment of fibrosis

Metavir grade	Ishak stage	Histological findings
F0	0	Normal liver
F1	1	Presence of fibrosis ± septal growth within some of the portal areas
F2	2-3	Presence of fibrosis ± septal growth of most portal areas Ishak stage 3 is differentiated by the presence of occasional portal-to-portal bridging fibrosis
F3	4-5	Fibrous expansion of portal areas with marked portal-to-portal and portal-to-central bridging fibrosis Ishak stage 5 is defined by the presence of occasional nodules
F4	6	Cirrhosis

and assessment of the severity of chronic liver disease. Chronic liver disease is characterised histologically by fibrosis and nodule formation. The severity of chronic liver disease is graded pathologically by the Metavir or Ishak staging systems, see table 5, above. A liver biopsy samples less than 1/50,000 of the liver parenchyma,[13] so sampling errors are possible. In addition, liver biopsy is disliked by patients and is relatively expensive, making serial measurements challenging.

Novel non-invasive markers

Because of the limitations of liver biopsy, there has been growing interest in the development of non-invasive markers to diagnose liver fibrosis and assess severity. The majority of these tests have been developed in the past decade and are subject to ongoing validation studies, but are beginning to be incorporated into routine diagnostic algorithms and clinical guidelines for the management of chronic liver disease.

Serum markers

Non-invasive serum markers of fibrosis are broadly divided into direct and indirect markers.

Direct biomarkers such as FIBROSpect II, [14] SHASTA index,[15] and the ELF panel [16] include products of extracellular matrix synthesis or degradation, or cytokines and chemokines associated with fibrogenesis e.g. procollagen types I and III, hyaluronic acid and tissue inhibitors of metalloproteinase.

Indirect markers e.g. APRI,[17] FibroTest/FibroSure,[18] and Hepascore[19] use alterations in markers of hepatic function rather than fibrogenesis e.g. serum aminotransferase levels, platelet count, INR, GGT, bilirubin, alpha-2-macroglobulin, and alpha-2-globulin (haptoglobin). Many of the tests within indirect algorithms are routine blood tests and are therefore easier to incorporate into everyday clinical practice. The more complex algorithms are becoming increasingly available through online calculators.

When interpreting these tests it is recognised that they may be falsely elevated by extra-hepatic inflammatory activity. Alternatively significant fibrogenesis may go undetected if there is minimal hepatic inflammation. Overall these markers are becoming increasingly reliable at detecting fibrosis although they correlate poorly with the stage of fibrosis.

Transient ultrasound elastography[20]

Transient ultrasound elastography (Fibroscan) measures fibrosis by placing an ultrasound probe on the liver. A pulse generator contained within the probe produces a shear wave, which spreads through the liver tissue and is detected by pulse wave ultrasound imaging. The shear wave velocity is measured and correlates with the level of fibrosis.

A measurement > 7 kPa is indicative of significant fibrosis (Metavir grade F2-F4) and > 11-14 kPa is consistent with cirrhosis, see table 5, left.

Compared with a standard biopsy, the Fibroscan will assess a much larger proportion of the liver and is therefore associated with fewer sampling errors. The measurements are painless and quick and as a consequence serial measurements for monitoring treatment response e.g. in chronic viral hepatitis, are feasible and acceptable to patients. Although reproducibility is generally very good, intraobserver variation still exists and its sensitivity is reduced in obese patients or those with significant ascites.

Acoustic radiation force impulse (ARFI)[21] is a further ultrasound-based tool, similar to Fibroscan that can also be used to measure liver stiffness.

POTENTIAL COMPLICATIONS

The following conditions are potential complications of chronic liver disease:

- **Variceal bleeding:** Oesophageal varices develop as a result of portal hypertension. They are present in a third of patients with compensated cirrhosis and two thirds of those with decompensated cirrhosis at diagnosis.[22] Oesophageal varices have a risk of bleeding of approximately 25% at two years.[23] The average mortality of the first episode of variceal bleeding in most studies is up to 50%.[24] Therefore variceal screening and surveillance is recommended in all patients with cirrhosis.
- **Ascites:** A common feature of cirrhosis and a further consequence of portal hypertension and activation of the renin angiotensin aldosterone system. Complications of ascites include spontaneous bacterial peritonitis and hepatorenal syndrome.
- **Hepatic encephalopathy:** At any point, a third of patients with cirrhosis will have evidence of overt hepatic encephalopathy (HE) and nearly all others will have minimal HE. Patients with cirrhosis have an annual risk of developing overt HE of around 20%.[25]
- **Anaemia, thrombocytopenia and coagulopathy:** Anaemia is common in cirrhosis and may result from folate deficiency, haemolysis, chronic blood loss or hypersplenism. Thrombocytopenia is usually secondary to hypersplenism. Coagulopathy results from decreased

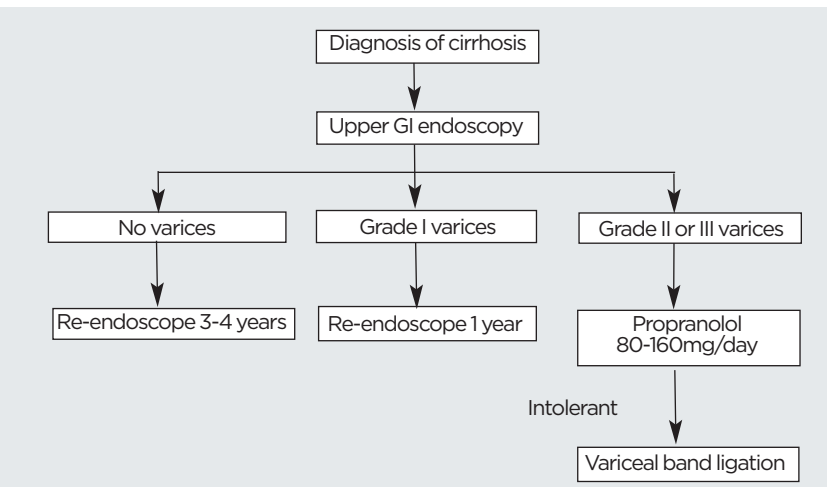


FIGURE 2
BSG proposed algorithm for variceal surveillance and primary prophylaxis [31]

Table 6

Risk factors for the development of hepatocellular carcinoma

Age	> 60[48]
Sex	Male sex[48]
Chronic viral hepatitis (B and C)	Worldwide approximately half of cases of HCC are attributed to hepatitis B and a third to hepatitis C[48] Co-infection with HIV further increases the risk of HCC[49]
Cirrhosis	One third of cirrhotic patients will develop HCC during their lifetime[50]
Alcohol	Excessive alcohol consumption is a risk factor for HCC independent of cirrhosis[48,51]
Metabolic syndrome	Diabetes, obesity and fatty liver[51,52]
Smoking	Smoking[51,53]
Haemochromatosis	Up to half of patients with untreated iron overload will develop HCC in their lifetime, although most patients will be non-cirrhotic at diagnosis[54]
Toxins	Aflatoxin B,[55] anabolic steroids[56]
Genetic predisposition	BRCA1/BRCA2/EGF gene[57,58]

hepatic production of coagulation factors.

- **Hepatocellular carcinoma:** Screening and surveillance is recommended as outlined below.

COMPENSATED CIRRHOSIS

Important management considerations for patients with compensated primary cirrhosis in primary care are detailed below.

Surveillance for hepatocellular carcinoma

Hepatocellular carcinoma (HCC) is a major complication of cirrhosis. HCC is often asymptomatic until late in the disease. Surveillance by six monthly ultrasonography has been associated with detection at an earlier stage, increased likelihood of receiving active treatment and longer overall survival.[26] High-risk individuals should therefore be monitored closely within surveillance programmes. Currently the European Association for the Study of the Liver (EASL) recommends HCC surveillance in the following:

- Cirrhotic patients, Child-Pugh stage A and B, see table 4, p17
- Cirrhotic patients, Child-Pugh stage C, see table 4, p17, awaiting liver transplantation
- Non-cirrhotic hepatitis B carriers with active hepatitis or family history of HCC
- Non-cirrhotic patients with chronic hepatitis C and advanced liver fibrosis

The BSG and EASL recommend surveillance should be performed by abdominal ultrasound every six months.[27] In addition the BSG guidelines on HCC, published in 2003, recommend that surveillance ultrasound should be combined with measuring serum alpha fetoprotein (AFP).[28] However, only 10-20% of small tumours will have an abnormal AFP level and its overall role in surveillance is debated.[28, 29]

In general, surveillance guidelines are poorly followed even in large centres.[26, 30] Reviewing cirrhotic patients in primary care therefore provides a valuable opportunity to ensure they have undergone recent HCC surveillance.

Variceal surveillance and primary prophylaxis

It is recommended that all patients diagnosed with cirrhosis should undergo variceal screening by diagnostic gastroscopy. Further surveillance is determined by endoscopic findings. In patients without varices, BSG guidelines published in 2000 recommend repeat endoscopy every 3-4 years.[31]

Primary prophylaxis with propranolol is indicated for all patients with grade 3 varices irrespective of the severity of the liver disease and those with grade 2 varices and Child-Pugh class B or C disease, see figure 2, p18. However, beta-blockers are recognised to have a deleterious effect on survival in patients with cirrhosis and significant hypotension or refractory ascites and are generally omitted in these situations.[32]

Nutrition

Malnutrition is present in 65-90% of patients with chronic liver disease. Despite being a common clinical finding it is frequently underdiagnosed and undertreated. Malnutrition can precipitate decompensation and overall nutritional state is recognised to be an important predictor of survival in cirrhosis.[33, 34]

In the UK, the Malnutrition Universal Screening Tool (MUST) developed by the Malnutrition Advisory Group of the British Association of Parenteral and Enteral Nutrition (BAPEN) is commonly used to screen for malnutrition in all healthcare settings.[35] The screening tool is composed of the patient's body mass index (BMI), weight loss score and acute disease effect score. In patients with cirrhosis, results of this tool should be interpreted with caution as patients with ascites or oedema will have an artificially elevated BMI.

Specific nutrition screening tools for cirrhotic patients in secondary care are being developed and validated and may supersede the use of MUST as a screening tool for malnutrition in inpatients with cirrhosis.[36] Blood tests e.g. serum protein or albumin are also of limited use in screening for malnutrition in patients with cirrhosis and are a much better predictor of severity of liver disease than malnutrition.

CONCLUSIONS

Chronic liver disease is an increasingly common clinical finding in primary care. Improved non-invasive markers are becoming more widely available to aid the stratification of patients and to guide referrals to secondary care.

Reviewing compensated cirrhotic patients in primary care provides an opportunity to ensure patients are under regular surveillance for HCC, and oesophagogastric varices.

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key points

SELECTED BY
Dr Peter Saul
GP, Wrexham and Associate GP Dean for North Wales

Cirrhosis is a condition that arises as a result of chronic liver damage, typically over many years. It is characterised by fibrosis and nodularity of the liver parenchyma. Cirrhosis interferes with the normal functions of the liver, reducing its ability to produce proteins, which can lead to coagulopathy, low serum albumin and raised bilirubin.

The incidence of cirrhosis is rising in the UK, this can primarily be attributed to increasing levels of alcohol consumption and obesity. Mortality from cirrhosis is also rising. The prevalence of cirrhosis is more common in the most deprived populations in England and Wales. Common causes of chronic liver disease include alcohol, non-alcoholic fatty liver disease and chronic viral hepatitis.

Nearly half of patients with cirrhosis are asymptomatic. As a result the condition may only be discovered incidentally as a result of abnormalities in liver function tests or imaging of the abdomen performed for other reasons. Alternatively patients may present with signs and symptoms of the complications of cirrhosis e.g. jaundice, ascites, variceal bleeding, hepatic encephalopathy or hepatocellular carcinoma. Detecting patients with cirrhosis in primary care usually relies on identifying common risk factors.

Currently, there are no standard criteria for the investigation of patients with suspected cirrhosis. If a patient is suspected of having cirrhosis, most GPs will arrange for blood tests and an ultrasound of the liver to be performed. The gold standard test for the diagnosis of cirrhosis remains a liver biopsy, however this is only available in secondary care and is associated with complications such as sub-capsular haemorrhage in up to 1% of cases. If any combination of these initial investigations is suggestive of chronic liver disease, referral to secondary care is advised.

The severity of chronic liver disease can be assessed clinically or pathologically. Staging of liver fibrosis is an important predictor of prognosis and is necessary to guide management. Variceal bleeding, ascites, hepatic encephalopathy, anaemia, thrombocytopenia, coagulopathy and hepatocellular carcinoma are potential complications of chronic liver disease. Malnutrition is present in 65-90% of patients with chronic liver disease and is frequently underdiagnosed and undertreated. Malnutrition can precipitate decompensation and overall nutritional state is recognised to be an important predictor of survival in cirrhosis.

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British Liver Trust
www.britishlivertrust.org.uk

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www.basl.org.uk