Liver transplantation: need, indications, patient selection and pre-transplant care

ABSTRACT

Chronic or acute liver failure and primary liver cancers can be effectively managed with liver transplantation. The range of indications for liver transplantation is increasing but there is a mismatch between the numbers of available donations and current needs. Specific criteria for listing patients exist but, at minimum, the predicted mortality without transplantation must exceed that with transplantation, coupled with a 50% predicted 5-year survival following liver transplantation. The risk posed by liver disease must be weighed against the risk of liver transplantation, considering the patient's comorbidities, age, nutritional status and behavioural factors in a complex assessment process. This article reviews current UK practice in the selection and care of patients being assessed for liver transplantation.

Liver transplantation is indicated in patients with advanced chronic liver disease, fulminant (sub) acute liver failure and primary liver cancer. Advanced liver disease has a poor prognosis without transplantation: refractory ascites is associated with 50% mortality at 1 year (Moreau et al, 2004) and decompensated liver disease has a median survival of 2 years and 25% survival at 5 years (D'Amico et al, 2006). Survival for adults following liver transplantation in the UK is 92% at 1 year and 80% at 5 years for elective transplantation and 90% and 80% respectively for super-urgent liver transplantation (Martin et al, 2015), offering patients a considerable survival benefit. However, despite the benefits of liver transplantation there is also considerable mortality and morbidity, so patient selection is crucial.

Increasing need and limited availability

Liver transplantation numbers are rising but the need is increasing more rapidly: 882 liver transplants were performed in the year to 2015 between the seven UK centres, rising from fewer than 700 per annum in the mid 2000s. However, the number of patients waiting for liver transplantation in the UK more than doubled between 2008 and 2015 with over 500 adult patients currently on the waiting list (Martin et al, 2015). The rise in liver transplantation numbers has been enabled by increasing use of livers from donors with cardiac death and a minimal increase in donations from donors with brain death. Owing to the current shortage of suitable donor livers, 2 years after joining the list 20% of adult patients will have died or been removed from the waiting list and 4% will still be waiting for transplantation (Martin et al, 2015).

Despite the relative scarcity of suitable donations the population requiring liver transplantation will continue to grow. Liver disease is increasing in prevalence (Williams et al, 2015) and many patients who may benefit from liver transplantation are not currently being assessed. A significant proportion of cirrhotic patients are never assessed for transplantation despite this treatment having the potential to offer greatest benefit. Many unassessed patients are correctly not referred as a result of comorbidities or other absolute contraindications, but there is likely a significant unmet need for liver transplantation in the UK and the scarcity of donations is a major barrier to the transplant programme.

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Indications for liver transplantation

For liver transplantation to be in a patient's interests predicted survival following liver transplantation must exceed that without liver transplantation. Furthermore, under current UK guidance, patients should have a predicted 5-year survival of >50% to ensure maximal utility for each liver transplanted and to avoid patients undergoing complex, major surgery with significant associated morbidity for lesser longer term benefit. Registration for liver transplantation therefore requires patients to meet minimum listing criteria within four broad indications: acute liver failure and three elective situations – chronic liver disease, variant syndromes and primary liver cancer (*Table 1*).

Acute liver failure

Acute liver failure is a syndrome characterized by rapid onset of liver dysfunction with associated coagulopathy and encephalopathy. It carries a high risk of mortality and all patients with acute liver failure should be discussed with a tertiary liver unit with transplantation facilities. There are specific and unique features to the clinical management of acute liver failure (Whitehouse and Wendon, 2013) which should be delivered in an intensive care unit environment. The listing criteria differ for acute liver failure caused by paracetamol toxicity and non-paracetamol acute liver failure and are derived from the King's College criteria (O'Grady et al, 1989). However, there are limitations to these criteria as some patients die from liver failure despite not meeting these criteria: the sensitivity and specificity of the King's College criteria for mortality are 58% and 89% for paracetamol toxicity (McPhail et al, 2016) and 68% and 82% for non-paracetamol liver failure (McPhail

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Table 1. Indications and minimum listing criteria for liver transplantation in the UK

Transplant category	Indication	Criteria
Super-urgent	Paracetamol toxicity	■ pH <7.25 after 24 hours following fluid resuscitation ■ Prothrombin time >100 s or international normalized ratio >6.5 and serum creatinine >300 µmol/litre or anuria and ≥grade 3 hepatic encephalopathy ■ Serum lactate >5 mmol/litre on admission or >4 mmol/litre after 24 hours fluid resuscitation and hepatic encephalopathy ■ 2/3 of point 2 with deterioration
	Acute viral hepatitis or cocaine or ecstasy induced	■ Prothrombin time >100 s or international normalized ratio >6.5 and any grade of hepatic encephalopathy ■ Any grade hepatic encephalopathy and 3 of: age >40 years, jaundice to hepatic encephalopathy time of >7 days, bilirubin >300 µmol/litre, prothrombin time >50 s or international normalized ratio >3.5
	Seronegative hepatitis or idiosyncratic drug-induced liver injury	■ Prothrombin time >100 s or international normalized ratio >6.5 ■ International normalized ratio>2 and two of: age >40 years, jaundice to hepatic encephalopathy time of >7 days, bilirubin >300 µmol/litre, prothrombin time >50 s or international normalized ratio >3.5
	Acute Wilson's or Budd–Chiari syndrome	Coagulopathy and any grade of hepatic encephalopathy
	Post liver transplantation	Hepatic artery thrombosis <21 days post liver transplant. Early graft dysfunction
	Post total hepatectomy or living related donation	
Chronic liver disease	Alcoholic liver disease Non-alcoholic fatty liver disease Chronic viral hepatitis Autoimmune liver diseases Hereditary haemochromatosis Wilson's disease α-1 antitrypsin deficiency Congenital hepatic fibrosis (and others) Secondary sclerosing cholangitis	United Kingdom End-stage Liver Disease score ≥49
Variant syndromes	Diuretic resistant ascites	Transjugular intrahepatic portosystemic shunt can be considered as an alternative
	Chronic hepatic encephalopathy	With ≥2 admissions per year
	Intractable pruritus	Owing to cholestatic liver disease
	Hepatopulmonary syndrome	In the absence of chronic lung disease
	Familial amyloid polyneuropathy	
	Familial hypercholesterolaemia	
	Polycystic liver disease	
	Hepatic epithelioid haemangioendothelioma	
	Sickle cell hepatopathy	
Liver tumours	Hepatocellular carcinoma	Single lesion ≤5 cm or up to 5 lesions all ≤3 cm or single lesion ≤7 cm with no evidence of progression or spread over 6 months No evidence of vascular invasion or distal spread

adapted from POL195/4 (NHS Blood and Transplant, 2015)

et al, 2010) with a negative predictive value of 47–92% (Pauwels et al, 1993; Anand et al, 1997; Dhiman et al, 2007; Simpson et al, 2009), suggesting that perhaps as few as half of patients who die from acute liver failure reach current listing criteria.

Elective transplantation

Chronic liver disease

Progressive liver disease is associated with deteriorating hepatic synthetic function, renal function and sodium homeostasis. These parameters are modelled by the United

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Kingdom End-stage Liver Disease (UKELD) score (*Figure 1*) which was developed from mortality data for patients listed for liver transplantation without hepatocellular carcinoma. A score of >49 predicts an annual mortality risk of 9% (Barber et al, 2011) which exceeds the first year mortality risk of undergoing liver transplantation, hence is used as a threshold for liver transplantation listing.

Despite the UKELD score's sensitivity for prediction of mortality, many patients with a qualifying UKELD score would not benefit from liver transplantation. For example patients with established chronic kidney disease may achieve a score >49 without intrinsic liver dysfunction. Hence patients with a qualifying UKELD are considered for liver transplantation only in a suitable clinical setting, e.g. with attendant ascites or hepatic encephalopathy.

Variant syndromes

Several clinical scenarios are associated with poor liver-related prognosis or poor quality of life and patients may gain benefit from liver transplantation independent of their UKELD score (*Table 1*). Common indications are diuretic-resistant ascites, chronic hepatic encephalopathy and recurrent cholangitis. The risk–benefit balance of liver transplantation for quality of life indications must be carefully considered and patients counselled accordingly.

Hepatocellular carcinoma

Liver transplantation has a key role in managing hepatocellular carcinoma where resection is not possible. Various listing criteria meet acceptable mortality outcomes for liver transplantation in the setting of hepatocellular carcinoma and the UK uses a modified version of the Milan criteria (*Table 1*) (Mazzaferro et al, 1996) which predict a low risk of relapse and death. Current UK outcomes for hepatocellular carcinoma managed by liver transplantation are 68.7% 5-year survival (NHS Blood and Transplant, 2014), and hepatocellular carcinoma accounted for 24% of adult liver transplantation in the year to March 2016 (NHS Blood and Transplant, 2016). Patients do not need to meet a minimum UKELD score but must have a predicted survival of at least 50% at 5 years with liver transplantation and not have adverse tumour biology. Downstaging hepatocellular carcinoma with radiofrequency ablation or transarterial (chemo)embolization to meet transplantation criteria is permitted.

Selection process

All patients with cirrhosis or acute liver failure should be considered for transplantation as currently it is the intervention that offers the greatest prognostic benefit. However, patients with a high predicted risk of graft failure, perioperative death or limited 5-year survival are not offered liver transplantation. It is imperative that patients who may benefit from liver transplantation are referred for assessment early. Patients who have absolute contraindications and could not qualify for transplantation should not be referred. Those who are not suitable for liver transplantation should be considered for referral to palliative care services because of the poor prognosis and high symptom burden of advanced liver disease.

Typically patients referred for liver transplantation assessment will be seen by a transplant hepatologist and other members of the multidisciplinary team for an assessment of their liver disease and comorbidities to determine a secure indication for liver transplantation, no contraindications (*Table 2*) and that patients are motivated for liver transplantation. Common barriers to transplantation can include cardiovascular fitness, poor nutritional state and behavioural, drug and alcohol disorders that may need to be assessed by specialists before further work up (see below).

Potential candidates undergo a comprehensive multidisciplinary assessment including hepatologists, transplant surgeons, specialist nurses in liver transplantation, anaesthetists, drug and alcohol services, nutritionists, psychologists and specialists from other clinical disciplines where indicated. The assessment typically occurs as an inpatient, which has several aims:

- Identify and optimize factors that may affect patient survival while on the waiting list, e.g. oesophageal varices, viral hepatitis or ascites
- Screen for contraindications to liver transplantation

Figure 1. United Kingdom End-stage Liver Disease (UKELD) score formula (Barber et al, 2011).

$$UKELD = [(5.395 \times \ln(\text{international normalized ratio})) + (1.485 \times \ln(\text{creatinine})) + (3.13 \times \ln(\text{bilirubin})) - (81.565 \times \ln(Na))] + 435$$

Table 2. Relative and absolute contraindications to liver transplantation

Absolute contraindications	Failure to meet criteria outlined in *Table 1*
	Acute alcoholic hepatitis (outside of trial setting)
	More than two episodes of returning to alcohol use after advice to stop
	Drinking alcohol while on liver transplant waiting list (alcohol-related liver disease only)
	Ongoing illicit intravenous drug use
	Recurrent non-adherence to medical care
	Active disseminated malignancy
	Comorbidities giving <50% predicted 5-year survival with liver transplant
	Severe pulmonary hypertension (non-responsive to medical therapy)
Relative contraindications	Age >65 years
	Chronic source of infection
	Technical considerations (may include portal venous thrombosis, aberrant vascular or biliary anatomy)
	Poor nutritional state (under- or overweight)
	Comorbidities including smoking

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Table 3. Investigations required during workup for liver transplantation

General investigations	Full history and examination
	Bloods for cross match, full blood count, liver function, renal function, coagulation screen, alpha fetoprotein, HIV screen
	Liver aetiology screen
	Electrocardiogram
	Transthoracic echocardiogram with estimated pulmonary artery pressures
	Chest X-ray
	Pulmonary function tests
	Arterial blood gas analysis
	Formal assessment of glomerular filtration rate
	Oesophagogastroduodenoscopy
	Computed tomography of liver (portal venous and arterial phase contrast)
	Cytomegalovirus and toxoplasma screening
	Urine protein:creatinine ratio
	Bone densitometry
Patient-specific investigations	Psychology assessment
	Random blood alcohol and drugs of abuse screen
	Right-sided cardiac catheter studies
	Coronary angiogram and/or myocardial perfusion scan
	Interferon gamma release assay
	Targeted cross-sectional imaging
	Liver biopsy
	Colonoscopy
	Cancer screening tests (as per general population)

- Identify predictors of high operative or anaesthetic risk (see linked articles in this symposium), e.g. cardiac dysfunction, pulmonary hypertension, pulmonary dysfunction and poor nutritional status
- Allow patients to meet the members of the transplant team and become familiar with the transplant unit
- Educate patients and their family about the transplantation process, postoperative and long-term care.

There is a common set of assessments for most patients (*Table 3*) and others will be tailored to individual patient's needs. Following assessment, each patient is discussed by the transplant multidisciplinary team. If a patient meets the listing criteria, will potentially gain benefit from liver transplantation and has no absolute contraindications he/she should be put forward for transplantation.

Patients with acute liver failure are listed on the national super urgent list. The selection process applies the same principles as for elective transplantation: a patient must meet minimum listing criteria as outlined in *Table 1*, he/she should have a predicted 5-year survival of more than 50% with transplantation and no absolute contraindications.

Risk assessment

Drugs and alcohol

Owing to the link between alcohol and drug dependency and some forms of liver disease special consideration is required regarding these issues. A detailed drug and alcohol history must be obtained from all patients to inform the aetiology of liver disease, optimize chronic liver disease management resulting from synergistic liver injury, identify other related pathology (e.g. neuropathy, cardiomyopathy, occult sepsis), assess social and psychological support and risk factors, and identify indicators for liver transplantation failure.

Where alcohol contributed to liver disease or there is a history of illicit drug use patients should be assessed by a substance misuse team. Active alcohol consumption following clinical recommendation of abstinence, coupled with a clear explanation to the patient of the implications of continuing to drink against medical advice, is an absolute contraindication to liver transplantation. Abstinence may result in recompensation of liver disease to the point that liver transplantation is no longer needed. In the UK there is no nationally stipulated minimum period of abstinence before transplantation is considered, but 6 months abstinence is commonly requested if the patient is able to wait.

Drug use is linked with liver disease because of the high prevalence of viral hepatitis among injecting drug users. Patients on stable drug replacement and maintenance therapy can be considered for transplantation, but illicit drug use raises considerable concerns. The overriding principles on drug and alcohol use relate to the potential for transplant failure. Drug and alcohol dependency raise the risk of drug-seeking behaviour taking primacy over engagement with health care and concordance with post-liver transplantation treatment such as immunosuppression, represent a risk for recurrent liver disease and a potential for harms such as infection from injection practices in the setting of immunosuppression.

A substance misuse team will advise the transplant multidisciplinary team of the predicted risk of recidivism and support and advise patients regarding long-term strategies to support abstinence and address contributing psychological or psychiatric comorbidities. Patients with a considerable risk of harm from ongoing illicit drug use or return to harmful alcohol consumption should not be offered a liver transplant.

Age and comorbidities

There are few absolute contraindications to liver transplantation (*Table 2*), but liver transplantation should only be offered if there is a 5-year predicted survival >50% with liver transplantation. Comorbidities and age may have an additive effect on predicted mortality and these factors need to be considered holistically.

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Age
There is no upper age limit for transplantation in the UK. Some studies showed that long-term survival decreases with age above 60 years (Collins et al, 2000; Malinis et al, 2014), mainly as a result of malignancy and infection, whereas others found no differences in outcomes for appropriately selected older recipients (Bromley et al, 1994; Garcia et al, 2001; Cross et al, 2007; Sonny et al, 2015).

Comorbidities
Common comorbidities are screened for with particular attention to those associated with the aetiology of liver disease, including coronary artery disease, hypertension and type 2 diabetes in patients with non-alcoholic fatty liver disease, autoimmune disease in those with immune-mediated liver diseases, inflammatory bowel disease and dysplasia in patients with primary sclerosing cholangitis, renal dysfunction in viral hepatitis and non-alcoholic fatty liver disease. Comorbidities should be optimally treated and their impact on projected survival following liver transplantation be considered cumulatively.

Malignancy
Prior, treated extra-hepatic malignancy is not an absolute contraindication to liver transplantation, but the risk of recurrence in the setting of long-term immunosuppression needs to be considered for each patient with input from an oncologist tailored to that patient and tumour biology. European guidelines suggest a 5-year interval from treatment before liver transplantation would be suitable to exclude recurrence, but there is little evidence for this approach (European Association for the Study of the Liver, 2016). Patients should undergo conventional screening for occult malignancy in line with national screening guidelines with a high index of suspicion for, for example, upper gastrointestinal tract, pulmonary and ear, nose and throat cancers, in patients with a history of alcohol or tobacco addiction. Active cancer, outside primary hepatocellular carcinoma, epithelioid haemangioendothelioma or hepatoblastoma and non-melanoma skin cancer is an absolute contraindication to liver transplantation.

Infections
Screening for infection with hepatotropic viruses, HIV infection, herpes viruses and toxoplasma is routine. Hepatitis B, C and HIV all have highly effective treatments that are tolerated in chronic liver disease and following transplantation and patients should be offered these when appropriate. Other latent infections, e.g. tuberculosis, should be considered and screened for. Active extra-hepatic sepsis is a contraindication to liver transplantation and the evolution of interval sepsis, including spontaneous bacterial peritonitis, will require delay of liver transplantation until resolved.

Smoking
This is not a contraindication to liver transplantation but patients are strongly encouraged to stop smoking as there is evidence of a raised risk of mortality (Leithead et al, 2008), malignancy (Watt et al, 2009), hepatic vascular complications (Pungpapong et al, 2002), biliary complications (Mathur et al, 2011) and an association with relapse to alcohol consumption (Rodrigue et al, 2013).

Nutrition
The evidence for an impact of obesity on liver transplantation outcomes is mixed. Some studies demonstrate an increase in mortality (Nair et al, 2002; Hilingsø et al, 2005; Dick et al, 2009), some show no increase in mortality but more complications, including longer length of stay post-liver transplantation or postoperative infections (Hakeem et al, 2013; Singhal et al, 2015), and others show no increase in complications (Braunfeld et al, 1996; Fujikawa et al, 2006) with obesity or morbid obesity. However, any mortality risk associated with obesity appears lower than the risks of non-transplantation in patients with qualifying indications for liver transplantation and there is no national upper body mass index limit for liver transplantation in the UK.

Malnutrition is common in patients with advanced liver disease and low body mass index has a negative impact on outcomes pre- and post-liver transplantation including survival and length of postoperative recovery (Dick et al, 2009; Merli et al, 2010; DiMartini et al, 2013; Ferreira et al, 2013; Ney et al, 2015). Low body mass index is a useful marker of prognosis but there is little evidence of a survival benefit with nutritional interventions (Langer et al, 2012) although nutritional indices, rate of recovery post-liver transplantation and other clinical indices improve with expert nutritional intervention (Ferriera et al, 2010; Langer et al, 2012).

Optimization
Many chronic liver disorders and complications of liver disease have effective treatments and care is taken to optimize the patient's clinical status while on the waiting list. This aims to reduce the risk of liver transplantation, improve long-term graft function and may lead to improvement to the point where liver transplantation is no longer required. *Table 4* outlines common diseases and complications of liver disease that should be treated before liver transplantation.

Care while on the list
A patient waiting for transplantation requires regular clinical review and assessment to monitor his/her clinical status including screening for de novo hepatocellular carcinoma or progression of established hepatocellular carcinoma, portal venous thrombosis, pulmonary hypertension and cardiac dysfunction. Progression of liver disease may prompt escalation of the patient's position on the waiting list. Specialist support for the psychological stresses associated with waiting for liver transplantation will be available. Currently each transplant unit identifies their priority cases for transplantation based upon clinical liver disease severity and projected mortality. This is due to change with the implementation of a national organ allocation process.

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Table 4. Medical strategies to optimize clinical status for patients while on the waiting list

Disease		Optimization strategy	Goal
Primary liver disease	Alcoholic liver disease	Psychological and substance misuse services support	Prevent relapse to drinking Develop strategies to maintain sobriety
	Autoimmune hepatitis	Glucocorticoids and immunomodulator therapy	Control active hepatitis
	Hepatitis B	Nucleotide analogue therapy	Suppression of viraemia Recompensation
	Hepatitis C	Direct acting antiviral drugs	Clearance of virus Prevent recurrence in graft
	Non-alcoholic fatty liver disease	Blood pressure, diabetes and lipid control Reduce body mass index	Reduce cardiac and anaesthetic risks Reduce surgical complexity
	Hepatocellular carcinoma	Loco-regional therapies	Prevent progression
	Haemochromatosis	Venesection	Limit disease progression and prevent secondary complications
	Wilson's disease	Chelation therapy	Limit disease progression
	Primary biliary cholangitis	Ursodeoxycholic acid	Optimal disease control
	Primary sclerosing cholangitis	Stenting of dominant strictures	Minimize risk of cholangitis and obstructive jaundice
	Thrombotic diseases	Anticoagulation	Prevent clot extension or de novo thrombosis
Complications of chronic liver disease	Hepatocellular carcinoma	6-monthly ultrasound scan, magnetic resonance or computed tomography Consider alpha fetoprotein monitoring	Early identification of hepatocellular carcinoma
	Ascites	Optimize diuretic regimen Consider transjugular intrahepatic portosystemic shunt	Reduce risk of spontaneous bacterial peritonitis Improve nutrition (calorific cost of ascites and distension) Improve mobility and functional reserve
	Varices	Beta-blockade Variceal band ligation	Avoid haemorrhage and subsequent decompensation
	Malnutrition	Specialist assessment Nutritional supplements Nasogastric or nasojejunal feeding	Improve mobility and functional reserve Reduce anaesthetic risk Improve wound healing
	Hepatic encephalopathy	Laxatives, rifaximin	Improve mobility, functional reserve and quality of life

Conclusions

Liver transplantation offers a significant survival benefit for patients with acute liver failure or chronic liver disease but demand is outstripping availability because of the limitations on organ availability and this is predicted to worsen as the prevalence of liver disease increases. Patient selection is critical to good patient outcomes and comprehensive multidisciplinary care is required to select and optimize patients for the transplant programme. Careful consideration of care for those for whom transplantation is not suitable is essential. A linked article (https://doi.org/10.12968/hmed.2017.78.5.278) discusses the medical management of patients post-liver transplantation. **BJHM**

Conflict of interest: none.

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KEY POINTS

- Liver transplantation offers a significant survival benefit for appropriately selected patients.
- There is a current mismatch between suitable donor organs and patient needs.
- Strict national listing criteria for transplantation for acute and chronic liver disease aim to equitably target scarce resources to patients who will benefit significantly.
- A range of factors including disease aetiology and severity, psychological, behavioural and social factors and nutrition must be considered when offering liver transplantation.
- Assessment of patients and care while awaiting transplantation is complex and requires multidisciplinary input.

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