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Adult liver transplantation in the United Kingdom (II): post-transplant management --Manuscript Draft--

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Adult liver transplantation in the United Kingdom (II): post-transplant management

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Adult liver transplantation in the United Kingdom (II): post liver transplant management.

Abstract

Medical care for patients following liver transplantation is complex and requires a holistic approach to management. Patients and clinicians are faced with multiple challenges: immunosuppressive regimens must be optimised to avoid and treat graft rejection, the risk and atypical features of sepsis in the immunocompromised patient must be recognised, steps are required to reduce the recurrence of liver disease and the long term increased risks of malignancy, renal failure and metabolic complication need managing. Despite the benefits of liver transplantation there are additional concerns regarding the impact upon quality of life. This review will focus upon the care of patients following liver transplantation. As these patients will present to a broad range of clinicians, an understanding of the common drugs used post transplantation and general approach to management of these patients will be of benefit to the general clinical audience.

Key Points and Key Words

Liver transplantation offers a survival benefit for patients with acute and chronic liver diseases and primary liver cancer

Immunosuppressive medications have interactions with many commonly prescribed drugs and prescribers should be aware of these

Immunosuppression regimens are individualised depending upon primary liver disease, rejection, co-morbidities and intolerances

The range of common infections affecting post-transplant patients differs from the general population and changes with time from transplantation

Acute cellular rejection is typically an early complication following transplantation

Patients are at increased risk of metabolic, cardiovascular and malignant and renal complications

Despite the clear mortality benefit for patients there are concerns regarding quality of life outcomes for some patients

Liver transplant, complications, quality of life, immunosuppression, infection, rejection

Liver transplantation (LT) is a life-saving treatment for patients with acute liver failure, decompensated chronic liver disease (CLD) and hepatocellular carcinoma. This article reviews the common immunosuppression regimens and complications including infection, graft rejection, metabolic complications, malignancy, disease recurrence, *de novo* renal disease and the impact upon quality of life following LT.

Survival after Liver Transplantation

In the pre LT era patients with decompensated CLD would die within months whereas LT recipients now have survival rates in excess of 90% and 80% at 1 and 5 years respectively. (Neuberger, 2016) The early survival following LT has steadily improved over the last 2 decades and this is likely to reflect experience in selection of patients, improved surgical technique and developments in the efficacy and tolerability of immunosuppressive therapy. (Watt et al., 2010, Adam et al., 2012) (Figure 1) Although LT outcomes are improving and the procedure is undoubtedly life saving for selected patients; survival after LT is significantly inferior to age matched non transplant recipients. (Barber et al., 2007) Moreover longer term survival after LT is less impressive with little significant reduction in late morbidity and mortality over the last 2 decades. (Adam et al., 2012, Lodhi et al., 2011) Ten year survival rates are 60% with the leading causes of death being cardiovascular, malignancy, infection and renal failure with liver related mortality from chronic rejection or disease recurrence contributing to a relatively small proportion of late mortality. (Watt et al., 2010)(Figure 2) With the number of liver transplants performed annually in the UK increasing combined with improved survival following LT this will result in general physicians/surgeons and general practitioners encountering a greater number of LT recipients in their daily practice. Thus a general awareness of the management of such patients and the longer term health problems they are likely to encounter needs to be appreciated.

Immunosuppression

Immunosuppression is routinely given after liver transplantation to block or interfere with the immune response and stop the recipient's immune system identifying the LT graft as foreign and attempting to destroy it. The common agents, their associated side effects and interactions with commonly prescribed medications are detailed in table 1. The initial choice of immunosuppression will be made by the LT centre taking into account the patient's clinical condition, aetiology of liver disease, and presence or absence of additional comorbidities. (e.g. renal failure, obesity etc.) Most centres will use a calcineurin inhibitor (CNI; tacrolimus or ciclosporin) as their principle immunosuppression with over 95% of LT recipients discharged from hospital on a CNI. (Wiesner and Fung, 2011) Amongst the CNIs tacrolimus is the favoured drug of choice with superiority over ciclosporin in mortality, graft loss and episodes of rejection. (O'Grady et al., 2007) In the immediate post LT period corticosteroids are routinely used but rapidly tapered over 4-6 weeks. Antimetabolites (azathioprine or mycophenolate mofetil) are often used in conjunction with CNIs to either augment immunosuppression to treat/prevent rejection or to reduce the dose of CNI therapy when side effects (ie. renal dysfunction) are present. (Wiesner et al., 2001) In current practice mammalian target of rapamycin inhibitors (mTOR) such as sirolimus and everolimus are reserved for those patients intolerant to the above therapies.

In patients with renal impairment pre-LT or who develop acute kidney injury peri-transplantation, alternative induction agents can be used to avoid the immediate introduction of CNI therapy and its associated nephrotoxic effects. Basiliximab is an anti-interleukin 2 receptor antibody and its use with the delayed introduction low dose CNI therapy significantly improves renal function after LT with no significant increased risk of graft rejection. (Neuberger et al., 2009)

Immunosuppression therapy has revolutionised survival after LT by significantly reducing the rate of graft loss from acute and chronic rejection. However immunosuppressive therapy itself contributes significantly to the increased morbidity and mortality LT recipients encounter when compared to the general population, increasing the risk of malignancy, metabolic syndrome and renal failure. (Doycheva et al., 2016, Fussner et al., 2015, Leithead et al., 2012) (Table 1) Moreover it is now evolving that selected patients can achieve tolerance of the graft and immunosuppressive therapy can be withdrawn with no long term risk to the graft, coupled with a reduction in immunosuppression related morbidity and mortality. (Adams et al., 2015). This approach is only considered in highly selected patients, in the setting of clinical trials, however identification of such patients is currently being evaluated via a coordinated national study within the United Kingdom.

Complications after Liver Transplantation

Complications following liver transplantation are best thought of in respect to their timing after the transplant operation. This is because the nature of complications and their prevalence changes as time from the LT operation evolves. Early complications, defined as a complication at < 6 months from the transplant and late complications, >6 months from the LT, are outlined in table 2 and medical complications are expanded on below. (Table 3)

Infections:

Infectious complications are a major cause of morbidity and mortality after LT, with in excess of 60% of recipients being affected. The prevention, early evaluation and diagnosis of post LT infections are critical in the management of a post LT patient. The prevalence of different infections following LT changes as the time from transplantation evolves. (Karuthu and Blumberg, 2012)

In the first weeks following LT the infections encountered by patients are similar to those seen in any post-surgical patient on ITU and include wound infections, pneumonia, line infections and urinary tract infection. The routine use of antimicrobial prophylaxis in the immediate post-LT period had decreased the incidence, severity and mortality from such infections. (Gavalda et al., 2012) As immunosuppressive therapy is established the patient becomes at risk of atypical infections including candida, *Pneumocystis jirovecii*, cytomegalovirus, herpes simplex virus and varicella zoster virus. (Hernandez Mdel et al., 2015) A low threshold of suspicion and investigation for such atypical infections is required in any post LT patient where infection is suspected. Cytomegalovirus and candida infection are the commonest opportunistic infections in LT recipients and have a significant morbidity and mortality if they are not treated early. In light of this many centres give routine CMV and candida prophylaxis for the first 3 months post-LT to cover the time when immunosuppression levels are often at their highest. (Mumtaz et al., 2015, Eschenauer et al., 2009)

Fever in the post-LT patient is an emergency, it must always be investigated and antibiotics started early if bacterial infection is suspected. Prevention strategies are important and all LT patients should be immunised against influenza and pneumococcus; hepatitis B and A vaccination should have been administered pre-LT. It is recommended that live vaccines are avoided following LT.

Graft rejection:

Acute and chronic graft rejection are beyond the scope of this article, however it should be noted that acute cellular rejection is common and mild acute cellular rejection is managed by augmentation of baseline immunosuppression and in moderate/severe rejection intravenous corticosteroids are typically used.

Metabolic syndrome and cardiovascular disease:

Cardiovascular disease (CVD) is increased significantly above that of the general population following LT. Death from CVD is the leading cause of non-liver related late mortality, accounting for almost 25% of deaths after 5-years. (Madhwal et al., 2012, Desai et al., 2010, Watt et al., 2009) The reason for this significant mortality is multifactorial. The metabolic syndrome, which incorporates insulin resistant diabetes mellitus, obesity, dyslipidaemia and arterial hypertension, affects between 50-60% of post LT recipients. (Watt and Charlton, 2010) Individually reported studies describe the prevalence of diabetes mellitus in 10-64% of LT recipients, obesity (BMI>30kg/m²) in 24-64%, dyslipidaemia in 40-66% and arterial hypertension in 40-85%. (Lucey et al., 2013, Luca et al., 2015)

Immunosuppression therapy is recognised to either exacerbate or cause *de novo* arterial hypertension, diabetes, dyslipidaemia and obesity in the post LT population (Barnard et al., 2016), thus increasing cardiovascular risk (Table 3). Moreover the conventional risk factors that place a patient at risk for the metabolic are often prevalent in pre-LT populations such as those transplanted for non-alcoholic fatty liver disease. Smoking is common in certain disease aetiologies pre-LT, including hepatitis C and alcohol related liver disease, and continuation to smoke further compounds the risk of cardiovascular disease post-LT.

Aggressive management of CVD risk factors post-LT and immunosuppressive minimisation where possible, is essential if a positive impact on late morbidity and mortality is to be achieved. Hypertension should be aggressively treated with a target blood pressure of 130/80. First line antihypertensive therapies are dihydropyridine calcium channel blockers (amlodipine / nifedipine). Statin therapy should be considered and commenced in patients with cardiovascular disease, type 2 diabetes and those with an elevated 10 year CVD risk of greater than 7.5%. Statin therapy may interact with CNI, resulting in increased statin concentrations and risk of rhabdomyolysis as both are

metabolised by cytochrome P450-3A4. Pravastatin and Fluvastatin are the statins of choice post-LT as they are not metabolised by the cytochrome P450-3A4. Finally the benefit of education regarding a healthy diet and regular exercise programs should not be discarded.

Malignancy:

De novo malignancy after CVD is the leading cause of late morbidity and mortality after LT. Liver transplant recipients have a 2-3 fold increased risk of solid organ cancers, a 30 fold increase in lymphoproliferative cancers and up to 70 fold increase in squamous / basal cell skin carcinomas compared to the general population. (Watt et al., 2009) The risk of solid organ cancers increases with time from LT. (Engels et al., 2011) Risk reduction is focussed on controlling modifiable risk factors including immunosuppression minimisation, sun avoidance, alcohol and smoking cessation, however many risk factors cannot be modified. (Carenco et al., 2015) (Immunosuppression, aetiology for LT, increasing patient and graft age) Despite the recognised increased relative risk of *de novo* cancers in the LT population, cancer surveillance strategies have yet to definitively prove an overall impact cancer related mortality.

Patients with alcohol related liver cirrhosis as their indication for LT are particularly at risk of upper gastrointestinal, oropharyngeal and lung cancers. A smoking history pre and post-LT further increases the risk of head/neck/lung carcinoma highlighting the importance of smoking cessation pre and long-term post LT. (Herrero et al., 2011, Watt et al., 2009) Patients with primary sclerosing cholangitis and associated inflammatory bowel disease are at a significantly increased risk of colorectal carcinoma and annual screening colonoscopies are recommended in such patients. (Watt et al., 2009)

Post-Transplant lymphoproliferative disorder (PTLD) primarily effects younger recipients and can occur any time following LT. Epstein Barr Virus (EBV) has an aetiological role in 80%; with EBV causing proliferation of B lymphocytes, which in the context of immunosuppression is not inhibited, resulting in mutations and PTLD. Symptoms include fever, weight loss, night sweats and lymphadenopathy; cytopaenias and a raised LDH on a blood count are suggestive, however for a definitive diagnosis histology is required. The management is a reduction in immunosuppression and if unsuccessful chemotherapy.

Disease Recurrence:

Certain liver pathologies resulting in the need for LT can reoccur following LT; with the frequency varying depending on the primary disease. (Figure 3) Conversely other causes of chronic liver disease are cured by LT; these include alpha 1 anti-trypsin deficiency, haemochromatosis and Wilson's disease.

To-date hepatitis C is reported in the literature as having the highest rate of recurrence post-LT, occurring in 100% of those patients who were HCV RNA positive at the time of LT. (Westbrook and Dusheiko, 2014) Progression of hepatitis C is accelerated following LT resulting in hepatitis C infected recipients having a poorer graft and patient survival. (Forman et al., 2002) Such patients should undergo regular assessment of graft fibrosis via a combination of some or all of transient elastography, liver histology and indirect measurement of portal pressure to identify those at greatest risk and whom will benefit from early HCV treatment. However given the recent advent of and increased access to direct acting anti-viral therapy it is now the norm for HCV to be eradicated prior to LT. Interferon-free, direct acting anti-viral regimens allow eradication of HCV infection, with high efficacy, in patients with decompensated liver disease whilst awaiting transplantation meaning this will become a much rare cause of disease recurrence post-LT in future years. (Gambato et al., 2014, Charlton et al., 2015) In those patients with hepatitis C recurrence following transplantation, there is growing evidence that direct acting antivirals have high sustained virological response rates despite immunosuppression (Suraweera et al., 2016). However, some regimens require careful monitoring and dose adjustment due to interactions with calcineurin inhibitors.

Hepatitis B virus can be prevented post-LT by the use of Hepatitis B immunoglobulin in the immediate post-LT period and nucleoside analogues (tenofovir/entecavir) long-term. (Gane et al., 2007, Fung et al., 2013)

Recurrent or *de novo* non-alcoholic fatty liver disease is commonly seen post-LT due to the increased prevalence of the metabolic syndrome secondary to immunosuppression use and its preventative management is detailed above.

The autoimmune liver diseases including primary biliary cirrhosis, autoimmune hepatitis and primary sclerosing cholangitis can all re-occur post LT in 10-50% of recipients, although actual rates of graft loss are significantly lower especially in primary biliary cirrhosis. (El-Masry et al., 2011)

Relapse rates to alcohol following LT for alcohol related liver cirrhosis are highly variable (10-50%) secondary to no accepted definition of relapse. (Faure et al., 2012) Whilst occasional drinking

may not impact on graft survival, 20% of relapsers will progress to harmful drinking which impacts on graft and patient survival. (Faure et al., 2012)

Finally patients transplanted for hepatocellular carcinoma (HCC) within Milan criteria, have a risk of HCC recurrence between 8-20% during the first 2-years with an associated very poor prognosis. (Clavien et al., 2012)

Renal Disease:

Renal disease is a well-recognised complication post-LT and is associated with an increase in long-term morbidity and mortality. Aetiology is multifactorial contributed to by CNI therapy, renal dysfunction pre-LT, peri-operative acute renal failure, diabetes and hypertension. Overall approximately 50% of post-LT patients will develop chronic kidney disease stage 3/4 with 5-9% requiring dialysis by 10-years post LT. (Ojo et al., 2003)

All LT patients should avoid nephrotoxic drugs (NASIDS) and should have their hypertension and diabetes aggressively controlled. In patients with progressive renal disease changing immunosuppressive therapy to a "CNI sparing / CNI free" regimen should be considered by the transplant centre.

Quality of life after Liver Transplantation

As discussed above LT, although life-saving, carries with it significant medical and surgical morbidity and mortality and many patients have valid concerns regarding quality of life (QOL) following LT as opposed to merely increased length of survival.

Quality of life has been assessed post-LT in several short term studies which have demonstrated encouraging results however data on the longer term evaluation of QOL is less convincing. (Yang et al., 2014) Physical and mental functioning along with life satisfaction scores improve short and long term post-LT. (De Bona et al., 2000) Whereas data regarding anxiety and depression show convincing short term improvement but less convincing longer term outcomes with anxiety regarding disease recurrence and side effects of medication predominating. The percentage of LT recipients who return to work after transplantation averages about 40%; with improved reported QOL in those employed vs. unemployed. (Aberg et al., 2012)

Sexual dysfunction improves post-LT but remains problematic with high rates of erectile dysfunction, reduced libido and difficulty reaching orgasm. For women of childbearing age fertility is restored and with it comes realistic prospects for starting a family.

Overall, QOL studies in post LT patients are similar to those in kidney, heart and lung transplant recipients, however they show inferiority when compared with sex and age matched healthy individuals.

Conclusions

Following liver transplantation, patients have complex care needs and optimal care will reduce the risk of recurrence of the primary liver disease, protect the graft from rejection and minimise the risk of complications of immunosuppressive drugs. Despite this there is an increased risk of malignancy, renal failure, metabolic and cardiovascular diseases. Focussed assessment and optimisation of these risks is key to improving long term survival, which remains below age-matched, non-transplanted controls.

Conflicts of interest:

The authors declare no conflicts of interest.

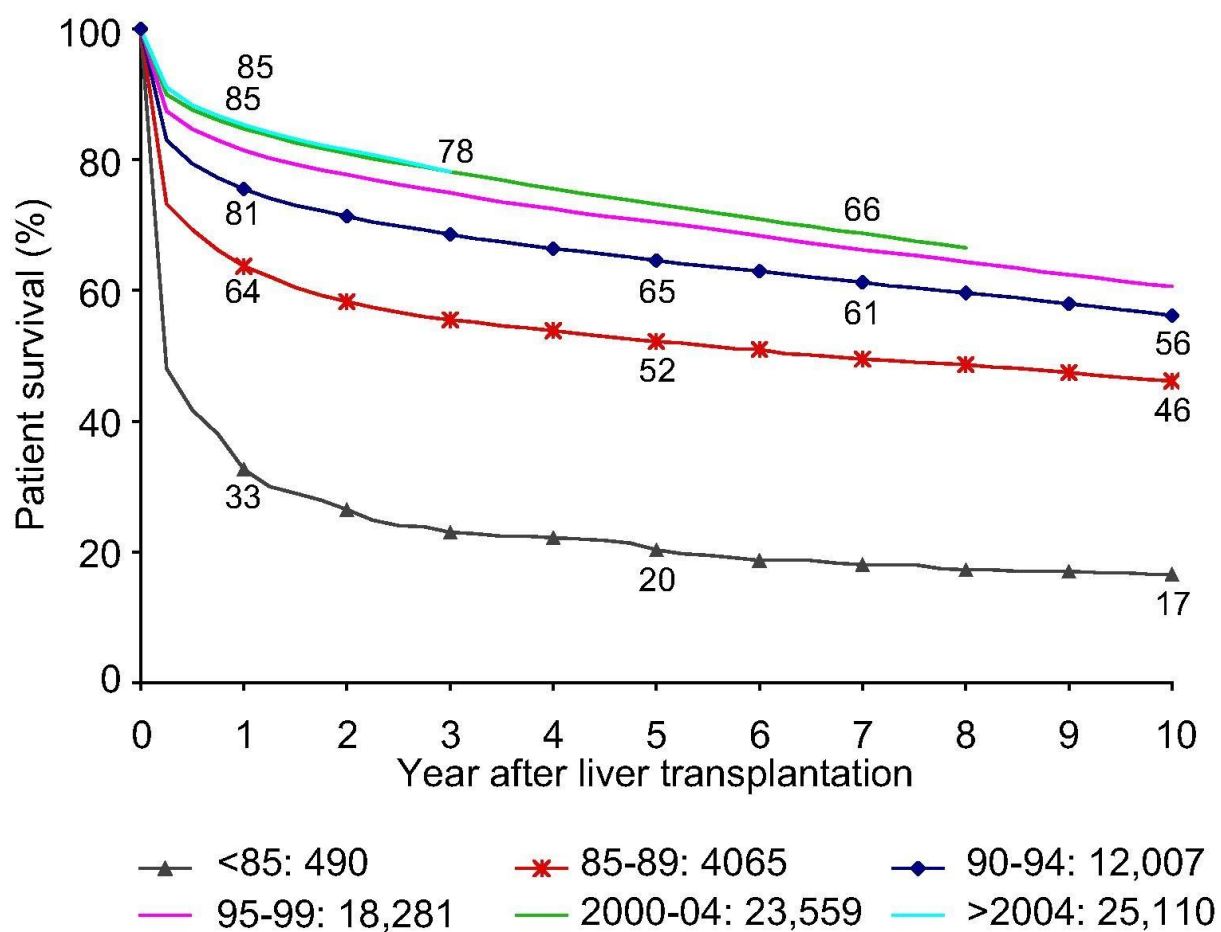
References

- Aberg, F., Hockerstedt, K., Roine, R. P., Sintonen, H. & Isoniemi, H. 2012. Influence of liver-disease etiology on long-term quality of life and employment after liver transplantation. *Clin Transplant*, 26, 729-35.
- Adam, R., Karam, V., Delvart, V., et al. 2012. Evolution of indications and results of liver transplantation in Europe. A report from the European Liver Transplant Registry (ELTR). *J Hepatol*, 57, 675-88.
- Adams, D. H., Sanchez-Fueyo, A. & Samuel, D. 2015. From immunosuppression to tolerance. *J Hepatol*, 62, S170-85.
- Barnard, A., Konyn, P., Saab, S. 2016. Medical Management of Metabolic Complications of Liver Transplant Recipients. *Gastroenterol Hepatol*, 12:601-8.
- Barber, K., Blackwell, J., Collett, D. & Neuberger, J. 2007. Life expectancy of adult liver allograft recipients in the UK. *Gut*, 56, 279-82.
- Carenco, C., Assenat, E., Faure, S., et al. 2015. Tacrolimus and the risk of solid cancers after liver transplant: a dose effect relationship. *Am J Transplant*, 15, 678-86.
- Charlton, M., Everson, G. T., Flamm, S. L., et al. 2015. Ledipasvir and Sofosbuvir Plus Ribavirin for Treatment of HCV Infection in Patients With Advanced Liver Disease. *Gastroenterology*, 149, 649-59.
- Clavien, P. A., Lesurtel, M., Bossuyt, P. M., Gores, G. J., Langer, B. & Perrier, A. 2012. Recommendations for liver transplantation for hepatocellular carcinoma: an international consensus conference report. *Lancet Oncol*, 13, e11-22.
- De Bona, M., Ponton, P., Ermani, M., et al. 2000. The impact of liver disease and medical complications on quality of life and psychological distress before and after liver transplantation. *J Hepatol*, 33, 609-15.
- Desai, S., Hong, J. C. & Saab, S. 2010. Cardiovascular risk factors following orthotopic liver transplantation: predisposing factors, incidence and management. *Liver Int*, 30, 948-57.
- Doycheva, I., Amer, S. & Watt, K. D. 2016. De Novo Malignancies After Transplantation: Risk and Surveillance Strategies. *Med Clin North Am*, 100, 551-67.
- El-Masry, M., Puig, C. A. & Saab, S. 2011. Recurrence of non-viral liver disease after orthotopic liver transplantation. *Liver Int*, 31, 291-302.
- Engels, E. A., Pfeiffer, R. M., Fraumeni, J. F., Jr., et al. 2011. Spectrum of cancer risk among US solid organ transplant recipients. *JAMA*, 306, 1891-901.
- Eschenauer, G. A., Lam, S. W. & Carver, P. L. 2009. Antifungal prophylaxis in liver transplant recipients. *Liver Transpl*, 15, 842-58.
- Faure, S., Herrero, A., Jung, B., et al. 2012. Excessive alcohol consumption after liver transplantation impacts on long-term survival, whatever the primary indication. *J Hepatol*, 57, 306-12.
- Forman, L. M., Lewis, J. D., Berlin, J. A., Feldman, H. I. & Lucey, M. R. 2002. The association between hepatitis C infection and survival after orthotopic liver transplantation. *Gastroenterology*, 122, 889-96.
- Fung, J., Chan, S. C., Cheung, C., et al. 2013. Oral nucleoside/nucleotide analogs without hepatitis B immune globulin after liver transplantation for hepatitis B. *Am J Gastroenterol*, 108, 942-8.
- Fussner, L. A., Heimbach, J. K., Fan, C., et al. 2015. Cardiovascular disease after liver transplantation: When, What, and Who Is at Risk. *Liver Transpl*, 21, 889-96.
- Gambato, M., Lens, S., Navasa, M. & Forns, X. 2014. Treatment options in patients with decompensated cirrhosis, pre- and post-transplantation. *J Hepatol*, 61, S120-31.

- Gane, E. J., Angus, P. W., Strasser, S., et al. W. 2007. Lamivudine plus low-dose hepatitis B immunoglobulin to prevent recurrent hepatitis B following liver transplantation. *Gastroenterology*, 132, 931-7.
- Gavalda, J., Vidal, E. & Lumberras, C. 2012. Infection prevention in solid organ transplantation. *Enferm Infecc Microbiol Clin*, 30 Suppl 2, 27-33.
- Hernandez Mdel, P., Martin, P. & Simkins, J. 2015. Infectious Complications After Liver Transplantation. *Gastroenterol Hepatol (N Y)*, 11, 741-53.
- Herrero, J. I., Pardo, F., D'avola, D., et al. 2011. Risk factors of lung, head and neck, esophageal, and kidney and urinary tract carcinomas after liver transplantation: the effect of smoking withdrawal. *Liver Transpl*, 17, 402-8.
- Karuthu, S. & Blumberg, E. A. 2012. Common infections in kidney transplant recipients. *Clin J Am Soc Nephrol*, 7, 2058-70.
- Leithead, J. A., Ferguson, J. W. & Hayes, P. C. 2012. Modifiable patient factors are associated with the late decline in renal function following liver transplantation. *Clin Transplant*, 26, E316-23.
- Lodhi, S. A., Lamb, K. E. & Meier-Kriesche, H. U. 2011. Improving long-term outcomes for transplant patients: making the case for long-term disease-specific and multidisciplinary research. *Am J Transplant*, 11, 2264-5.
- Luca, L., Westbrook, R. & Tsochatzis, E. A. 2015. Metabolic and cardiovascular complications in the liver transplant recipient. *Ann Gastroenterol*, 28, 183-192.
- Lucey, M. R., Terrault, N., Ojo, L., et al. 2013. Long-term management of the successful adult liver transplant: 2012 practice guideline by the American Association for the Study of Liver Diseases and the American Society of Transplantation. *Liver Transpl*, 19, 3-26.
- Madhwal, S., Atreja, A., Albeldawi, M., Lopez, R., Post, A. & Costa, M. A. 2012. Is liver transplantation a risk factor for cardiovascular disease? A meta-analysis of observational studies. *Liver Transpl*, 18, 1140-6.
- Mumtaz, K., Faisal, N., Husain, S., Morillo, A., Renner, E. L. & Shah, P. S. 2015. Universal prophylaxis or preemptive strategy for cytomegalovirus disease after liver transplantation: a systematic review and meta-analysis. *Am J Transplant*, 15, 472-81.
- Neuberger, J. 2016. Liver transplantation in the United Kingdom. *Liver Transpl*.
- Neuberger, J. M., Mamelok, R. D., Neuhaus, P., et al. 2009. Delayed introduction of reduced-dose tacrolimus, and renal function in liver transplantation: the 'ReSpECT' study. *Am J Transplant*, 9, 327-36.
- O'grady, J. G., Hardy, P., Burroughs, A. K. & Elbourne, D. 2007. Randomized controlled trial of tacrolimus versus microemulsified cyclosporin (TMC) in liver transplantation: poststudy surveillance to 3 years. *Am J Transplant*, 7, 137-41.
- Ojo, A. O., Held, P. J., Port, F. K., et al. 2003. Chronic renal failure after transplantation of a nonrenal organ. *N Engl J Med*, 349, 931-40.
- Suraweera, D., Sundaram, V., & Saab S. 2016. Treatment of Hepatitis C Virus Infection in Liver Transplant Recipients. *Gastroenterol Hepatol* , 12, 23-30.
- Watt, K. D. & Charlton, M. R. 2010. Metabolic syndrome and liver transplantation: a review and guide to management. *J Hepatol*, 53, 199-206.
- Watt, K. D., Pedersen, R. A., Kremers, W. K., Heimbach, J. K. & Charlton, M. R. 2010. Evolution of causes and risk factors for mortality post-liver transplant: results of the NIDDK long-term follow-up study. *Am J Transplant*, 10, 1420-7.

- Watt, K. D., Pedersen, R. A., Kremers, W. K., Heimbach, J. K., Sanchez, W. & Gores, G. J. 2009. Long-term probability of and mortality from de novo malignancy after liver transplantation. *Gastroenterology*, 137, 2010-7.
- Westbrook, R. H. & Dusheiko, G. 2014. Natural history of hepatitis C. *J Hepatol*, 61, S58-68.
- Wiesner, R., Rabkin, J., Klintmalm, G., et al. 2001. A randomized double-blind comparative study of mycophenolate mofetil and azathioprine in combination with cyclosporine and corticosteroids in primary liver transplant recipients. *Liver Transpl*, 7, 442-50.
- Wiesner, R. H. & Fung, J. J. 2011. Present state of immunosuppressive therapy in liver transplant recipients. *Liver Transpl*, 17 Suppl 3, S1-9.
- Yang, L. S., Shan, L. L., Saxena, A. & Morris, D. L. 2014. Liver transplantation: a systematic review of long-term quality of life. *Liver Int*, 34, 1298-313.

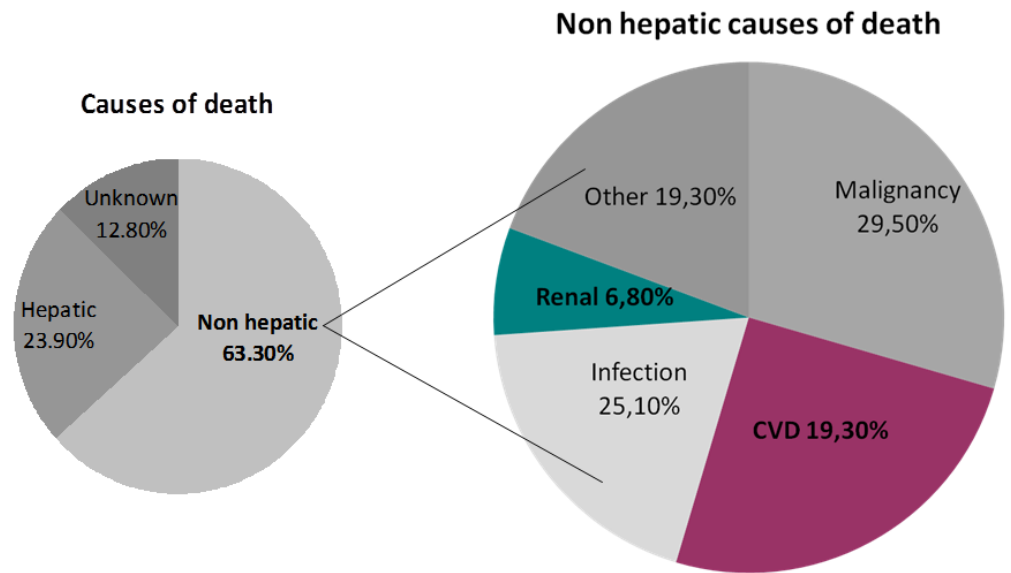
Figure 1: Improving survival in liver transplantation over the last 20 years.



Taken from: Evolution of indications and results of liver transplantation in Europe. A report from the ELTR. Adam R, Karam V, Delvart V et al. J Hepatol. 2012

Figure 2: Causes of late mortality following Liver Transplantation

Long-term mortality after liver transplantation



Watt 2010 Am J Transpl

Medication	Side effects	Drug interactions
Corticosteroids	Diabetes Hypertension Hyperlipidaemia Cosmetic changes (weight gain) Impaired wound healing Cataracts Reduction in Bone Mineral Density Adrenal suppression	
Calcineurin Inhibitors (CNI) (Cyclosporin, Tacrolimus)	Renal Impairment Hypertension Hypercholesterolemia Diabetes (Tacrolimus) Neurotoxicity – tremor, headache, confusion seizures Hirsutism Gingival hyperplasia	Decrease CNI levels • Anticonvulsants (Carbamazepine / Phenytoin) • Antibiotics (Rifampicin, isoniazid) • St John's wort Increase CNI levels • Antifungals (fluconazole, voriconazole) • Antibiotics (clarithromycin, erythromycin) • Calcium channel blockers (Diltiazem, verapamil)
Mycophenolate Mofetil	Bone marrow suppression Gastrointestinal upset (abdominal pain, nausea, vomiting, diarrhoea)	
Azathioprine	Bone marrow suppression Gastrointestinal side effects (nausea, pancreatitis) Dermatitis	Allopurinol
Mammalian target of rapamycin (mTOR) inhibitors (sirolimus, everolimus)	Hypertriglyceridaemia Pneumonitis (sirolimus) Nephrotic syndrome (sirolimus) Mouth ulcers (sirolimus) Impaired wound healing	

Table 1: Common adverse effects of immunosuppressive agents used in liver transplantation

Table 2: Complications following Liver Transplantation.

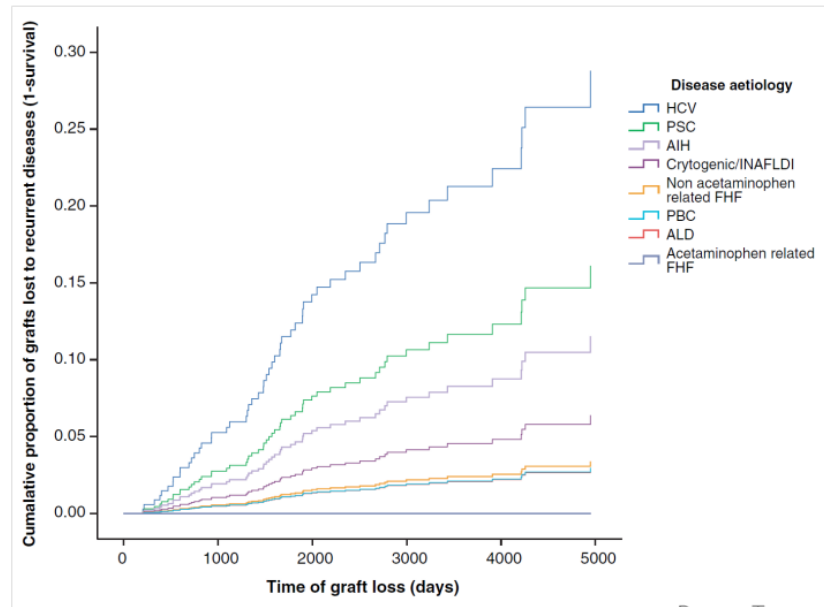
<u>Early < 6 months</u>	
Graft	<ul style="list-style-type: none"> • Primary non function • Delayed graft function
Surgical	<ul style="list-style-type: none"> • Bleeding • Hepatic artery thrombosis • Venous thrombosis • Bile leak • Anastomotic stricture – Biliary
Medical	<ul style="list-style-type: none"> • Infections • Rejection
<u>Late > 6 months</u>	
Graft	<ul style="list-style-type: none"> • Ischaemic cholangiopathy
Surgical	<ul style="list-style-type: none"> • Biliary anastomotic stricture • Vascular stricture • Hepatic artery thrombosis • Incisional hernia
Medical	<ul style="list-style-type: none"> • Infections • Late rejection / chronic rejection • Malignancy • Cardiovascular disease • Renal impairment • Disease recurrence

Table 3: Long Term Complications of Liver Transplantation

Health Problem	Incidence	Risk Factors	Associated Immunosuppression
Mood disorders	20-25%	Hepatitis C	
Hypertension	40-85%		Tacrolimus Ciclosporin Corticosteroids
CVS Disease	9-25%	Male Ethnicity FHx HT DM NASH	
Dyslipidaemia	45-69%		Sirolimus Ciclosporin Steroids
Diabetes	30-40%	Ethnicity Obesity FHx Pre LT Diabetes	Corticosteroids Tacrolimus
Renal insufficiency	14-25%	Age Diabetes Hypertension Post LT acute kidney injury	Tacrolimus Ciclosporin
Obesity	30-35%		Corticosteroids
Malignancy		Sun Exposure Smoking	Ciclosporin Tacrolimus Azathioprine
Bone Disease	30-35%	Poor nutrition Immobility Smoking Sarcopenia Smoking Alcohol	Corticosteroids Ciclosporin

Figure 3: Graft loss secondary to disease recurrence by aetiology of liver disease.

Proportion of all grafts lost after 90 postoperative days to disease recurrence by aetiology of liver disease



Rowe, Transpl int 2008