

# Long Term Follow-up of Liver Transplant Recipients: Considerations for Non-transplant Specialists

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## ABSTRACT

Patient and liver graft survival rates have improved significantly in the last decades, leading to complications mainly related to long-term immunosuppression. Prevention of, screening for metabolic syndrome, cardiovascular disease, de novo diabetes mellitus, renal dysfunction, and malignancies and their management are mandatory due to important causes of morbidity and mortality in this patient population. Quality of life (QoL) and functional benefits are clearly better compared to preoperative status; however, post-liver transplantation (LT) complications may impair and alter QoL scores. Individualized immunosuppression managed by transplant physicians and collaboration with other non-transplant specialists for recognition and treatment of medical complications and comorbidities after LT is the key to enhanced QoL and life expectancy of this patient population.

**Key words:** metabolic complications – cardiovascular profile – malignancy – liver transplantation.

**Abbreviations:** BMI: body mass index; CKD: chronic kidney disease; CNI: calcineurin inhibitors; CVD: cardiovascular disease; CYP3A4: cytochrome P450 3A4; DDI: drug-drug interactions; DEXA: dual energy x-ray absorptiometry; LT: liver transplantation; MS: metabolic syndrome; mTOR: mammalian target of rapamycin; NAFLD: non-alcoholic fatty liver disease; NASH: non-alcoholic steatohepatitis; NODAT: new onset diabetes after transplantation; QoL: quality of life; PTLT: post transplant lymphoproliferative disorder.

## INTRODUCTION

Currently, liver transplantation (LT) is being performed with excellent 5 and 10-year survival. The outcome and quality of life (QoL) of LT recipients has markedly improved in the last 3 decades [1, 2]. The better outcomes are related to various improvements in the management of these patients: selection and optimization of candidates, donor selection and matching, organ procurement and preservation, early post-operative care, immunosuppression as well as management of recurrent disease, complications and comorbidities [3]. A study from UK outlined that outcomes of LT recipients that survived over 6 to 12 months after LT were

very good, with an overall life expectancy of 22.2 years, but this represented a loss of seven life years. The loss of life years is greater in the younger recipients due to the fact that the increased risk of malignancy and infection are likely to be less related to age, but rather to the duration of immunosuppression [4]. After the first three years following LT, non-hepatic, non-transplant-related causes account for most late deaths in LT recipients, most commonly from cardiovascular disease (CVD) and de novo malignancies [5]. All these data support the need for aggressive screening and management of the complications following LT.

Compared to the general population, LT recipients have significantly higher overall prevalence of hypertension, diabetes, obesity, dyslipidemia, metabolic syndrome, higher incidence of *de novo* malignancies, non-Hodgkin's lymphoma, non-melanoma skin cancer and fractures/osteoporosis [6]. The identification and treatment of the above mentioned long-term comorbidities has become a critical element of the management of these patients. Often, initiating or follow-up therapy for these complications is the responsibility of non-transplant specialists, practicing gastroenterologists or general practitioners, but all concurrent medications need to be approved by the transplant team due to possible drug-drug interactions (DDI) [7-11].

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## METABOLIC SYNDROME

The presence of metabolic syndrome (MS) post-LT was detected in 43–58% of recipients, compared to 30% of non-transplanted patients [12]. Metabolic syndrome is defined as in non-LT recipients if three or more of the following five criteria are met: waist circumference over 102 cm in men or 88 cm in women, blood pressure over 130/85 mmHg, fasting triglyceride (TG) level over 150 mg/dl, fasting HDL cholesterol level less than 40 mg/dl in men or 50 mg/dl in women and fasting blood sugar over 100 mg/dl [13]. Male gender and other risk factors present prior to LT such as high body mass index (BMI), type 2 diabetes mellitus or even only a low threshold of glycosylated haemoglobin  $\geq 5\%$  and hypertension were all related to the development of *de novo* MS [14, 15].

Prolonged exposure to immunosuppressive drugs may increase the risk of metabolic complications because they are associated with all components of the MS. Corticosteroids, usually used in the early post-transplant phase, can act directly on pancreas beta cells increasing insulin resistance, obesity and hypertension; calcineurin inhibitors (CNIs) can affect the development of diabetes mellitus (particularly for tacrolimus), of hypertension (mainly cyclosporine) and hyperlipidemia (cyclosporine more than tacrolimus). Dyslipidemia is often related to the use of mammalian target of rapamycin (mTOR) inhibitors, whereas the use of anti-metabolites such as mycophenolate has fewer detrimental effects on MS related comorbidities [12, 16]. Moreover, mTOR inhibitors impair also glucose metabolism and  $\beta$ -cell proliferation [17]. That is why newer protocols often combine several drugs with different mechanisms of action and toxicities allowing dosage adjustment. There is also a trend towards tailored immunosuppressive regimens according to the etiology of liver disease and comorbidities such as renal dysfunction and CVD.

Liver transplant recipients who develop MS are at a higher risk of developing graft steatosis, leading to an increase in the recurrence or in the development of *de novo* non-alcoholic fatty liver disease (NAFLD). *De novo* NAFLD rates range from 20 to 40%, but they can increase up to 80% when we consider patients transplanted for non-alcoholic steatohepatitis (NASH) [18]. Patients who are at a high risk of developing MS after LT should undergo regular surveillance in order to achieve an earlier diagnosis and treatment. Weight loss through diet and lifestyle modifications were associated with resolution of NASH and improvement in liver fibrosis, and should be implemented in overweight LT recipients, with an objective of 7–10% reduction in bodyweight [19]. An early diagnosis of MS will limit associated comorbidities, thereby reducing the risk of cardiovascular events.

## CARDIOVASCULAR EVENTS

Cardiovascular events are a leading cause of morbidity and mortality after LT and their incidence is projected to rise further because of the growing prevalence of NASH as a transplant indication and because of the advanced age of LT recipients. In order to estimate the long-term risk of significant CVD morbidity that may alleviate the use of a scarce donor organ, a point-based risk score (the CAR-OLT score) and risk

calculator for clinical use was developed to assist clinicians in accurately predicting CVD risk after LT [20]. This clinical model includes preoperative recipient age, gender, race, education, employment status, history of atrial fibrillation, pulmonary hypertension, systemic hypertension, diabetes mellitus, heart failure, presence of hepatocellular carcinoma and ventilator dependence at the time of LT and predicted 1-year CVD complications after LT with good discrimination (c-statistic=0.78).

The incidence rates for CVD complications post-LT in the published articles vary widely according to outcome definition and follow-up duration. The incidence rate of CVD complications within one month after LT ranges from 1.1 to 23.2%; within 1 to 6 months of LT from 1.1% to 50%; and more than 6 months post-LT from 0% to 32.1% [20–22].

According to the American Heart Association, CVD includes ischemic heart disease, heart failure, thromboembolism, and stroke [23]. The Framingham score demonstrates a higher 10-year probability of coronary heart disease in LT recipients (11%) in comparison to the general population (7%) [24]. Several studies have identified predictors of cardiac complications and mortality in LT recipients: intraoperative cardiovascular events, preoperative history of heart disease, integrated MELD score (calculated by MELD, sodium, and age), prior stroke, postoperative sepsis, increased interventricular septal thickness, atrial fibrillation after LT, presence of left ventricular hypertrophy, presence of moderate-severe tricuspid valve regurgitation, estimated pulmonary artery systolic pressure on echocardiography (with a sub-hazard ratio 1.79 per 5 mm Hg increase in pulmonary artery systolic pressure) [25–27]. The use of beta-blockers in the perioperative period was associated with a protective effect on death after LT. Multiple echocardiographic parameters provide valuable prognostic information for long-term mortality in patients with chronic liver disease undergoing evaluation for LT. These patients require regular assessment and testing to identify CVD and determine the risk of CVD on their potential transplant outcome. The management of risk factors for CVD should be active and should comprise a multidisciplinary team of physicians.

## HYPERTENSION

Hypertension, an uncommon finding in patients with end-stage liver disease before LT, develops in up to 70% of patients, with systolic blood pressure increasing by up to 40 to 50 mmHg over the first few weeks after LT [28]. The pathogenesis of *de novo* arterial hypertension is complex and multifactorial. Early post-LT hypertension is mediated by endothelin-1 and the renin-angiotensin-aldosterone system is still stimulated 12 months after LT. The main determinants for occurrence of *de novo* hypertension are the CNIs causing renal afferent arteriole vasoconstriction and chronic sympathetic activity, as well as the corticosteroids through mineralocorticoid effects. The chronic kidney disease (CKD) and denervation due to the surgery itself can also contribute to the development of hypertension in these patients [11].

Lifestyle modifications, such as weight loss, physical activity and dietary sodium restriction are considered for all patients.

Dihydropyridine calcium channel blockers (e.g., amlodipine, nifedipine), causing vasodilation of renal afferent arterioles, are the favored first-line agents.

After the first year posttransplant period, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers with a nephroprotective effect are preferred, especially in diabetic patients with proteinuria. Beta-blockers can be used as adjuvant therapy; however, it should be mentioned that carvedilol can enhance the level of CNIs. The same is true for non-dihydropyridine agents such as diltiazem or verapamil. Thiazide or loop diuretics should be used with close follow-up due to the risk for hyperuricemia and the potential for electrolyte abnormality and renal dysfunction. Antisymphathetic antihypertensives such as clonidine and doxazosin may be used for poorly controlled hypertension [5, 11, 29, 30].

## DYSLIPIDEMIA

Dyslipidemia occurs in all solid-organ transplantation, with the lowest prevalence rates in LT recipients (30 to 60%), being a major risk factor for posttransplant cardiovascular-related morbidity and mortality, and often persists despite dietary modifications. A fasting lipid profile should be performed every year in all LT patients. Hypertriglyceridemia is the most common dyslipidemic change. Life-style modifications should be encouraged when the low-density lipoprotein cholesterol level is above 100 mg/dL, although dietary modification alone is often inadequate, making pharmacotherapy necessary, especially in recipients with moderate or high risk for CVD [31]. Risk factors for posttransplant hypercholesterolemia include female gender, cholestatic liver disease, pretransplant high cholesterol level, diabetes mellitus, weight gain, use of beta-blockers, diuretics and immunosuppressive agents (mainly sirolimus/everolimus) [30]. Similar to non-transplant patients, statins are the drug of choice being usually well tolerated. Low initial doses with titration as needed and close follow-up should be considered; attention should be paid to the potential increased risk of statin-related myopathy or toxicity due to metabolism using cytochrome P450 3A4 (CYP3A4) pathway, similar to immunosuppressive drugs. Pravastatin and fluvastatin are not metabolized by the CYP3A4 isoenzyme and should be prioritized in post-LT patients [32]. Ezetimibe that acts through inhibition of enterohepatic recirculation of lipids, proved to effectively treat hypercholesterolemia with few side effects and no interaction with immunosuppressive regimens [33]. Fibrates (fenofibrate, gemfibrozil) can be also safely used, but caution is required when co-administrated with statins due to high risk of myotoxicity and renal dysfunction. For patients with hypertriglyceridemia, fish oil can be used with minimal side effects except potential increase of low-density lipoprotein level [11, 30, 31].

## OBESITY

Weight gain after successful LT is beneficial when it compensates for the weight loss, sarcopenia and severe malnutrition experienced by the patient before LT. However, one-year post-LT, weight gain usually slows, but could

continue, leading to a new-onset obesity incidence of 22% at 2 years and up to 38% at 3 years post-LT. Obesity could also delay the improvement in physical QoL after LT [31, 34].

High BMI ( $\geq 30 \text{ kg/m}^2$ ) at 1 year following LT is associated with increased risk of long-term all-cause mortality in LT recipients; overall, obese LT recipients have a 2-fold higher risk of long-term all-cause mortality compared to normal weight LT recipients [35], underlying the necessity of an adequate post-LT BMI on long-term survival after LT. The cause of postoperative weight gain is multifactorial, an interplay of genetic, physiological, behavioral and environmental factors, similar to posttransplant diabetes and hyperlipidemia. A recent Swiss study [36] identified the following factors associated with post-LT new onset obesity: male gender, alcoholic liver disease, hepatocellular carcinoma at LT, while genetics remained marginal significant. In the same study, post-LT cardiovascular events were predicted by new-onset obesity and higher age at LT. Therefore, maintaining an adequate post-LT BMI via a weight management program early after LT might reduce the risk for cardiovascular events.

Post-LT obesity management should include the same steps as in other obese persons: diet and exercise, pharmacologic therapy and bariatric surgery. Orlistat, acting by directly blocking absorption of about 30% of dietary triglycerides, was evaluated in the post-LT setting and proved to be safe [37], but there are no data regarding its efficacy. Liraglutide, a long-acting glucagon-like peptide-1 (GLP-1), appears to have no interactions with the immunosuppressive therapies and to have also cardio-protective effects in patients with known atherosclerotic disease or heart failure, making it an attractive option in these high-risk patients. Phentermine-topiramate seems to have the highest weight loss potential, by directly blocking absorption of about 30% of dietary triglycerides, but possible side effects (neuropsychiatric disorders, cardiovascular comorbidities, and DDI) could limit their use. There are no known interactions with posttransplant immunosuppressants [38].

Bariatric surgery is also possible after LT, but may be more technically demanding, and associated with increased morbidity when compared with non-LT patients [35]. There is no specific immunosuppression scheme that has been shown to be effective in preventing weight gain after LT; however, immunosuppression should be tailored to reduce as much as possible the risk of metabolic complications.

## DIABETES MELLITUS

New onset diabetes after transplantation (NODAT) in LT recipients is rather common with incidence rates ranging from 15% to 25% and negatively impacting QoL and graft survival.

Several risk factors for NODAT were described: new-onset hyperglycaemia ( $< 30$  days), cold ischaemia time  $> 9$  hours, male recipient and with increased age  $> 50$  years, BMI  $> 25 \text{ kg/m}^2$ , hepatitis C, post-transplant intensive care unit stay  $> 15$  days, cytomegalovirus infection, corticosteroid and sirolimus-based immunosuppression. Tacrolimus also inhibits insulin production and depletes pancreatic beta-cell insulin mRNA and protein, but in a dose-dependent manner [38]. That is why long-term use of low doses of tacrolimus is not associated

with impaired pancreatic beta-cell secretion capacity. It is very important to follow-up these patients and to treat them appropriately because NODAT adversely affects long-term survival after LT comparable to pre-existing diabetes [39].

The principles of managing NODAT should follow the conventional approach for patients with type 2 diabetes mellitus. Dietary and lifestyle modification are of great importance, but are usually unsatisfactory in this population, with most patients requiring pharmacological therapy with oral agents or insulin. One of the most used and safe oral antidiabetic drugs in LT recipients is glimepiride (up to 4 mg per day) [40].

## RENAL DYSFUNCTION

The significance of advanced CKD [defined as glomerular filtration rate (GFR)  $<30 \text{ mL/min/1.73 m}^2$ ] in LT recipients was illustrated by an analysis of UNOS data [41]. In this rather old study, the cumulative incidence of advanced CKD was observed in up to 18% of patients by 5 years post-LT and was associated with more than a four-fold increased risk of recipient death. In addition, after year 2004, in the MELD era, prioritizing LT candidates with pre-existing renal dysfunction has increased the incidence of renal dysfunction following LT [1, 42]. In the study by Sharma et al [42], the 5-year cumulative incidence of post-LT advanced CKD in patients with and without pre-LT renal dysfunction was 34% and 10%, respectively.

Prevention of post-transplant advanced CKD is based mainly on diabetes and hypertension control, as well as on renal sparing immunosuppression strategies. Angiotensin converting enzyme inhibitors and angiotensin receptor blockers can help prevent CNIs nephrotoxicity. Care must be taken not to use potential nephrotoxins in treating these patients (e.g., avoid non-steroidal anti-inflammatory drugs, unnecessary contrast agents). Immunosuppression management is the task of the transplant center. Currently, the CNIs minimization should be done on a regular basis and represents the most rational approach for preserving post-LT renal function. The most used strategies to prevent or improve renal function are: 1) reduced-dose tacrolimus in association with mycophenolate mofetil or mTOR inhibitor; 2) switching to mTOR inhibitors (especially everolimus) with complete elimination of tacrolimus or 3) CNIs delay (up to fifth day) with antibody induction such as basiliximab and a non-nephrotoxic immunosuppressant [43].

## OSTEOPOROSIS

Bone loss and fracture rates after LT are highest in the first 6 to 12 months. In some studies, spine bone mineral density declined by 2 to 24% during the first year. Skeletal fracture rates range from 13 to 65% [44].

Adult LT recipients should be evaluated for osteoporosis, especially if they have additional risk factors, such as a history of smoking, heavy alcohol intake, physical inactivity, cholestatic liver disease, postmenopausal state, advanced age, hypogonadism, fracture(s) following minimal trauma or corticosteroid use for more than 6 months. The preferred method to evaluate osteoporosis is a dual energy x-ray absorptiometry (DEXA) scan. If the DEXA scan is abnormal,

treatment is indicated [29]. DEXA should be performed every 2-3 years after LT.

Non-pharmacologic therapies include alcohol and smoking cessation, increased exercise activity, maintain a normal body weight and a healthy diet with adequate calcium intake (based on a calcium calculator launched by the International Osteoporosis Foundation (<https://www.iofbonehealth.org/calcium-calculator>) and daily vitamin D targeting an optimal level of  $>30 \text{ ng/mL}$  [30]. Treatment for osteoporosis in LT recipients is not different from other patients and drugs used are not usually toxic to the liver; however, therapy should be carefully individualized and followed.

Calcitonin and calcitriol have been used in older studies, while oral (etidronate, alendronate, risedronate) and intravenous bisphosphonates (pamidronate, ibandronate, zoledronic acid) have been used in most recent ones [45].

Although, denosumab could be an alternative anti-resorptive treatment, it has not been extensively studied in patients after LT. Denosumab therapy was well-tolerated and improved bone density in a small study including a group of solid organ transplant recipients [46]. Our clinical experience also showed that denosumab could be a viable therapeutic option for transplanted patients with osteoporosis, especially in those with renal function impairment or bisphosphonate intolerance. To date, other agents including raloxifene, and osteoanabolic medications such as teriparatide and abaloparatide, have not been well studied in patients with LT [45].

## GOUT

Hyperuricemia is rather frequent following transplantation (7%). Usually, this condition occurs as a result of decreased uric acid excretion related to CNIs. Allopurinol is administered in order to prevent attacks. Another strategy is to avoid added medications such as thiazide diuretics, low-dose aspirin and nicotinic acid. Acute gout attacks are treated with colchicine and corticosteroids as second line treatment [11, 29].

## DE NOVO EXTRAHEPATIC MALIGNANCY

Long-term immunosuppression increases malignancy risk and screening guidelines should be adhered to. The risk of de novo extrahepatic malignancy after LT is 2 to 4 times higher in LT recipients than in the general population, increasing with time since the LT and affecting 2 to 22% of patients [11, 47]. This pathology accounts for one third of the non-hepatic deaths in this patient population [47]. Increased recipient age, intensity and type of immunosuppression, current or former smoking and history of sun exposure, primary sclerosing cholangitis or alcohol related liver disease increase the probability of developing any solid organ de novo malignancy after LT. Most often described cancers are dermatological, gastrointestinal, lymphoproliferative, lung, head and neck neoplasms. Whether other common types of cancer such as vulva, cervix, breast, renal and prostate cancer also occur more frequently in LT recipients than in the general population is still not clear [40]. Recurrent hepatocellular carcinoma will not be discussed in



**Table I.** Recommended screening protocols for malignancies in LT recipients [11, 50]

| Malignancy           | Recommended examination and interval                                                                                                                                                          |
|----------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Breast cancer        | Annual mammography starting at 40 years of age                                                                                                                                                |
| Cervical cancer      | Pelvic examination and Pap smear                                                                                                                                                              |
| Colon cancer         | Colonoscopy every 5 to 10 years if no history of colonic dysplasia or neoplasia or IBD, every 3 to 5 years with history of neoplasia or advanced adenomas, yearly in patients with IBD        |
| Esophageal cancer    | Esophagogastroduodenoscopy in patients with Barrett's esophagus and those at high risk for esophageal cancer (smokers and those transplanted for alcoholic cirrhosis)                         |
| Gastric cancer       | Every 1 or 2 years esophagogastroduodenoscopy in countries with high incidence of gastric cancer                                                                                              |
| Lung cancer          | Chest x-ray every 1 to 2 years in smokers and those transplanted for alcoholic cirrhosis                                                                                                      |
| Oropharyngeal cancer | Otolaryngological examination every year in smokers and those transplanted for alcoholic cirrhosis                                                                                            |
| Prostate cancer      | Digital rectal examination and annual prostate-specific antigen starting with age of 50 years                                                                                                 |
| Skin cancer          | Annual skin examination; special attention in patients with history of skin cancer or actinic skin damage, patients who received a transplant for alcoholic liver disease, and white patients |

this review, similar to specific liver complications (recurrent liver disease, rejection, biliary or vascular complications) following LT that should be managed only in transplant center by prompt patient referral.

The 5- and 10-year probability of skin cancer is estimated at 5.9% and 10.8%, respectively [47]. These basal and squamous cell carcinomas tend to be much more aggressive in transplant recipients, with greater local invasion, higher tendency for multiple lesions and metastatic disease and higher risk of recurrence [48]. Clinical evaluation by a dermatologist with expertise in organ transplant complications is desirable for the optimal management of skin manifestations in these patients.

After solid organ transplantation, the incidence of lymphoproliferative disorders (PTLDs) increases. The risk is highest in the first year after transplant, falling subsequently, and then increasing again after  $\geq 5$  years. The incidence of LT-PTLD is highest in children, while patient survival is significantly worse in adults [49]. Symptoms associated with PTLD include fever, night sweats, malaise, weight loss, and other constitutional symptoms, with or without lymphadenopathy. Most lymphomas developing in transplanted patients are linked to Epstein-Barr virus reactivation and are B-cell lymphomas. T-cell lymphomas are uncommon and often unrelated to Epstein-Barr virus infection. Anaplastic large-cell lymphoma is the T-cell PTLD most regularly encountered in transplant recipients. Reduction of immunosuppression should be considered in these patients; survival rate is significantly better in patients undergoing tacrolimus regimens compared to cyclosporine [50]. Multidisciplinary approaches are required in this case to decrease the incidence or recurrence from PTLDs.

Head and neck cancers are less common (7 to 15%), but they are still the most serious *de novo* malignancy in LT population, associated with a poor prognosis. LT recipients have a 20 times higher incidence of *de novo* cancer of head and neck area compared to the general population [51]. Alcohol consumption and smoking are the best identified factors to head and neck cancer in LT recipients.

Lung cancer accounts for about 26% of the total deaths related to post-LT *de novo* malignancy and its incidence was 2 to 3-fold higher compared to the general population. However, the survival rate in both LT individuals and in the healthy population after being diagnosed with lung cancer was

similar. Therefore, the most significant variable is represented by stopping cigarette smoking [52].

Several studies have shown that patients transplanted for primary sclerosing cholangitis have an increased risk of developing colorectal cancer compared with patients transplanted for other causes. Similarly, it has been demonstrated that LT patients with inflammatory bowel diseases have a higher standardized incidence ratio of colon cancer [30, 53]. Finkenstedt et al. [54] have shown that a screening colonoscopy performed 3 years after LT performed for any indication can decrease mortality.

Adherence to screening protocols is recommended, to detect malignancies in early stages associated with increased probability of patient survival. The recommended screening intervals for malignancies for LT recipients are shown in Table I.

## PREGNANCY

The restoration of menstruation and childbearing potential is successful in around 97% of previously fertile female LT recipients [55]. Pregnancy is recommended after the first year after LT with improved outcomes for both mother and child (a life birth rate  $>70\%$  with favorable maternal and fetal outcome). The management of pregnant LT recipients should be performed by a multidisciplinary team including the transplant hepatologist. Pregnancy is associated with a 10% risk of organ rejection and requires more frequent monitoring of immunosuppressant levels to maintain the therapeutic range [56]. Other possible maternal complications are hypertension (in up to 45% of LT recipients), preeclampsia (22%) and diabetes (5%) [57]. Renal dysfunction before conception has a very strong association with adverse outcomes of pregnancy in LT patients. Prematurity and low birth weight represent the most frequent fetal complications (10 to 55% of pregnancies). Teratogenic effects due to in utero exposure to immunosuppressant agents are possible, but the birth defects are overall similar to general population. Mycophenolate mofetil is contraindicated during pregnancy and should be interrupted with at least 6 weeks before conception, being included in category D of medications [55]. Many prospective studies have demonstrated that azathioprine, another inhibitor of the purine pathway, is safe for the fetus

**Table II.** Common drug interactions of calcineurin inhibitors and mTOR inhibitors [11, 39]

|                                                                            |                                                                                                                                                                                                            |
|----------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Drugs that may increase level of calcineurin inhibitors or mTOR inhibitors | Antibiotics: macrolides (azithromycin, erythromycin, clarithromycin)                                                                                                                                       |
|                                                                            | Antifungals: azoles (fluconazole, itraconazole, voriconazole, clotrimazole, ketoconazole)                                                                                                                  |
|                                                                            | Calcium channel inhibitors: nondihydropyridine (diltiazem, verapamil), nicardipine, nifedipine                                                                                                             |
|                                                                            | Statins: simvastatin, atorvastatin, other statins                                                                                                                                                          |
| Drugs that may decrease level of calcineurin inhibitors or mTOR inhibitors | Others: protease inhibitors, amiodarone, omeprazole, rabeprazole, lansoprazole, cimetidine, metoclopramide, allopurinol, colchicine, bromocriptine, grapefruit juice, ethinylestradiol, methylprednisolone |
|                                                                            | Antimicrobials: rifampicin, rifabutin, nafcillin, isoniazide, caspofungin                                                                                                                                  |
|                                                                            | Anticonvulsants: carbamazepine, phenytoin, phenobarbital                                                                                                                                                   |
|                                                                            | Others: St John's wort, orlistat, ticlopidine, octreotide                                                                                                                                                  |

mTOR: mammalian target of rapamycin.

during pregnancy [58]. However, benefit versus risk must be weighed carefully before using azathioprine in patients of reproductive potential. Most transplant recipients may safely breastfeed their infants. The benefits of breastfeeding while receiving corticosteroids, cyclosporine, tacrolimus or azathioprine outweigh the risks of drug exposure. Reproductive counselling is a clear priority for most women of childbearing age, before and after LT. However, it is inconsistently provided, and generally felt incomplete for guiding patient decisions surrounding contraception and pregnancy planning [59].

The use of oral contraceptives in LT recipients depends on the allograft function: in a good functioning allograft it is unnecessary to restrict the exposure to estrogen or progesterone, while patients with a dysfunctional liver should not receive combination hormones. Other contraceptive choices such as intrauterine devices, progesterone-only pills, injections or implants are a reasonable alternative in the majority of patients [60].

## QUALITY OF LIFE

Assessment and recovery of QoL after LT is of expending concern. Multiple studies showed a statistically significant increase in QoL after LT compared to pre-LT in physical health, sexual function, daily activities, general health related QoL and social function, but smaller progress in psychological health. Occupational counselling and creating an exercise program postoperatively are suggested to increase the awareness of good health. Psychological interventions should be introduced to modify health perceptions and to encourage return to work [29, 52]. The paper by Dew et al. [61] found that the presence of depression was associated with a 65% increased risk of posttransplant mortality due to graft loss. In contrast, anxiety did not significantly increase mortality or morbidity risks. Depression is an easily treatable disorder, and many pharmacologic and psychotherapeutic interventions exist. Thus, ongoing screening for depression at routine posttransplant follow-up may be allowed.

## DRUG-DRUG INTERACTIONS

Transplant recipients receive multiple medications metabolized by the CYP3A4 and P-glycoprotein and non-transplant physicians should take care regarding polypharmacy and side effects due to DDI. Table II exemplifies the significant DDI.

## CONCLUSIONS

The success of LT on the long-term outcome of LT recipients has changed the priority of recipients' care from long-term survival to an excellent recipient QoL. Long-term benefits of LT require an individualized immunosuppression plan aimed at increasing tolerability, safety and adherence to a life-long therapy, as well as screening and management of various metabolic and malignant complications. Additionally, the permanent engagement of both the recipient and multidisciplinary care team and a trusting patient – transplant physician relationship are the pillars of global improvements in long-term LT outcome.

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## REFERENCES

1. Durand F. How to improve long-term outcome after liver transplantation? *Liver Int* 2018;38 Suppl 1:134-138. doi:[10.1111/liv.13651](https://doi.org/10.1111/liv.13651)
2. Desai R, Jamieson NV, Gimson AE, et al. Quality of life up to 30 years following liver transplantation. *Liver Transpl* 2008;14:1473-1479. doi:[10.1002/lt.21561](https://doi.org/10.1002/lt.21561)
3. Charlton MR. Roadmap for improving patient and graft survival in the next 10 years. *Liver Transpl* 2016;22:71-78. doi:[10.1002/lt.24602](https://doi.org/10.1002/lt.24602)
4. Barber K, Blackwell J, Collett D, Neuberger J; UK Transplant Liver Advisory Group. Life expectancy of adult liver allograft recipients in the UK. *Gut* 2007;56:279-282. doi:[10.1136/gut.2006.093195](https://doi.org/10.1136/gut.2006.093195)
5. Neal DA, Tom BD, Luan J, et al. Is there disparity between risk and incidence of cardiovascular disease after liver transplant? *Transplantation* 2004;77:93-99. doi:[10.1097/01.TP.0000100685.70064.90](https://doi.org/10.1097/01.TP.0000100685.70064.90)
6. Sheiner PA, Magliocca JF, Bodian CA, et al. Long-term medical complications in patients surviving > or = 5 years after liver transplant. *Transplantation* 2000;69:781-789. doi:[10.1097/00007890-200003150-00018](https://doi.org/10.1097/00007890-200003150-00018)
7. Vallejo GH, Romero CJ, de Vicente JC. Incidence and risk factors for cancer after liver transplantation. *Crit Rev Oncol Hematol* 2005;56:87-99. doi:[10.1016/j.critrevonc.2004.12.011](https://doi.org/10.1016/j.critrevonc.2004.12.011)

8. Stein E, Ebeling P, Shane E. Post-transplantation osteoporosis. *Endocrinol Metab Clin North Am* 2007;36:937–963. doi:[10.1016/j.ecl.2007.07.008](https://doi.org/10.1016/j.ecl.2007.07.008)
9. Biancifiore G, Davis CL. Renal dysfunction in the perioperative liver transplant period. *Curr Opin Organ Transplant* 2008;13:291–297. doi:[10.1097/MOT.0b013e328300a058](https://doi.org/10.1097/MOT.0b013e328300a058)
10. Kadayifci A. Metabolic syndrome and liver transplantation. *Panminerva Med* 2009;51:205–213.
11. Singh S, Watt KD. Long-term Medical Management of the Liver Transplant Recipient: What the Primary Care Physician Needs to Know. *Mayo Clin Proc* 2012;87:779–790. doi:[10.1016/j.mayocp.2012.02.021](https://doi.org/10.1016/j.mayocp.2012.02.021)
12. Becchetti C, Dirchwolf M, Banz V, Dufour JF. Medical management of metabolic and cardiovascular complications after liver transplantation. *World J Gastroenterol* 2020;26:2138–2154. doi:[10.3748/wjg.v26.i18.2138](https://doi.org/10.3748/wjg.v26.i18.2138)
13. Grundy SM, Cleeman JJ, Daniels SR, et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung and Blood Institute scientific statement. *Circulation* 2005;112:2735–2752. doi:[10.1161/CIRCULATIONAHA.105.169404](https://doi.org/10.1161/CIRCULATIONAHA.105.169404)
14. Thoenner LB, Rostved AA, Pommergaard HC, Rasmussen A. Risk factors for metabolic syndrome after liver transplantation: A systematic review and meta-analysis. *Transplant Rev (Orlando)* 2018;32:69–77. doi:[10.1016/j.trre.2017.03.004](https://doi.org/10.1016/j.trre.2017.03.004)
15. Sprinzl MF, Weinmann A, Lohse N, et al. Metabolic syndrome and its association with fatty liver disease after orthotopic liver transplantation. *Transpl Int* 2013;26:67–74. doi:[10.1111/j.1432-2277.2012.01576.x](https://doi.org/10.1111/j.1432-2277.2012.01576.x)
16. Jacob S, Cicinnati VR, Beckebaum S. Current immunosuppressive approaches in liver transplantation. *Panminerva Medica* 2009;51:215–225.
17. Fatourou EM, Tsochatzis EA. Management of metabolic syndrome and cardiovascular risk after liver transplantation. *Lancet Gastroenterol Hepatol* 2019;4:731–741. doi:[10.1016/S2468-1253\(19\)30181-5](https://doi.org/10.1016/S2468-1253(19)30181-5)
18. Dumortier J, Giostra E, Belbouab S, et al. Non-alcoholic fatty liver disease in liver transplant recipients: another story of “seed and soil”. *Am J Gastroenterol* 2010;105:613–620. doi:[10.1038/ajg.2009.717](https://doi.org/10.1038/ajg.2009.717)
19. Germani G, Laryea M, Rubbia-Brandt L, et al. Management of recurrent and de novo NAFLD/NASH after liver transplantation. *Transplantation* 2019;103:57–67. doi:[10.1097/TP.0000000000002485](https://doi.org/10.1097/TP.0000000000002485)
20. VanWagner LB, Ning H, Whitsett M, et al. A point-based prediction model for cardiovascular risk in orthotopic liver transplantation: The CAR-OLT score. *Hepatology* 2017;66:1968–1979. doi:[10.1002/hep.29329](https://doi.org/10.1002/hep.29329)
21. Josefsson A, Fu M, Bjornsson E, Kalaitzakis E. Prevalence of pre-transplant electrocardiographic abnormalities and post-transplant cardiac events in patients with liver cirrhosis. *BMC Gastroenterol* 2014;14:65. doi:[10.1186/1471-230X-14-65](https://doi.org/10.1186/1471-230X-14-65)
22. Dare AJ, Plank LD, Phillips AR, et al. Additive effect of pretransplant obesity, diabetes, and cardiovascular risk factors on outcomes after liver transplantation. *Liver Transpl* 2014;20:281–290. doi:[10.1002/lt.23818](https://doi.org/10.1002/lt.23818)
23. Go AS, Mozaffarian D, Roger VL, et al. Heart disease and stroke statistics—2014 update: a report from the American Heart Association. *Circulation* 2014;129:e28–e292. doi:[10.1161/01.cir.0000441139.02102.80](https://doi.org/10.1161/01.cir.0000441139.02102.80)
24. Neal DA, Gimson AE, Gibbs P, Alexander GJ. Beneficial effects of converting liver transplant recipients from cyclosporine to tacrolimus on blood pressure, serum lipids, and weight. *Liver Transpl* 2001;7:533–539. doi:[10.1053/jlts.2001.24637](https://doi.org/10.1053/jlts.2001.24637)
25. Safadi A, Homsy M, Maskoun W, et al. Perioperative risk predictors of cardiac outcomes in patients undergoing liver transplantation surgery. *Circulation* 2009;120:1189–1194. doi:[10.1161/CIRCULATIONAHA.108.847178](https://doi.org/10.1161/CIRCULATIONAHA.108.847178)
26. Kia L, Shah SJ, Wang E, et al. Role of pretransplant echocardiographic evaluation in predicting outcomes following liver transplantation. *Am J Transplant* 2013;13:2395–2401. doi:[10.1111/ajt.12385](https://doi.org/10.1111/ajt.12385)
27. Gallegos-Orozco JF, Charlton MR. Predictors of Cardiovascular Events After Liver Transplantation. *Clin Liver Dis* 2017;21:367–379. doi:[10.1016/j.cld.2016.12.009](https://doi.org/10.1016/j.cld.2016.12.009)
28. Lim KBL, Schiano TD. Long-Term Outcome After Liver Transplantation. *Mt Sinai J Med* 2012;79:169–189. doi:[10.1002/msj.21302](https://doi.org/10.1002/msj.21302)
29. McGuire BM, Rosenthal P, Brown CC, et al; American Society of Transplantation. Long-term management of the liver transplant patient: recommendations for the primary care doctor. *Am J Transplant* 2009;9:1988–2003. doi:[10.1111/j.1600-6143.2009.02733.x](https://doi.org/10.1111/j.1600-6143.2009.02733.x)
30. Ousteky DH, Riera AR, Rothstein KD. Long-Term Management of the Liver Transplant Recipient: Pearls for the Practicing Gastroenterologist. *Gastroenterol Clin N Am* 2011;40:659–681. doi:[10.1016/j.gtc.2011.06.006](https://doi.org/10.1016/j.gtc.2011.06.006)
31. Charlton MR. Improving Long-Term Outcomes After Liver Transplantation. *Clin Liver Dis* 2014;18:717–730. doi:[10.1016/j.cld.2014.05.011](https://doi.org/10.1016/j.cld.2014.05.011)
32. Rowan CG, Brunelli SM, Munson J, et al. Clinical importance of the drug interaction between statins and CYP3A4 inhibitors: a retrospective cohort study in The Health Improvement Network. *Pharmacoepidemiol Drug Saf* 2012;21:494–506. doi:[10.1002/pds.3199](https://doi.org/10.1002/pds.3199)
33. Almutairi F, Peterson TC, Molinari M, Walsh MJ, Alwayn I, Peltekian KM. Safety and effectiveness of ezetimibe in liver transplant recipients with hypercholesterolemia. *Liver Transpl* 2009;15:504–508. doi:[10.1002/lt.21710](https://doi.org/10.1002/lt.21710)
34. Reuben A. Long-Term Management of the Liver Transplant Patient: Diabetes, Hyperlipidemia, and Obesity. *Liver Transpl* 2001;7(11 Suppl 1):S13–S21. doi:[10.1053/jlts.2001.29167](https://doi.org/10.1053/jlts.2001.29167)
35. van Son J, Stam SP, Gomes-Neto AW, et al. Post-transplant obesity impacts long-term survival after liver transplantation. *Metabolism* 2020;106:154204. doi:[10.1016/j.metabol.2020.154204](https://doi.org/10.1016/j.metabol.2020.154204)
36. Beckmann S, Denhaerynck K, Stampf S, et al. New-onset obesity after liver transplantation—outcomes and risk factors: the Swiss Transplant Cohort Study. *Transpl Int* 2018;31:1254–1267. doi:[10.1111/tri.13308](https://doi.org/10.1111/tri.13308)
37. Cassiman D, Roelants M, Vandenplas G, et al. Orlistat treatment is safe in overweight and obese liver transplant recipients: a prospective, open label trial. *Transpl Int* 2006;19:1000–1005. doi:[10.1111/j.1432-2277.2006.00379.x](https://doi.org/10.1111/j.1432-2277.2006.00379.x)
38. Ling Q, Xu X, Xie H, et al. New-onset diabetes after liver transplantation: a national report from China Liver Transplant Registry. *Liver Int* 2016;36:705–712. doi:[10.1111/liv.13042](https://doi.org/10.1111/liv.13042)
39. Bhat V, Tazari M, Watt KD, Bhat M. New-Onset Diabetes and Preexisting Diabetes Are Associated With Comparable Reduction in Long-Term Survival After Liver Transplant: A Machine Learning Approach. *Mayo Clin Proc* 2018;93:1794–1802. doi:[10.1016/j.mayocp.2018.06.020](https://doi.org/10.1016/j.mayocp.2018.06.020)
40. Bente D, Staufer K, Sterneck M. Orthotopic liver transplantation and what to do during follow-up: recommendations for the practitioner. *Nat Clin Pract Gastroenterol Hepatol* 2009;6:23–36. doi:[10.1038/ncpgasthep1312](https://doi.org/10.1038/ncpgasthep1312)
41. Ojo AO, Held PJ, Port FK, et al. Chronic renal failure after transplantation of a nonrenal organ. *N Engl J Med* 2003;349:931–940. doi:[10.1056/NEJMoa021744](https://doi.org/10.1056/NEJMoa021744)
42. Sharma P, Welch K, Eikstadt R, Marrero JA, Fontana RJ, Lok AS. Renal outcomes after liver transplantation in the model for end-stage liver disease era. *Liver Transpl* 2009;15:1142–1148. doi:[10.1002/lt.21821](https://doi.org/10.1002/lt.21821)
43. Zhang W, Fung J. Limitations of current liver transplant immunosuppressive regimens: renal considerations. *Hepatobiliary Pancreat Dis Int* 2017;16:27–32. doi:[10.1016/s1499-3872\(16\)60167-4](https://doi.org/10.1016/s1499-3872(16)60167-4)

44. Ebeling PR. Transplantation osteoporosis. *Curr Osteoporos Rep* 2007;5:29-37. doi:[10.1007/BF02938620](https://doi.org/10.1007/BF02938620)
45. Anastasilakis AD, Tsourdi E, Makras P, et al. Bone disease following solid organ transplantation: A narrative review and recommendations for management from The European Calcified Tissue Society. *Bone* 2019;127:401-418. doi:[10.1016/j.bone.2019.07.006](https://doi.org/10.1016/j.bone.2019.07.006)
46. Brunova J, Kratochvilova S, Stepankova J. Osteoporosis Therapy With Denosumab in Organ Transplant Recipients. *Front Endocrinol (Lausanne)* 2018;9:162. doi:[10.3389/fendo.2018.00162](https://doi.org/10.3389/fendo.2018.00162)
47. Watt KD, Pedersen RA, Kremers WK, Heimbach JK, Sanchez W, Gores GJ. Long-term probability of and mortality from de novo malignancy after liver transplantation. *Gastroenterology* 2009;137:2010-2017. doi:[10.1053/j.gastro.2009.08.070](https://doi.org/10.1053/j.gastro.2009.08.070)
48. Naldi L, Venturuzzo A, Invernizzi P. Dermatological Complications After Solid Organ Transplantation. *Clin Rev Allergy Immunol* 2018;54:185-212. doi:[10.1007/s12016-017-8657-9](https://doi.org/10.1007/s12016-017-8657-9)
49. Tajma T, Hata K, Haga H, et al. Post-transplant lymphoproliferative disorders after liver transplantation: A retrospective cohort study including 1,954 transplants. *Liver Transpl* 2021 Mar 2. doi:[10.1002/lt.26034](https://doi.org/10.1002/lt.26034)
50. Eshraghian A, Imanieh MH, Dehghani SM, et al. Post-transplant lymphoproliferative disorder after liver transplantation: Incidence, long-term survival and impact of serum tacrolimus level. *World J Gastroenterol* 2017;23:1224-1232. doi:[10.3748/wjg.v23.i7.1224](https://doi.org/10.3748/wjg.v23.i7.1224)
51. Park MJ, Roh JL, Choi SH, Nam SY, Kim SY, Lee YS. De novo head and neck cancer arising in solid organ transplantation recipients: The Asan Medical Center experience. *Auris Nasus Larynx* 2018;45:838-845. doi:[10.1016/j.anl.2017.11.006](https://doi.org/10.1016/j.anl.2017.11.006)
52. Bhat M, Al-Busafi S, Deschênes M, Ghali P. Care of the liver transplant patient. *Can J Gastroenterol Hepatol* 2014;28:213-219. doi:[10.1155/2014/453875](https://doi.org/10.1155/2014/453875)
53. Vera A, Gunson BK, Ussatoff V, et al. Colorectal cancer in patients with inflammatory bowel disease after liver transplantation for primary sclerosing cholangitis. *Transplantation* 2003;75:1983-1988. doi:[10.1097/01.TP.0000058744.34965.38](https://doi.org/10.1097/01.TP.0000058744.34965.38)
54. Finkenstedt A, Graziadei IW, Oberaigner W, et al. Extensive surveillance promotes early diagnosis and improved survival of de novo malignancies in liver transplant recipients. *Am J Transplant* 2009;9:2355-2361. doi:[10.1111/j.1600-6143.2009.02766.x](https://doi.org/10.1111/j.1600-6143.2009.02766.x)
55. Ziogas IA, Hayat MH, Tsoulfas G. Obstetrical and gynecologic challenges in the liver transplant patient. *World J Transplant* 2020;10:320-329. doi:[10.5500/wjt.v10.i11.320](https://doi.org/10.5500/wjt.v10.i11.320)
56. Cardonick E, Moritz M, Armenti V. Pregnancy in patients with organ transplantation: A review. *Obstet Gynecol Surv* 2004;59:214. doi:[10.1097/01.ogx.0000115774.42302.d4](https://doi.org/10.1097/01.ogx.0000115774.42302.d4)
57. Rao S, Ghanta M, Moritz MJ, Constantinescu S. Long-Term Functional Recovery, Quality of Life, and Pregnancy After Solid Organ Transplantation. *Med Clin North Am* 2016;100:613-629. doi:[10.1016/j.mcna.2016.01.010](https://doi.org/10.1016/j.mcna.2016.01.010)
58. Natekar A, Pupco A, Bozzo P, Koren G. Safety of azathioprine use during pregnancy. *Can Fam Physician* 2011;57:1401-1402.
59. Ritchie J, Seidman D, Srisengfa Y, Perito ER, Sarkar M. Family Planning in Liver Transplant: Patient and Provider Knowledge and Practices. *Liver Transpl* 2020;26:1233-1240. doi:[10.1002/lt.25835](https://doi.org/10.1002/lt.25835)
60. Cimino FM, Snyder KA. Primary Care of the Solid Organ Transplant Recipient. *Am Fam Physician* 2016;93(3):203-210.
61. Dew MA, Rosenberger EM, Myaskovsky L, et al. Depression and Anxiety as Risk Factors for Morbidity and Mortality After Organ Transplantation: A Systematic Review and Meta-Analysis. *Transplantation* 2015;100:988-1003. doi:[10.1097/TP.0000000000000901](https://doi.org/10.1097/TP.0000000000000901)