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Follow-up of liver transplant recipients

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A B S T R A C T

The number of surviving liver allograft recipients is increasing almost exponentially. The quality and length of life is increasing but most recipients have reduced survival and quality of life compared with healthy matched individuals.

Causes of premature death include cardio and cerebrovascular disease, renal failure, graft failure, de novo malignancy and recurrent disease.

Follow-up is needed lifelong to ensure graft and patient health and ensure that complications are recognised and treated early. Immunosuppression is kept to the appropriate minimum and prophylactic interventions are given early, such as use of statins and tight control of blood pressure and blood sugar.

Recipients will require life-long follow-up, and this is placing an increasing burden on transplant units. Follow-up is best done by close collaboration between the Liver Transplant Unit, the local hospital and primary care team. Involvement of other health care practitioners, such as recipient coordinators, pharmacists, dermatologists and addiction specialists may improve outcomes.

Key to successful follow-up are agreed protocols and good communication between the recipients and all relevant health care providers.

Use of IT allows for better communication and will support use of video and telephone consultations in selected instances.

The most appropriate follow-up will depend on many factors, including logistic and geographic issues, local experience.

The provision of well-funded and supported registries at local, national and international levels will allow for improvements in management.

Introduction

The number of liver transplants recipients alive is increasing. More people are receiving a transplant and survival is increasing. For example, in the US, as of June 30, 2016, 79,188 liver transplant recipients were alive with a functioning graft, including 68,970 who underwent liver transplant as adults; two years later, there were 88,715 liver transplant recipients were alive with a functioning graft, including 77,626 who underwent liver transplant as adults [1]. In the UK, in 2017, it was estimated that there were 9800 living liver transplant recipients [2]. This almost exponential rise in the number of those requiring follow-up will result in an increasing burden on clinicians to provide adequate care and support. The major causes of death with a functioning graft are shown in Fig. 1 [3].

Death after transplant may be caused by pre-existing disease, conditions as a consequence of immunosuppression or acquired diseases. The effect of immunosuppression may be a consequence of the relatively broad impact of immunosuppression itself such as the increased risk of some de novo malignancies or infections, a class effect such as renal failure associated with calcineurin inhibitors or osteopenia associated with corticosteroids or a drug-specific effect such as impaired wound healing with sirolimus.

Because the impact of many of these conditions can be modified by appropriate timely interventions, they are discussed in greater detail elsewhere in this volume. In this chapter, the follow-up of the well recipient is discussed. Investigation and management of the many causes of graft dysfunction are covered elsewhere.

Survival after transplant

Transplant units, regulators and registries publish 1, 5, 10 or 20-year survival rates. This information is of course important but
should not be taken as the sole outcome measure. Recipients may die from graft failure, from transplant-related factors (such as immunosuppression related conditions or technical problems) or from unrelated disease. Thus, some registries distinguish between patient survival (survival from transplant), graft survival (survival from transplant to graft failure) and transplant survival (survival with a functioning graft).

Outcomes of 106086 patients transplanted between 1988 and 2015 is shown in Table 1 [4]. Outcomes are dependent on many factors including age, indication and year of transplant. Thus, using current data for the UK, current 1- and 5-year patient survival for adults receiving their first graft are 94% and 83% respectively and for adults having a super-urgent transplant, the 1- and 5- year survival rates are 88% and 82% [5].

For liver transplant (LT) candidates, survival from listing is another key metric that is not only relevant to the patient but also a useful measure of the impact of the transplant unit: in the UK, it has been found that some units which have a survival rate higher than the median from listing (whether adjusted for known risk factors or unadjusted) but a lower survival rate after transplant. This may reflect the difference in acceptance rates of deceased donor organs [5].

Survival after transplant is increasing, primarily because of a reduction in early mortality but is, for the majority of recipients, significantly less than the equivalent age and sex matched controls [6]. The reduction in survival depends on gender, age at transplant and indication (Table 2). As the age of patients at transplant increases, non-transplant related factors become an increasing cause of death [7]. Extrapolation from older series must be done with caution as the major causes of graft loss and premature death are Hepatitis C virus recurrence and liver cell cancer recurrence. The former is now much less of an issue because of the use of highly effective antiviral therapy and the latter as indications for HCC are becoming more precise as those factors associated with recurrence become better defined.

Causes of death

The risk and cause of death after transplant vary during the period of follow-up (Fig. 1). Overall, the main causes of death in the first year after LT are multiple organ failure and cerebrovascular, cardiovascular, pulmonary, and renal complications. However, after the first post-LT year, mortality from technical complications, infections and general complications significantly decrease, while recurrence of primary liver diseases (particularly malignancies) and cardiovascular disease increase [8]. Watt [9] analysed data up to 2003 in the National Institute of Diabetes and Digestive and Kidney Diseases LT Database of 798 recipients transplanted between 1990 and 1994. Causes of death after 1 year: 28% hepatic, 22% malignancy, 11% cardiovascular, 9% infection, 6% renal failure. Renal-related death increased dramatically over time. Univariate analysis of risk factors for death identified male gender, age, decade of transplant, pre-LT diabetes, post-LT diabetes, post-LT hypertension, post-LT renal insufficiency, re-transplantation after 1 year, pre-LT malignancy, alcoholic disease and metabolic liver disease; with similar risks noted for death after 5 years. Hepatitis C, re-transplantation, post-LT diabetes, hypertension and renal insufficiency were significant risk factors for liver-related death. Cardiac

### Abbreviations

| Abbreviation | Definition |
|--------------|------------|
| eGFR         | estimated glomerular filtration rate |
| HCV          | Hepatitis C Virus |
| IT           | Information Technology |
| LT           | Liver Transplant |
| PBC          | Primary Biliary Cholangitis |
| QALY         | Quality adjusted life year |
| SIR          | Standardised incidence ratio |
| US           | United States |

Table 1

| Indication                | 1 year | 5 year | 10 year | 14 year | 20 year |
|---------------------------|--------|--------|---------|---------|---------|
| Acute liver failure       | 75%    | 65%    | 59%     | 55%     | 46%     |
| Chronic liver disease     | 84%    | 72%    | 60%     | 51%     | 38%     |
| Metabolic                 | 87%    | 79%    | 71%     | 65%     | 57%     |
| Malignant cancer          | 84%    | 63%    | 49%     | 40%     | 31%     |
| Benign cancer             | 89%    | 84%    | 75%     | 66%     | 57%     |
| Other                     | 77%    | 68%    | 61%     | 56%     | 47%     |

Fig. 1. Causes of death with a functioning liver allograft (From Neuberger et al. [3]).
As discussed elsewhere in this volume, quality of life after outcomes should be better (not similar) to the age and sex matched transplantation gives survival similar to the healthy population, (PBC primary biliary cholangitis).

47%, respectively. Excluding those who died within the transplant units. Patient and graft survival at 20 years was 53% and the ‘exclude those with non-hepatic life threatening disease whereas remembered that the transplant population is carefully selected to outcome similar to the normal population is reassuring, it should be increased throughout follow-up. While the demonstration of an prevalence of arterial hypertension, renal failure and obesity all malignancy (19.9%) were the most common causes of death. The 10 years cumulative rates of cardiovascular events and de novo tu-

Comparison of predicted outcome with age and sex matched population of those who survived 6 months after transplant [6].

None of these simple outcome measures include quality of life. As discussed elsewhere in this volume, quality of life after transplant is usually much greater than pre-transplant but often fails to reach levels seen in a normal, matched healthy population. Simply reporting the incidence of causes of death or de novo malignancies for example will not give a full picture. Increasing age in the non-immunosuppressed person is associated with, for example, a greater risk of developing renal failure, heart disease and cancer. All these potential causes of death may also be associated with immunosuppression. Therefore, standardised incidence rates as well as absolute rates need to be considered in measuring outcomes. For example, in one study in the UK, of about 25000 kidney recipients, 117 developed breast cancer: in an age and sex matched population 122 cases would be anticipated, so the standardised incidence ratio (SIR) for kidney transplant recipients is 1.0 and 0.8 for liver recipients (no significant difference) [13]. Thus, suggesting there is no need for additional monitoring for breast cancer in liver and kidney transplant recipient.

Ongoing costs of transplants

Liver transplantation is expensive and, while costs are greatest in the first year, there are significant costs during follow up. While measuring costs of liver transplantation is a challenge and extrapolation from one jurisdiction to another is problematic, data are scarce, but liver transplantation is expensive. A recent report from the US [14] showed that during the first post-transplant year, the average reimbursement for liver recipients with primary Medicare coverage at the time of transplant in 2008–2013 was US$185k. For those who survived the first year with a functioning graft, the average reimbursement for recipients who survived the first year posttransplant with a functioning graft was US$154k. This rose to US$388k for recipients who required re-transplant, 252% of the cost for those who ended the year alive with function. Average per-patient costs in the second year posttransplant were US$28k. Relative to the US$25k average per person per year expenditure for recipients who were alive with function at the end of the second year, US$123k was spent for those who required re-transplant and US$145k for those who died with function. As expected, costs are higher for sicker patients (such as MELD>35 or with acute liver failure). In the UK in 2003, the estimated costs of a transplant for PBC was £53k and for ALD £66k, including the cost of assessment and the mean incremental cost per quality-adjusted life-year from time of listing to 27 months for patients with PBC, ALD, and PSC are £29k and £48k, respectively [15]. A similar study in Finland [16] reported in 2011 that the median costs after LT were €142k and €178k for 1 and 5 years, respectively. The costs of the first year were 80% of the 5-year costs whereas the main cost during years
2–5 was immunosuppression drugs (59% of the annual costs). The cost/QALY ratio improved from €158k/QALY (quality adjusted life year) at 1 year to €45k/QALY at 5 years.

There are costs too for the recipient. The main costs include living and medication costs, transportation for the patient and carer, relocation expenses, and income loss [17]. These costs will depend on many local factors, as medication may be covered by insurance companies or the state. In those jurisdictions where recipients have to bear some or all costs of medication (a major cause of out of pocket expenses), sometimes LT recipients have to make decisions about how they wish to spend limited financial resources. Serper [18] and colleagues did a prospective study of 201 transplanted recipients (103 liver) in Chicago and Atlanta between 2011 and 2012. 17% of patients reported medication trade-offs; the most common trade-offs were inability to afford a prescription in the past 12 months and making choices between prescriptions and food. In a multivariable analysis, insurance type, limited health literacy and 3 or more comorbid conditions were associated with trade-offs. Of concern, those who had to make trade-offs were more likely to report nonadherence to medications and these were associated with a greater risk of post-transplant hospital admissions. Trade-offs included delaying buying medication, reducing the frequency of taking medication or choosing to buy food. These observations, that some recipients have to make decisions whether to spend limited resource on necessary medication or necessary food has significant implications for patients, their families, their health care practitioners, insurance companies and wider society [19].

Follow-up of transplant recipients

The purpose of follow-up is to ensure the recipient is remaining healthy and potential problems are identified early and where appropriate, interventions put in place to mitigate complications [20]. As the number of recipients increase, follow-up is becoming an increasing burden. Given that many recipients live at a distance from their transplant unit, the logistic and socio-economic burden placed on recipients may be considerable. There are surprisingly few data on the most effective method of follow-up of the recipient. However, close collaboration between the transplant unit and both secondary and primary care is necessary [21,22].

A survey in the United States conducted over a decade ago [23] found considerable variation in practice. Hepatologists, primary care physicians and surgeons were primarily responsible for the overall care of liver recipients 1 year or more after liver transplantation. Hepatologists felt that metabolic complications were common, but few strongly agreed that major co-morbidities such as hypertension, chronic renal insufficiency, diabetes mellitus, dyslipidemia, and bone disease were well controlled. The majority of hepatologists indicated that these should be managed by the primary care doctor, but this was not often done. In practice, guidelines for the primary care physician are available [24].

The purposes of outpatient follow-up are listed in Table 3.

Table 3

| Purposes of routine outpatient follow-up for liver transplant candidates. |
|---|
| Monitoring and adjusting treatment |
| Ensuring optimal health |
| Detect deterioration and arrange appropriate investigation and intervention |
| Prevent admission |
| Meet patient expectations |
| Maintain patient access to secondary services |

In transplant units, the hepatologists usually play a significant role in follow-up [25] but follow-up may be successfully done by recipient transplant coordinators [26].

Some units have set up clinical pathways which would allow clearer pathways [27]. The recent Covid-19 pandemic has encouraged transplant units to make greater use of video and/or telephone consultations [28]. Such clinics have been evaluated over several decades. Alternatives to the traditional face-to-face outpatient appointment held in the transplant unit include remote monitoring and telephone or video-link appointment. There has been some hesitancy to adopt these alternatives for a variety of reasons including concerns with locally available IT infrastructure and support, data protection, loss of remuneration from clinical commissioning groups and discrimination against patients less comfortable with necessary technology [29]. Remote monitoring is an umbrella term used to describe any technology that allows patients to submit personalised data. These data can be used to reassure and support patients to achieve health goals through self-management and allow data transfer back to clinical teams for interpretation and clinical monitoring from a distance. Several hospitals have developed portals that are used for data sharing and processes incorporated that can alert clinical teams to potential clinical problems leading to a more formal review. Such portals also allow patients to communicate directly with a relevant health care professional.

Telephone or video conferencing can lead to a face-to-face conference if needed. The option saves the patient making a trip to the transplant unit with the attendant reduction in financial costs and time of travel and waiting in clinic but for the liver allograft recipient, the clinician will require additional information that includes measurement of weight and blood pressure together with results of blood tests (such as liver and renal function) and, where appropriate, therapeutic drug monitoring. Thus, there needs to be robust mechanisms in place where the patient will attend for venesection and for the laboratory reports to be sent to the clinician who will need to review them and, if necessary, act on them. These remote clinics will not allow for some investigations (such as imaging) or review of skin lesions.

A Cochrane review in 2015 concluded that the effectiveness of telemedicine (TM) depends on a number of different factors, including those related to the study population such as the severity of the condition and the disease trajectory of the participants, the function of the intervention whether it is used for monitoring a chronic condition, or to provide access to diagnostic services, as well as the healthcare provider and healthcare system involved in delivering the intervention [30]. They also commented that the use of telemedicine in the management of heart failure appears to lead to similar health outcomes as face-to-face or telephone delivery of care; there is evidence that TM can improve the control of blood glucose in those with diabetes. The cost to a health service, and acceptability by patients and healthcare professionals, is not clear due to limited data reported for these outcomes.

In the field of liver transplantation, Le [31] and colleagues in Los Angeles evaluated 21 matched telemedicine patients and found patient satisfaction was similar between the two groups and those
Factors to be considered in routine follow-up outpatient clinic for liver allograft recipients.

| Aspect to be assessed   | Measure                                      |
|-------------------------|----------------------------------------------|
| Graft health            | Liver Tests                                  |
| Cardiovascular risk factors | Blood pressure                               |
|                         | Blood lipids                                 |
| Renal function          | eGFR, urea, creatinine                       |
| Diabetes mellitus       | Blood sugar/Hba1c                             |
| Malignancy              | Chest X-ray, colonoscopy<sup>a</sup>         |
| Immunosuppression       | Full blood count, Therapeutic blood monitoring |
| Bone health             | Risk factors                                 |
| Other                   | DEXA scan                                    |
|                         | Sexual health                                |
|                         | Dental care                                  |
|                         | Travel                                       |
|                         | Work/employment                              |
|                         | Immunisations                                |
|                         | Other medications                            |

<sup>a</sup> Especially for those transplanted for alcohol related liver disease.  
<sup>b</sup> Especially for those with colitis.

in the telemedicine group were just as satisfied with communication and interpersonal approach compared to clinic patients, they experienced significantly less commute and shorter waiting times. 19 of the 21 of the telemedicine patients opted to use the service again. A prospective study has been set up [32] in Birmingham, UK, where stable liver patients between 1- and 5-years post-transplant will be randomised in equal numbers to video clinic appointments or standard face-to-face appointments. The intervention group will have outpatient appointments from home via a secure video link accessed through the hospital patient portal. Outcomes will include patient satisfaction, costs, clinical contacts and user experience.

The key to a successful video or telephone conference is patient selection. There are increasing IT resources able to support these clinics but a robust and functional IT system, with excellent administrative support is essential for the success of these approaches.

The out-patient appointment with the liver recipient

Whether the appointment is face-to-face, by telephone link or video link and whether the appointment is with the transplant unit, the local liver/gastroenterology unit or the primary care clinician, the purpose is the same. Areas that need to be considered, in addition to the graft health relate primarily to minimising the effect of immunosuppressive agents and preventing premature death by focussing on the causes of premature death or comorbidity (see Table 4). The use of a protocolised approach may result in better patient and graft outcomes [33].

Management of most of the main causes of graft failure and comorbidity are covered in detail elsewhere in this volume and so will not be discussed here.

Skin clinics: as discussed elsewhere in greater detail, immuno-suppressed recipients have an increased risk of skin problems: these range from infections (viral, bacterial and fungal) which may be superficial or deep, tumours such as Kaposi’s sarcoma, cutaneous anaplastic large-cell lymphoma, Merkel cell carcinoma and more commonly non-melanoma skin cancers and malignant melanoma. Less common are drug-related skin rashes, graft-versus host disease and immunosuppressive drug related conditions such as sebaceous hyperplasia and acniform rash. Transplant recipients should be given advice about avoiding sun exposure and the need to report any new or changing skin lesion at an early opportunity. The American Society of Transplantation recommends full-body skin examinations by ‘a qualified health professional, with experience in diagnosing skin cancer’ every year, with more frequent assessments for those who may be at higher risk because of a previous skin cancer [34] but the increasing number of all allograft recipients might place unrealistic demands on the dermatology service. For recipients at high risk of skin cancer, regular review in a specialist clinic allows for more rapid diagnosis and treatment [35] and will pick up skin cancers missed by either the patient or the clinician [36] but it is not yet clear whether this affects outcome.

**Pharmacist review:** pharmacists are often under-recognised as a key health care professional in transplant follow-up. Patient induced medication errors are not uncommon and are associated, at least in renal transplantation, with worse outcomes [37] so it is likely that a full medication review is likely to improve liver outcomes too. Face to face involvement may be more effective than pre-clinic chart review [38].

Adoption support: Those transplant recipients who had alcohol or other drug abuse and those who have mental health issues may also benefit from support at clinic visits: the association of an alcohol addiction unit was associated with a reduction in recidivism [39].

**Dental care:** dental care is often overlooked in the liver transplant recipient [40,41]. Many patients with liver disease have dental problems and these may be exacerbated post-transplant. These patients also had a high index of xerostomia, caries, peri-odontal disease, apical lesions, and fungal infections, which may be exacerbated by immunosuppressive drugs and other treatments. Those transplanted for autoimmune liver diseases may also have sicca syndrome which is associated with dental problems. In one study of 40 paediatric liver allograft recipients in Switzerland, just under half presented at least one carious lesion and two-thirds had more than 20% of sites with plaque and gingival inflammation [41]. Gingival hypertrophy is associated especially with use of cyclosporin and some other drugs as nifedipine. Thus, it is recommended that all recipients have regular dental check-ups.

**Bone health:** many patients with chronic liver disease especially those with cholestatic liver disease and those on long-term corticosteroids, have impaired bone health as evidenced by a decrease in bone mineralisation and an increased risk of fractures. After liver transplant, some of the risk factors for osteopenia, such as cholestasis, malabsorption, immobility and poor nutrition, may improve but liver allograft recipients remain at risk of low bone mineral density and its consequences. Thus, it is recommended that recipients be assessed for osteopenia and offered appropriate advice and, if indicated, medication. Vitamin D and calcium supplementation should be considered in all recipients; for those with low bone mineral density, alendronate and pamidronate may be effective in reducing further bone loss [42].

**Self-management:** the recipient must, of course, share responsibility with the health care professionals. A recent study [43] identified areas of self-management including medication non-adherence, alcohol recidivism and health maintenance. Reported rates of medication nonadherence ranged from 8% to 66%. Medication nonadherence was related to recipients’ age, gender, time since transplant and history of pre-transplant substance/alcohol abuse. Adherence should be sought at each visit and, if suspected, investigated and managed appropriately. Other areas of self-management include avoidance of smoking, obesity, use of immunisations where indicated and maintaining a healthy life
style.

Exposure to infection and immunisations: liver allograft recipients, like other immunosuppressed individuals, are at greater risk of some infections, bacterial, viral, protozoal and fungal. Immunisation plays an important role in preventing disease and allows recipients to travel more widely. Immunosuppression may lead to a sub-optimal response to immunisation and most liver vaccines should be avoided so ideally immunisation should be offered before liver transplantation [44]. In general travel should not be discouraged although recipients need to be aware of the local risks as well as making plans for adequate medical care. For those intending to travel to more exotic areas, expert and current advice is required [45]. Patients should be advised on vaccine-preventable illnesses as well as any need for prophylaxis such as malaria. Advice should be given for modifiable risks and exposures such as food and water safety, and insect bite prevention [46].

Exercise and wellbeing: as discussed elsewhere in this volume, quality of life after transplantation and employment rates are both below those of matched controls.

Physical exercise is important in the liver allograft recipient as it is in the general population and improves quality of life and helps depression symptoms. In a study from Italy, Totti [47] conducted a randomised trial of 40 LT recipients with stable liver function who were assigned to either interventional exercise attending 3 supervised training sessions per week or usual care where they were given general advice. Of the 29 who completed the study, maximum workload and BMI increased in both groups, but the blood glucose fell and arm muscle strength increased in the active group. Vitality and general and mental health domains significantly improved after physical exercise. Other groups have reported similar results both in liver and renal transplant recipients [3,48,49]. Barriers to exercise include physical limitations, insufficient energy, fear and associated comorbidities. Others have found that factors associated with lower levels of physical activity post-transplant include younger age, female gender, not actively working, physical limitations and low self-confidence. The Transplant Games were set up to encourage transplant recipients to take part in physical exercise, provide a forum for peer support for both recipients and their families and to act as a showcase for the benefits of organ donation. Transplant Games are also held nationally and are designed to promote desirable health behaviours and discourage unhealthy ones.

Importance of registries

There are many liver transplant registries, at the local, national and international level. These registries are playing an increasingly important role in understanding the outcomes of liver transplantation, understanding the risks and benefits, causes of morbidity and mortality. Combining data on the organ donor, the transplant process, recipient details and follow-up allows a far greater appreciation of outcomes and how to improve them. The many publications from registries (231 listed on PubMed for 2019 alone) indicates the wealth of information that can be gleaned. Key to the success of registries is the need for completeness of data and agreement on common terminology. Linkage of transplant registries with other registries (such as cancer or death registries) allows improved outcomes. Registries need adequate funding to ensure data collection is complete and timely, to allow for changes in terminology (such as the use of non-alcoholic fatty liver disease) and new treatments (such as introduction of new immunosuppressive agents). There is also the need not only for involvement of appropriate statisticians but also clinical oversight and ownership by the transplant community. Electronic submission of data and linkage of databases allow easier, more accurate and more reliable transfer of information from original source to the database. The introduction of laws on data protection does add a layer of cost and bureaucracy but commissioners should continue to insist that organisations involved in organ donation, transplantation and follow-up submit accurate data in a timely manner.

Furthermore, the recipient and clinicians must be aware of donor transmitted diseases, especially cancer and these must be reported immediately to the appropriate regulatory authority so that the recipients of other organs from the index donor can be assessed and offered treatment [52].

Practice points

- Survival after liver transplant is increasing but remains, for many, less than that of an age and sex matched population
- Causes of premature death include graft failure, cardiovascular disease, de novo malignancies, infection and renal failure
- Follow-up requires collaboration between healthcare professionals in tertiary, secondary and primary care
- Use of agreed protocols will allow for safer follow-up
- Outpatient follow-up requires active assessment of the patient and the graft and management of risk factors including good control of blood pressure, blood sugar and lipids, maintain renal function, advice on healthy lifestyle such as taking exercise, avoiding obesity, smoking and excess alcohol, appropriate immunisation and advice on dental and sexual health and ensuring the immunosuppression regimen is appropriate
- The increasing number of surviving liver allograft recipients is putting an increasing burden on transplant units and innovative ways of managing the recipients, such as sharing care with local liver units and primary care clinicians and use of telemedicine will allow a more tailored approach.

Research agenda

More research is needed to: establish why the length of survival
and quality of life for liver transplant recipients is often below that of the general population. How best to minimise immunosuppression. Understand the causes and remedies for non-compliance. Agree follow-up protocols.

Declaration of competing interest
I have no conflicts of interest to declare.

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