LIVER

Life expectancy of adult liver allograft recipients in the UK

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Background: Liver transplantation is a very successful therapy for those with end stage disease. Although there are numerous data on patient and graft survival after liver transplantation, life expectancy and possible loss of life (compared with a normal matched population) in those who survive remains unknown.

Aims: To assess the life expectancy and life years lost of adult liver allograft recipients, compared with an age and sex matched UK population to provide patients with more information and to improve the use of a scarce resource.

Methods: Using the National Transplant Database held by UK Transplant, on over 3600 adult liver allograft recipients transplanted between 1985 and 2003, we analysed survival of all adults who survived more than six months after transplantation and compared survival after transplantation with national age and sex matched controls to assess life years lost.

Results: Estimated median survival time of the analysis cohort of 2702 adult liver allograft recipients was 22.2 years (95% confidence interval 19.3–25.6), with an estimated loss of seven life years compared with an age and sex matched population.

Conclusions: Overall, female recipients have a longer life expectancy and lose fewer life years than male recipients. While younger recipients have a longer life expectancy, they also lose more life years. Those transplanted for cancer, hepatitis C virus infection, and alcoholic liver disease had the greatest loss of life years.

Liver transplantation is associated with a major and significant improvement both in survival and quality of life.^{1–2} However, liver allograft recipients remain at increased risk of morbidity and mortality because of technical problems, recurrence of disease, associated diseases such as diabetes mellitus, and the complications of immunosuppression, such as cardiovascular and renal disease, and an increased risk of malignancy.^{3–4} It is therefore unlikely that the life expectancy of the recipient is normal.

Although there are abundant data published from individual centres and from registries on graft and patient survival, there is no information about the individual's life expectancy compared with an expected survival in the normal individual. As many of the liver allograft recipients are young, it is important for them and their family to have a reasonable understanding of their life expectancy so that, for example, informed decisions can be made about a return to work or whether to start a family. Over the past two decades there have been many major advances in the selection and postoperative management of recipients. Improvements in the management of the donor, better selection of the recipient, improvements in surgical and anaesthetic techniques, and a wider choice of antimicrobials and immunosuppressive agents are some of the reasons why survival rates have shown a consistent improvement over time. However, these improvements have been balanced by other factors that may reduce outcome, such as a greater use of extended criteria grafts ("marginal" livers) and split livers, and acceptance of sicker and older recipients. None the less, most of the improvement has been associated with a reduction in the mortality within the first six months (fig 1A); thereafter, mortality rates have been fairly stable.

The aim of the present study was to examine data from the National Transplant Database to provide survival estimates and determine the extent of reduction in survival compared with an age and sex matched normal population. We restricted survival estimation to those who survived six months after transplantation because, as illustrated in fig 1B, mortality rates of those

who have survived six months after transplantation show no significant change with year of transplantation ($p = 0.3$). This is true for the whole cohort of adult patients as well as for those in the major diagnostic groups, such as primary biliary cirrhosis (PBC), hepatitis C virus infection (HCV), and alcoholic liver disease (ALD).

METHODS

Liver allograft recipients

Data were obtained from the National Transplant Database on 3600 adult orthotopic liver allograft recipients who had survived six months after their first elective deceased heart beating liver only transplant in the UK between 1 January 1985 and 31 December 2003. This database is maintained by UK Transplant on behalf of transplant services in the UK and Republic of Ireland. The follow up time of the group of patients transplanted between 1985 and 2003 ranged from six months to 18 years.

Adult recipients were defined as patients aged 17 years or older at the time of transplantation. Patient survival time was calculated as the time from first liver transplant to patient death. For analysis purposes, six months (182 days) was subtracted from each patient survival time as we selected only those who had survived six months. Based on clinical judgement, the factors considered in the modelling process were patient age, sex, year of transplant, and primary liver disease. Age was categorised into five groups: 17–34, 35–44, 45–54, 55–64, and 65 years and over, and primary liver disease was categorised into nine groups: PBC, autoimmune cirrhosis, hepatitis B virus infection (HBV), sclerosing cholangitis, cryptogenic cirrhosis, ALD, HCV, cancer (all types, due to small numbers), and other. Until March 1994, patients were categorised on the database according to their primary diagnosis (such as cirrhosis from HCV or liver cell cancer) and

Abbreviations: AFT, accelerated failure time; ALD, alcoholic liver disease; HCV, hepatitis C virus; HBV, hepatitis B virus; PBC, primary biliary cirrhosis

Figure 1 Kaplan-Meier estimates by year of transplant for adult liver allograft recipients in the UK, transplanted between 1 January 1985 and 31 December 2003. (A) Entire dataset ($n=4184$); (B) survival for those who survived six months ($n=3600$).

it was not until 1 March 1994 that secondary diagnoses (for example, HCV and liver cell cancer) were recorded. Because of concerns that this may lead to an underestimate of the effect of cancer on outcome, we undertook a further analysis. Using the subset of patients transplanted between 1994 and 2003, we categorised patients with any type of cancer into the cancer group, whether or not cancer was the primary diagnosis. Life expectancies estimated from this database were very similar to those found using the entire cohort of data from 1985 to 2003. This suggests to us that where recipients had a large tumour, recipients may have been categorised in the cancer group but where the cancer was incidental, the recipient was categorised according to the underlying disease.

Data were randomly divided into two datasets. One dataset comprised 75% of the data (2702 observations) and was used for the development of the model (modelling dataset). The second dataset comprised the remaining 25% of data (898 observations) and was used to validate the final model (validation dataset).

Parametric accelerated failure time (AFT) models⁵ were considered for survival times of recipients in the modelling dataset. Weibull, log logistic, and log normal AFT models were developed and the suitability of each of the three distributions assessed. Of these, the Weibull model was found to provide the most satisfactory description of survival times.

Using the modelling dataset, parameter estimates of the risk factors included in the fitted model were obtained, together with the risk scores of the individuals in this dataset. Patients were then divided into three groups on the basis of their risk scores, with patients in each group having high, medium, and low risk of death, respectively. The adequacy of the fitted model was demonstrated by taking the validation dataset and using the parameter estimates from the fitted model to estimate

survivor functions for individuals with risk scores in each of the three groups previously defined, and comparing these with the corresponding Kaplan-Meier estimates from the actual data.⁵

The model included patient age group, sex, and primary liver disease group. Although year of transplant was considered as a factor in the model building process, it was not found to be significant ($p=0.4$), and was excluded from the model.

The life expectancy of individual liver allograft recipients was then taken to be their model based estimate of median survival time plus six months (182 days). This leads to estimates of median survival times for the different patient age, sex, and primary liver disease groups, from time of transplant.

UK population dataset

UK population data were obtained from the Office for National Statistics.⁶ Using the table of life expectancies for males and females of various ages at particular times, a regression model was fitted in order to predict the equivalent UK population life expectancy for each patient at the time of transplant. These life expectancies were then compared with the estimated median life expectancies of the liver allograft recipients for each age group and sex.

RESULTS

Estimated median life expectancy of the 2702 adult liver allograft recipients was 22.2 years (95% confidence interval 19.3–25.6), and the estimated life expectancy of the equivalent UK population was 29.2 years. Thus the number of life years lost was seven on average. Estimated median life expectancy for males and females and patients in the different age groups is presented in table 1.

Overall, female liver allograft recipients had a longer life expectancy and lost fewer life years than male liver allograft

Table 1 Median life expectancy of adult liver allograft recipients in the UK, transplanted between 1 January 1985 and 31 December 2003, by recipient sex, age, and primary liver disease group

Risk factor	Life expectancy (y) of allograft recipients*	National population life expectancy (y)	No of life years lost	No of allograft recipients	No of deaths
Sex					
Male	18.3 (15.6–21.5)	27.6	9.3	1474	287
Female	26.8 (22.3–32.3)	31.1	4.3	1228	218
Age group (y)					
17–34	28.8 (19.2–43.3)	51.2	22.4	221	35
35–44	24.6 (18.7–32.4)	38.3	13.7	440	80
45–54	25.3 (20.5–31.2)	29.7	4.4	933	158
55–64	19.5 (16.1–23.6)	21.8	2.3	905	183
65+	12.2 (8.8–17.0)	16.2	4.0	203	49
Primary liver disease					
PBC	35.8 (28.1–45.6)	29.2	–6.6	704	105
Autoimmune cirrhosis	24.5 (15.8–38.2)	29.2	4.7	148	26
HBV	24.2 (15.0–39.2)	29.2	5.0	147	22
Sclerosing cholangitis	26.0 (18.4–36.8)	29.2	3.2	284	44
Cryptogenic cirrhosis	33.9 (21.9–52.7)	29.2	–4.7	207	27
ALD	15.0 (12.2–18.6)	29.2	14.2	533	117
HCV	12.0 (9.2–15.7)	29.2	17.2	339	70
Cancer	5.3 (3.9–7.1)	29.2	23.9	107	46
Other	16.5 (12.0–22.9)	29.2	12.7	233	48
Median life expectancy (y) of allograft recipients	$\{ \exp [9.92 + (0.03 \times \text{sex}) - (0.27 \times \text{age}_{35\text{to}44}) - (0.27 \times \text{age}_{45\text{to}54}) - (0.56 \times \text{age}_{55\text{to}64}) - (1.09 \times \text{age}_{65\text{andover}}) - (0.56 \times \text{AC}) - (0.48 \times \text{HBV}) - (0.48 \times \text{SC}) - (0.14 \times \text{CC}) - (0.98 \times \text{ALD}) - (1.20 \times \text{HCV}) - (2.05 \times \text{CA}) - (0.97 \times \text{other})] + 182 \} / 365.25$				

*Median (95% confidence interval).

ALD, alcoholic liver disease; HCV, hepatitis C virus; HBV, hepatitis B virus; PBC, primary biliary cirrhosis.

Final model: values of risk factors included:

Sex: Sex = 1 if male, 0 if female.

Age group: $\text{age}_{35\text{to}44} = 1$ if patient aged between 35 and 44 years, 0 otherwise; $\text{age}_{45\text{to}54} = 1$ if patient aged between 45 and 54 years, 0 otherwise; $\text{age}_{55\text{to}64} = 1$ if patient aged between 55 and 64 years, 0 otherwise; $\text{age}_{65\text{andover}} = 1$ if patient aged 65 years or over, 0 otherwise.

Primary liver disease: AC = 1 if patient has autoimmune cirrhosis, 0 otherwise; HBV = 1 if patient has HBV, 0 otherwise; SC = 1 if patient has sclerosing cholangitis, 0 otherwise; CC = 1 if patient has cryptogenic cirrhosis, 0 otherwise; ALD = 1 if patient has ALD, 0 otherwise; HCV = 1 if patient has HCV, 0 otherwise; CA = 1 if patient has cancer, 0 otherwise; other = 1 if patient has an other liver disease to those categorised, 0 otherwise.

recipients. Younger liver allograft recipients had a longer life expectancy than older allograft recipients, but they also lost more life years. As age increased, estimated median life expectancy of the liver transplant recipients did not decrease as sharply as life expectancy of the equivalent UK population.

Estimated median life expectancy of the liver allograft recipients with different primary liver diseases varied quite substantially, as shown in table 1. Patients who were transplanted for PBC had a better outcome compared with patients transplanted for cancer, HCV, or ALD, and no life years were lost compared with the life expectancy of the equivalent UK population. Similar observations were made for patients transplanted for cryptogenic cirrhosis.

Although it was of great interest to estimate the life expectancies for every combination of patient age and primary liver disease, due to insufficient patients one could not expect the prediction model accurately to predict these life expectancies.

The model that can be used to predict median life expectancies of liver allograft recipients is presented in table 1.

DISCUSSION

It is now well established that for the great majority of patients, liver transplantation is associated with an increase in both the quality and length of life.^{2–8} The benefit of liver transplantation on the length of life becomes apparent when the model for end stage liver disease score prior to transplantation exceeds 15.⁷ However, life after transplantation is not normal and both patient and graft survival may be affected by a variety of factors, including the effects of recurrent disease, the

consequences of immunosuppression, such as increased risks of infection and malignancy, as well as cardiovascular and cerebrovascular diseases, diabetes mellitus, and renal failure.^{8–9} Previous studies have focused on survival of the graft or the patient, but the aim of the present study was to determine both the life expectancy of adults who have undergone liver transplantation and to see whether, for those who survived the perioperative complications, there was any reduction in life expectancy, in comparison with an age and sex matched population. We have already found that this information is especially important for those recipients who need to make informed decisions about long term plans, such as starting a family or work plans.

For those adult liver allograft recipients who survived six months after transplantation, outcomes were very good, with an overall life expectancy of 22.2 years, but this represents a loss of seven life years. Those transplanted for cancer, HCV, and for ALD did worse. In part, the poorer outcomes in these recipients are explained by either recurrent disease or associated comorbidities. That the loss of life years is greater in the younger recipients is likely to be due to the fact that the consequences of immunosuppression (such as increased risk of malignancy and infection) are likely to be less related to age but rather to duration of immunosuppression. Thus we have reported that while the absolute risk of de novo malignancy in liver allograft recipients is greatest in the older recipient, the relative risk is greater in younger recipients.¹⁰

During the evolution of the transplant programme in the UK, there have been many changes in both the selection and management of recipients. Many studies have found that one

year survival rates increase over time¹¹; however, survival of those who have survived the first postoperative year has not changed: this is likely to represent the change in case mix, with a greater number of patients who are older and with indications such as HCV where recurrence is associated with poorer outcomes.¹² We estimated survival in those who survived six months after transplantation as most of the immediate consequences of surgery would be past, but when one year survivors were assessed, no significant differences were observed.

The predicted life expectancy and estimated loss of life years must be treated with some caution: median survival of all adult liver allograft recipients transplanted between 1985 and 2003 (n = 4184) is at least 15 years so estimates of survival greater than 15 years will have a wide confidence interval. Caution must be used when extrapolating data from a population to an individual. Furthermore, comparison with the age and sex matched normal population is likely to overestimate survival and underestimate the loss of life years as those who have undergone transplantation will be selected and, unlike those in the general population, those with significant extrahepatic comorbidities will be excluded. These observations may explain the observation that the older recipient will have an estimated survival similar to the age and sex matched population and that those grafted for PBC and for cryptogenic cirrhosis appear to have a greater probability of survival than age and sex matched controls. It must also be stressed that over the evolution of the liver transplant programme there have been many changes in the selection of patients for transplantation, quality of grafts, as well as the follow up of patients with respect to immunosuppression, and greater awareness and treatment of complications such as diabetes and hypertension. In addition, criteria for selection of patients both with hepatocellular carcinoma and cholangiocarcinoma have been refined, and the advent of effective treatment for HBV infection has allowed effective transplantation of these patients. If newer treatments for HCV infection will improve survival, then estimates of survival and life years lost will need significant revision. Finally, the limitations of the database must be acknowledged, and the possible confounding effects of single diagnosis recording before 1994 must be recognised.

None the less, despite these concerns about extrapolating data applicable to a population to the individual, we have

discovered that liver allograft recipients find the prognostic information provided by this study of great practical help.

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The analyses described in this paper were carried out at UK Transplant, who maintain the National Transplant Database on behalf of transplant centres in the UK. UK Transplant has exemption from the data protection act under section 60 of the Health and Social Care Act 2001. This allows UK Transplant to use patient identifiable information for medical purposes without the consent of patients.

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