Midterm cost-effectiveness of the liver transplantation program of England and Wales for three disease groups

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Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
Liver transplantation was investigated for three separate disease groups. More specifically, primary biliary cirrhosis (PBC), alcoholic liver disease (ALD) and primary sclerosing cholangitis (PSC).

Type of intervention
Other: transplantation.

Economic study type
Cost-utility analysis.

Study population
The study population comprised adult patients with PBC, ALD or PSC, who were listed for an isolated liver transplant.

Setting
The setting of the study was a transplant centre. The economic study was set at six liver transplant centres in England. These were Addenbrooke's Hospital in Cambridge, the Freeman Hospital in Newcastle, King's College Hospital in London, the Queen Elizabeth Hospital in Birmingham, the Royal Free Hospital in London, and St. James's Hospital in Leeds.

Dates to which data relate
The start of the recruitment period was staggered between the centres for logistical reasons. The start of the 12-month recruitment periods was between December 1995 and December 1996, thus overall recruitment continued from December 1995 to December 1997, with a maximum follow-up period of 27 months. Data on the survival of patients who did not receive the transplant were estimated from studies published between 1985 and 1999. The costs were estimated using 1998 to 1999 prices (financial year).

Source of effectiveness data
The survival and quality of life of patients who were placed on the transplant waiting list were observed directly from patients listed for a liver transplant at the six transplant centres. The survival in the absence of transplantation was estimated from published prognostic models, using clinical data from the transplanted patients, such that each transplanted patient acted as his or her own control in analysis. Each patient's pre-transplant EQ-5D data were used to estimate quality of life without transplant.

Link between effectiveness and cost data
Resource use data were collected for all patients listed for transplantation alongside the information on their survival.
and quality of life.

**Study sample**
Power calculations were not relevant and therefore were not carried out. There were 122 patients in the PBC group, of which 11.4% were men. The median age was 57 years (interquartile range: 51 - 62). Of these, 81 underwent liver transplantation. There were 155 patients in the ALD group, of which 73.6% were men. The median age was 51 years (interquartile range: 46 - 57). Of these, 82 underwent liver transplantation. Finally, there were 70 patients in the PSC group, of which 68.6% were men. The median age was 50 years (interquartile range: 38 - 56). Of these, 45 underwent liver transplantation. The patients were identified at the six transplant centres during the recruitment period.

**Study design**
This was an observational study in which a single cohort of patients, who were on the waiting lists for liver transplantation at the six study centres, was followed for 27 months from the date they were placed on the list. The analyses then differentiated between those who received and those who were still waiting for a liver transplant. No external control group was used. Although survival data were available for all patients, only 86% of the patients responded to the questionnaire (at least one assessment available). The proportion of patients with usable questionnaire data at the main time-points ranged from 48% (6-month post-listing) to 76% (12-month post-transplantation).

**Analysis of effectiveness**
All patients included in the initial study were considered in the effectiveness analysis. The health outcomes used in the study were survival and quality of life values. Patient survival (rather than graft survival) was assessed using the area under the curve method (Kaplan-Meier survival). Published prognostic models were used to estimate what would have been the survival of each patient, given their disease severity, had they not undergone transplantation (shadow survival). Quality of life was estimated using the EuroQol EQ-D5 classification system. This was administered by postal questionnaire at the time of listing, then at 3-month intervals until transplantation took place, and then at 3, 6, 12 and 24 months post-transplantation. An imputation approach was used for missing values. Observed survival from listing of patients who received a transplant was compared with their estimated survival without transplant, calculated by applying coefficients of published prognostic models to their individual clinical/demographic characteristics. Utility values were estimated for both patients who received a transplant and those who did not (using pre-transplantation values and assuming that the last pre-transplantation value remained constant until death or the end of the follow-up period). Zero values for patients who died after transplantation were included.

**Effectiveness results**
At one year, the observed mean survival was 0.91 (95% confidence interval, CI: 0.85 - 0.97) for PBC, 0.93 (95% CI: 0.88 - 0.98) for ALD and 0.91 (95% CI: 0.83 - 0.98) for PSC. At 2 years, the observed mean survival was 1.91 (95% CI: 1.79 - 2.05) for PBC, 1.87 (95% CI: 1.72 - 1.98) for ALD and 1.89 (95% CI: 1.65 - 2.05) for PSC.

At one year, the shadow mean survival was 0.84 (95% confidence interval, CI: 0.79 - 0.90) for PBC, 0.88 (95% CI: 0.83 - 0.92) for ALD and 0.99 (95% CI: 0.97 ; 1.0) for PSC. At 2 years, the shadow mean survival was 1.56 (95% CI: 1.40 ; 1.70) for PBC, 1.29 (95% CI: 1.15 - 1.43) for ALD and 1.67 (95% CI: 1.54 ; 1.79) for PSC.

The results of the Euro-Qol were only presented graphically to compare quality of life in transplanted and non-transplanted patients. The results suggested that, for PSC and PBC patients, there was an increase in quality of life post-transplantation that started to level off at 24 months post-transplantation. The quality of life of ALD patients improved after transplantation, but showed a non significant decrease after 12 months post-transplantation. In all three study groups, the quality of life values were always lower than those of the UK general population.

**Clinical conclusions**
Liver transplantation improved the quality of life of patients with PSC, PBC or ALD. However, post-transplantation values were well below those of the general UK population.
Outcomes assessed in the review
The disease-specific prognostic models that could be used to estimate ‘without transplant’ survival were identified in the review.

Study designs and other criteria for inclusion in the review
The models were based on historical cohort data. The Beclere model was used for ALD, the Royal Free and European models were used for PCB, and an international model was selected for PSC.

Sources searched to identify primary studies
Not stated.

Criteria used to ensure the validity of primary studies
A three-step decision model was used to choose the most valid model among those found in the literature.

Methods used to judge relevance and validity, and for extracting data
Not stated.

Number of primary studies included
Seven primary studies were used to identify relevant prognostic models for assessing survival. Four were included for primary analysis and a further three were used in the sensitivity analysis.

Methods of combining primary studies
A single prognostic model was used for each analysis. Except in one case where it was not possible to determine between two models using the three-step decision model. In this case the means results of the two models were used.

Investigation of differences between primary studies
The predicted survival without transplantation from the prognostic models for each of the three disease groups was compared with each other.

Results of the review
As the estimated survival was calculated based on the observed clinical characteristics, the results have been presented under the estimates of effectiveness fields.

Measure of benefits used in the economic analysis
The summary benefit measure was the number of quality-adjusted life-years (QALYs) gained with transplantation over no transplantation. A discount rate of 1.5% was used to reflect the timeframe of the study (27 months). The QALYs were calculated by combining survival and quality of life data, which were estimated from the observational cohort (for the transplantation group) and from the published prognostic models (for the no transplantation group). The utility values were derived from the sample of patients.

Direct costs
A discount rate of 6% was applied to the costs, which were incurred during 27 months. The unit costs and the quantities of resources used were not presented separately. The categories of costs were hospital stay, outpatient visits, high cost/high volume drugs, blood products, nutrition, physiotherapy sessions, dietician sessions, tests, treatments and...
the length of the transplant operation. Research activity costs were not included, but costs associated with the transplant patient’s assessment were considered. The costs for patients who did not receive a transplant were calculated on the basis of the mean daily costs, which were then multiplied by the predicted survival. The perspective of the NHS transplant centre was adopted. Information on resource use was derived using data estimated from the sample of patients who were included in the effectiveness analysis. The unit costs came from the study centres, while the drug costs were estimated from the British National Formulary. Since the costs varied across the centres, mean weighted averages were calculated. The costs were estimated in the 1998 to 1999 fiscal year.

Statistical analysis of costs
A regression model was used to account for the increase in costs observed in the month before death among patients who did not receive a liver transplant. Bias-adjusted bootstrapping was used to estimate CIs for the estimated costs (and QALYs).

Indirect Costs
The indirect costs were not included.

Currency
UK pounds sterling (€).

Sensitivity analysis
Univariate sensitivity analyses were conducted to assess the robustness of the estimated cost per QALY to variations in several factors. The factors investigated were the use of alternative prognostic models, the deterioration of quality of life without transplantation, and the inclusion of donor organ costs. The lowest and highest values for the unit costs and estimated costs of non-transplanted patients were used alternately. The ranges used were derived from authors’ assumptions, CIs or estimates from the literature.

Estimated benefits used in the economic analysis
For PBC, the estimated mean QALYs were 1.30 (95% bootstrap CI: 1.18 - 1.43) with transplantation and 0.76 (95% bootstrap CI: 0.65 - 0.91) without transplantation. This led to an incremental QALY of 0.54 (95% bootstrap CI: 0.39 - 0.69).

For ALD, the estimated mean QALYs were 1.12 (95% bootstrap CI: 0.97 - 1.24) with transplantation and 0.57 (95% bootstrap CI: 0.48 - 0.69) without transplantation. This led to an incremental QALY of 0.55 (95% bootstrap CI: 0.40 - 0.69).

For PSC, the estimated mean QALYs were 1.41 (95% bootstrap CI: 1.20 - 1.57) with transplantation and 0.83 (95% bootstrap CI: 0.68 - 0.98) without transplantation. This resulted in an incremental QALY of 0.58 (95% bootstrap CI: 0.40 - 0.75).

Cost results
For PBC, the estimated mean costs were 52,525 (95% bootstrap CI: 46,000 - 61,000) with transplantation and 37,301 (95% bootstrap CI: 27,000 - 54,000) without transplantation. This led to an incremental cost of 15,224 (95% bootstrap CI: 0 - 28,000).

For ALD, the estimated mean costs were 66,049 (95% bootstrap CI: 57,000 - 81,000) with transplantation and 40,336 (95% bootstrap CI: 29,000 - 60,000) without transplantation. This resulted in an incremental cost of 25,712 (95% bootstrap CI: 7,000 - 41,000).

For PSC, the estimated mean costs were 60,612 (95% bootstrap CI: 49,000 - 77,000) with transplantation and 48,430
Synthesis of costs and benefits
The incremental cost-effectiveness ratios were presented via the cost-effectiveness acceptability curve. The mean incremental cost per QALY gained with transplantation over no transplantation was 29,000 (95% bootstrap CI: 1,000 - 59,000) for PBC, 48,000 (95% bootstrap CI: 12,000 - 83,000) for ALD and 21,000 (95% bootstrap CI: -23,000 - 60,000) for PSC.

The results of the sensitivity analysis showed that the use of alternative prognostic models affected the conclusions of the study, but that there were only small differences in the estimated cost per QALY. The results were sensitive to variations in the cost estimates.

Authors’ conclusions
Liver transplantation improved quality-adjusted survival among all patients in comparison with no transplantation. However, when the high cost of the intervention and the benchmark value for what the National Health Service (NHS) is willing to pay for a QALY (30,000) were considered, the cost-effectiveness of liver transplantation was poor for patients with alcoholic liver disease (ALD) but better for patients with primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC).

CRD COMMENTARY - Selection of comparators
The rationale for the choice of the comparator was clear. No liver transplantation was selected because there is no active comparator for these disease groups, and additionally there are still doubts about the incremental cost-effectiveness of liver-transplantation. You should decide whether it is a valid comparator in your own setting.

Validity of estimate of measure of effectiveness
The measure of effectiveness was derived from a prospective observational study. This was appropriate for the study question given that a long-term randomised prospective trial was impossible for ethical reasons. For each transplanted patient, the control was their estimated experience calculated from their estimated survival based on applying their characteristics to published prognostic models. Quality of life data for those patients who did not receive a liver transplant were estimated from the same cohort for the period spent on the waiting list. The evidence came from six centres and this made the data used more representative of a variety of treatment patterns. Survival data for patients in the no transplantation group were derived from published models, which were selected so as to ensure a high validity of the data. The data were aggregated, when required, by calculating the mean values.

Validity of estimate of measure of benefit
QALYs were selected as the benefit measure. This choice appears to have been appropriate as QALYs capture the impact of the disease on both length and quality of life. Discounting was applied in accordance with UK NHS recommendations. Utility weights were based on patients’ values and were varied in the sensitivity analysis.

Validity of estimate of costs
The authors stated the perspective applied in the study and all the relevant categories of costs were included. However, the unit costs and the quantities of resources were not presented separately. Statistical tests were carried out on the cost estimates, which were calculated from weighted averages of values estimated at the six study centres. The issue of variability in the data was also addressed by performing sensitivity analyses in which low- or high-cost scenarios were considered. The fiscal year during which the costs were estimated was reported. The authors suggested that the relative cost-effectiveness of PALD could be improved by better evaluating patients prior to assessment so reducing the number of patients assessed but not accepted for transplant.
Other issues
Comparisons were made with the costs observed in other studies. In addition, the authors discussed the role played by modelling when reliable trial data were not available. Due to the uncertainty in some estimates, the sensitivity analysis was helpful to ensure the robustness of the results and to generalise the conclusions of the study to other settings. However, the authors noted that the analysis was relevant to UK practice and may not be directly generalisable to other settings. Ideally a longer timeframe would have been more appropriate, but this would have introduced more uncertainty into the analysis.

Implications of the study
Liver transplantation could be a cost-effective approach for patients with PBC and PSC. ALD patients should be selected more carefully in order to obtain the greatest benefits at an acceptable cost.

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