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A SYSTEMATIC REVIEW OF THE COST-EFFECTIVENESS OF LIVER TRANSPLANTATION

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Additional information

Conflict of interest. The authors have no conflict of interest to declare

Abstract

Background. The efficacy of liver transplantation (LT) in treating liver disease has been established through prospective and retrospective observational studies. Although LT is now regarded as the treatment of choice for liver disease, the evidence on its cost-effectiveness is lacking.

Methods. In this study we conducted a systematic review of the studies that have attempted to assess the cost-effectiveness of LT. The aim is not only to assess the value for money of this particular intervention but also to investigate the sources of evidence on probabilities, costs and quality of life values used in the economic evaluations.

Results. 6 studies were included in the systematic review, of which 5 were of moderate to high quality. The systematic review identified three separate questions: 1) Cost-effectiveness of LT vs no intervention; 2) LT vs alternative treatments for hepatocellular carcinoma (HCC) and 3) type of LT, specifically donation after brain death (DBD) against donation after cardiac death (DCD). Given that randomized control trials of LT versus no transplantation are neither practical nor ethical, we find the two most common methods of investigation are decision analytic models and observational studies (prospective and retrospective). In the case of models, values for probabilities, costs and utilities are mainly derived from the literature (or expert opinion). In observational studies, instead a hypothetical comparison group is created and values for this group estimated either from prognostic models or from the patients in the waiting list for transplantation. In both cases, sources of uncertainty are multiple because of the use of many assumptions.

Conclusions. The evidence reviewed suggests that LT is cost-effective when compared to no transplantation; whilst evidence on LT vs alternative treatment for HCC is inconclusive and evidence on type of LT is dependent on the data which parametrize the model.

Key words: Liver Transplantation, Cost-Effectiveness, Systematic Review

JEL classification: I1: Health

1 Introduction

In UK liver disease constitutes the third most common cause of death in working age people (18-65 years old). Unlike the major improvements in other disease areas, such as stroke, heart disease and cancer, mortality rates in liver disease have increased 400% since 1970, and in people in working age have risen by almost five-times [1]. Liver transplantation (LT) is the treatment of choice in chronic and acute end-stage liver disease (ESLD) still, as reported by the Lancet Commission [1], liver transplant rates for the UK population are about half of those of other European countries. The effectiveness of LT has been assessed through prospective and retrospective observational studies, where the observed survival in patients undergoing transplantation is compared to the survival predicted by validated prognostic models in patients remaining on the waitlist for transplantation. Evidence from this type of studies showed that LT is an effective therapy in ESLD patients [2, 3]. Evidence shows that LT has a three-month survival rate of about 91.2%, a five-year survival of about 73.3% and a ten-year survival of about 60% [4-6]

Less evidence is available on the cost-effectiveness of LT. The UK National Health System (NHS), like other national health systems in the world, is characterised by a slow health spending growth against an accelerated growth in the demand for health care, due to demographic and lifestyle factors. Considerations on cost-effectiveness of health care interventions are paramount in the context of constrained resources. This particularly applies to transplantations where considerations on high expenses go hand in hand with others on the limited supply of donors.

The aim of this paper is to review the evidence on the cost-effectiveness of LT. Clinical trials are considered the gold standard for establishing the effectiveness of health care interventions or therapies and over the past twenty years there has been a growing trend to collect data (health resource use, costs and effects) that allow an economic evaluation alongside clinical trials. Furthermore, these data represent an invaluable source of evidence in model-based economic evaluation. In ESLD, clinical trials are less feasible due to a lack of ethical alternatives. In this review, we are particularly interested in investigating the sources that have been used to collect data on health resource use, costs and effects, given the unfeasibility of collecting these data in clinical trials. We are going to look at incremental cost-effectiveness ratios in relation to the relevant thresholds for cost-effectiveness to assess the value for money of LT. At the same time we expect that uncertainty surrounding data sources may play a big part in the results of these investigations; therefore, in this review, we are also going to unfold the ways that different studies have tackled this uncertainty.

2 Methods

2.1 Search Terms

A search strategy was developed in MEDLINE (OVID) using free text terms and controlled vocabulary terms. Validated terms for LT were combined with terms for cost effectiveness. No language or date limits were applied to the search strategy.

The MEDLINE search strategy was adapted for use in each of the other databases searched. The searches are available in the Appendix A and B.

2.2 Data Sources

The following databases were searched in the first instance from January 1st 1996 to August 31st 2015: Ovid MEDLINE, Ovid MEDLINE In-Process, Ovid MEDLINE Epub Ahead of Print, Ovid EMBASE, Ovid PsycINFO, NHS Economic Evaluations Database (NHS EED) via CRD's interface, Proquest CINAHL, Ebsco EconLIT, IDEAS/REPEC. In the remainder of the paper we will refer to this search as the main search. In August 2017 the following databases were searched: CINAHL (EBSCO) 1981-present, EconLit (EBSCO) 1886 – present, Embase Classic+Embase 1947 to 2017 August 10, IDEAS (RePeC), Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present, NHS EED - NIHR Centre for Reviews and Dissemination - CRD Database, PsycINFO 1806 to August Week 1 2017. The searches were updated to include the period of time from August 31st 2015 to August 15th 2017 and we will refer to this as the updated search. We run the updated searches in all the databases.

2.3 Selection Criteria

The following inclusion criteria were applied:

Population: Patients with liver disease

Intervention: Liver transplantation

Comparator: Any intervention or no intervention

Outcomes: Incremental cost per effect or incremental cost per QALY

Study design: economic evaluations and economic modelling

The following exclusion criteria were applied: costing studies; cost-outcome evaluations; cost-effectiveness of therapies following LT.

2.4 Study Selection

Titles and abstracts from the two sets of searches were screened for relevance by two researchers (RL and AY) based on the selection criteria above. Any disagreements were resolved through discussion or consultation with the wider research team. Full text articles were obtained for potentially relevant records and study selection was conducted. The data extracted (Table 1) included type of study and analysis, perspective, outcome measure, sources of data, cost-effectiveness results and sensitivity analyses.

2.5 Quality Assessment

The methodological quality of included studies was assessed according to a 24-item checklist of the Consolidated Health Economic Evaluation Reporting Standards (CHEERS), a statement endorsed by the ISPOR Health Economic Evaluations Publication Guidelines Task Force [7]. Studies were rated as high, moderate or low quality on the basis of meeting >75%, <75->50% or less than <50% of points respectively. See Table 2 CHEERS Checklist for the quality of the included studies.

2.6 Synthesis

Given heterogeneity in patient selection and study design we conducted a narrative synthesis of findings from included studies

3 Results

From the main search, six peer-reviewed studies were included (see Figure 1 for study flow diagram). We conducted a broad search of the literature which retrieved 7168 records. After screening twenty-eight studies were identified as potentially meeting the inclusion criteria of the review. Of these, eighteen were excluded after full-text screening as they were costing studies, two more were excluded because only abstracts were available and other two because were not economic evaluations. Specifically, the last two studies were cost-outcome descriptions which are evaluations where no comparison of alternative interventions is made. The aim of one of the studies, Van Agthoven et al [8], was to compare the average cost per chronic patient to the average cost per acute patient (who still lived after 1 year of the transplant). The cost analysis was conducted thoroughly, with a micro-costing exercise, but an average cost-effectiveness ratio fails to capture the issue of displacement and the concept of opportunity cost and therefore it is not meaningful in the UK decision-making context. The same issue is encountered with the other study excluded, Aberg et al. [9]. The aim was to conduct a cost-utility analysis of liver transplant at 1 year and at 5 years for acute liver disease, chronic liver

disease and different Model for End-Stage Liver Disease (MELD) scores. The results though are expressed as cost/QALY and not as incremental effectiveness ratios (ICERs).

From the updated searches, we retrieved 1245 records. After screening nine studies were identified as potentially useful. All of them were excluded with reasons which are specified in Figure 2.

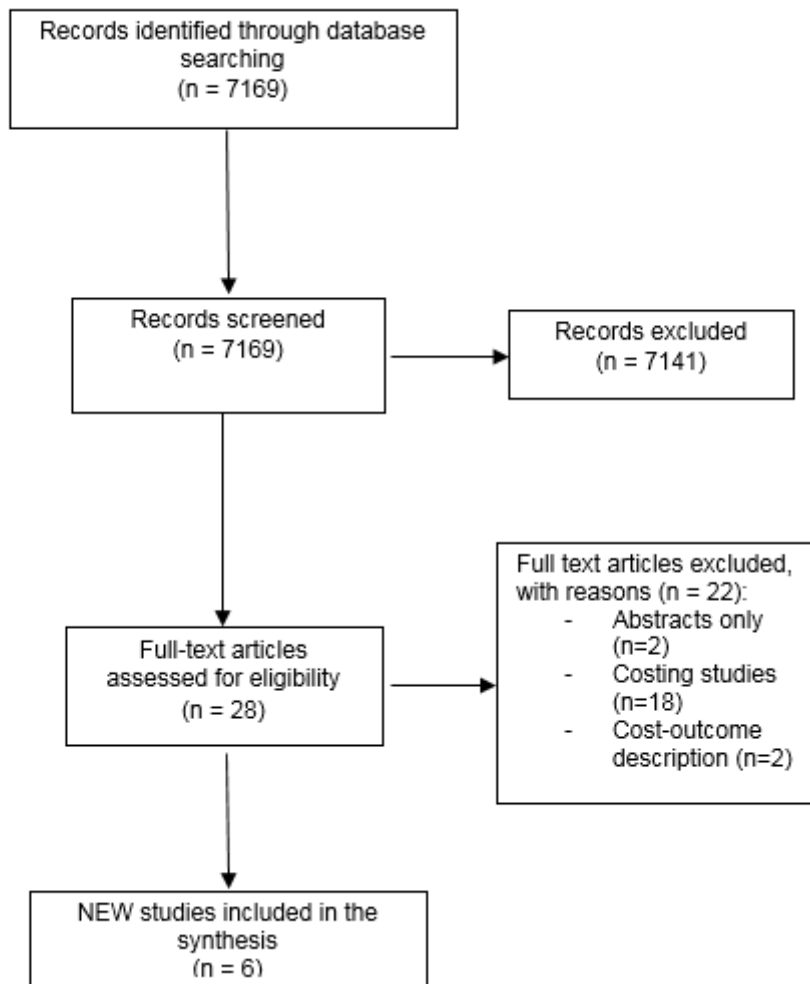


Figure 1 PRISMA flow diagram: Initial search

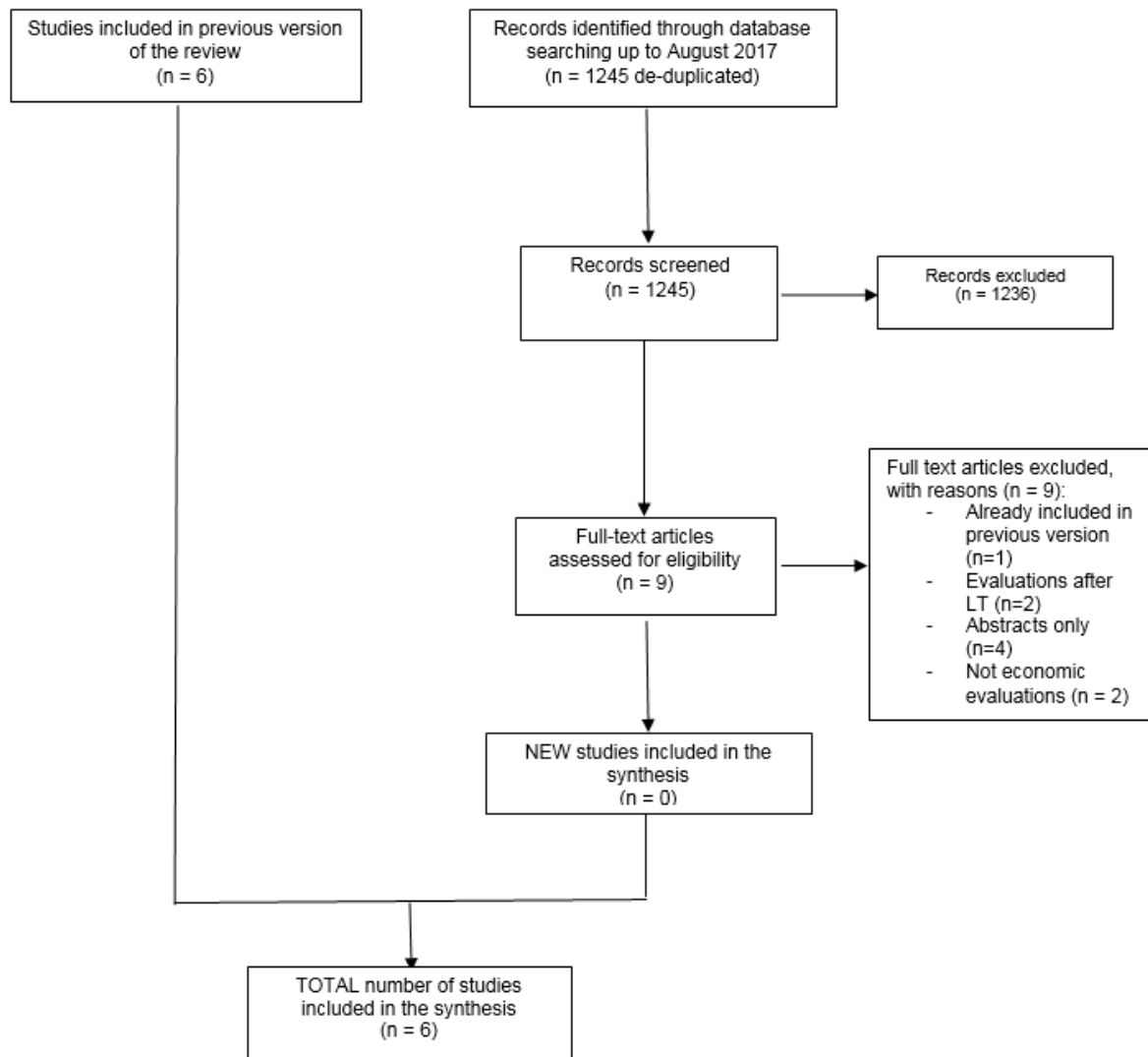


Figure 2 PRISMA flow diagram: Updated search

Generally, studies were of high or moderate quality (5 out of 6). One study, Ouwens et al. [10], was low quality and scored 33% (Table 2).

The majority of the studies conducted cost-utility analyses, which is the type of economic evaluation looking at comparing alternative interventions in terms of their costs and consequences, the latest measured in Quality-Adjusted Life Years (QALYs).

As for the country of origin, three studies were from the US – with one looking at a triple setting (US, Singapore and Switzerland); only one was from England and Wales; the remaining studies were European (the Netherlands and Finland).

The assumed perspective was either societal or that of the health care provider/transplant centres, except for Longworth et al. [11] and Lim et al. [12] and who assumed the perspective of the national health system.

Four studies contained Markov models with time horizon either 10 years or a lifetime (Table 1). The range of comparators varied considerably: no intervention, hepatic resection, LT from cerebral death or cardiac death donors.

Two studies compared LT with no transplantation, Ouwens et al. [10] and Longworth et al. [11]. The aim of [10] was to carry out a head-to-head comparison of costs and effects of three transplantation programmes in the Netherlands, included LT. The study was in turn based on three Dutch studies (Medical Technology Assessments) which estimated costs and utility values of the comparator group (no intervention) from patients put in the waitlist for transplant. The authors concluded that LT has the most favourable incremental ratio for cost-effectiveness. However the study scored the lowest in our quality assessment.

The populations of interest in the only UK study, [11], were three particular groups of ESLD: Primary biliary cirrhosis (PBC), alcoholic liver disease (ALD) and primary sclerosing cholangitis (PSC). The study recruited prospective cohorts of patients undergoing liver transplants at the six liver transplant centres in England. All patients were followed for 27 months from the date they were placed on the waiting lists. A total of 122 PBC, 155 ALD, and 70 PSC patients were assessed for a liver transplant during the study. Of these, the numbers who underwent transplantation during the study were 81, 82, and 45 for PBC, ALD, and PS respectively. Health resource use, survival rates and utility values were observed directly from the patients who underwent transplantation. The same type of data for the comparator group, the 'shadow' group, were estimated by using validated prognostic models specific to PBC, ALD and PSC. The obtained ICERs were £28,716 for PBC, £48,355 for ALD and £21,332 for PSC. The majority of bootstrap estimates shows that ICERs fall in the top-right quadrant of a cost-effectiveness plane; meaning that the intervention is more costly and more effective than no intervention; although estimates for PSC show that transplantation in this group of patients could also be cost-saving. Cost effectiveness acceptability curves (CEACs) show that ALD had the lowest probability; whilst PSC had the highest probability of being cost-effective at the relevant threshold of £30,000.

There is some evidence that a valuable alternative to LT exists for patients with hepatocellular carcinoma and that is liver resection. Two of the studies in this review compared these two alternatives. The study that obtained the highest quality score, Landman et al. [13], is an American study which compared hepatic resection (HR) or locoregional therapy (LRT) followed by salvage orthotopic liver transplantation (SOLT) against primary orthotopic liver transplantation (POLT). Results of the Markov model showed that POLT dominates the alternative strategy, meaning that provides more QALYs at a

lower cost. Transition probabilities and costs were estimated from the literature; it is not clear though the source of utility values. The uncertainty surrounding the model parameters was addressed with a range of sensitivity analyses, included probabilistic sensitivity analysis (PSA) which confirmed that POLT dominates at all clinically relevant values. Lim et al. [12] was also scored high in terms of quality. The authors built a lifetime Markov model and found that ICERs of cadaveric liver transplantation (CLT) against liver resection (LR) ranged from \$111,821/QALY in Singapore to \$156,300 in Switzerland, and concluded that CLT is not cost-effective although it improves life expectancy. Transition probabilities, costs and utilities were all estimated from the literature. Finally, one-way sensitivity analysis, scenario and PSA confirmed results of the main analysis.

Two studies looked at comparing donation after brain death (DBD) against donation after cardiac death (DCD). Jay et al. [14], another high quality study, built a Markov model with time horizon 10 years to assess the cost-effectiveness of transplantation with DCD livers against remaining on the waitlist until DBD is available according to MELD-based allocation. Transition probabilities are mainly based on data from a national registry, while costs and utilities are literature based. Results are divided by MELD score bands: DCD is dominated (provides less QALYs at a higher cost) except for patients in MELD 15-20, 21-30 and >30 for which DCD is not deemed cost-effective. The uncertainty in the model was tackled with one-way sensitivity analyses and PSA which confirmed that for patients with MELD <15 DCD is dominated. For patients in MELD >20 there is an increase in effectiveness in all Monte Carlo iterations but DCD is still considered not cost-effective in reference to the US threshold for cost-effectiveness at \$75,000-\$100,000/QALY.

Finally, Dageforde et al. [15] used a Markov model to assess the cost-effectiveness of LT using DBD organs only against LT using DBD and DCD organs. Transition probabilities, costs and utilities were based on systematic reviews of the literature and the study was judged of moderate quality. Results showed that the strategy in which both types of organs were used, DBD and DCD, dominates the DBD only strategy. One and two-way sensitivity analyses and PSA confirm DBD/DCD dominates at all clinically relevant values.

4 Discussions

Evidence of the cost-effectiveness of health care interventions is fundamental in guaranteeing the sustainability of national health systems. Assessment of cost-effectiveness is even more important for interventions like LT where considerations on high expenses go hand in hand with others on the limited supply of donors.

This systematic review has identified three separate questions: 1) Cost-effectiveness of LT vs. no intervention; 2) LT vs alternative treatment for HCC and 3) type of LT (DBD vs. DCD). Longworth et

al. [11] address the first question and suggest LT is cost-effective, with respect to no intervention, for PBC and PSC patients, at least at a 27 month horizon. The main limitation of this study is that the authors did not use a decision analytic model for the observed listed patients – in fact only used models for the ‘shadow’ data. An economic model would have allowed for extending evidence to an appropriate time horizon and helped better quantification of uncertainty. Since median survival for recipients is >10 years and for those patients who are not transplanted survival is <2 years, the cost-effectiveness of transplantation will improve substantially in the follow-up period if an appropriate horizon is used. The other study identified in this context, Ouwens et al. [10], indicates that LT is likely to be cost effective. In summary, these studies suggest that LT vs. no intervention provides value for money.

Lim et al [12] Landman et al. [13] and have looked at the question of LT vs alternative treatment for HCC. There is not a clear answer to this question as [13] indicates that LT dominates all other strategies, whilst [12] indicates that LT is not cost-effective against liver resection. It is unsure though that Lim’s study is well calibrated to clinical practice – in fact, the QALY gain from LT seems low.

A conclusion on the type of transplant (DBD vs. DCD) is dependent on the data that are used to parameterise the model. For instance, the US data used in Jay et al [14] has since been updated and this might change the estimate of cost effectiveness. Dageforde et al. [15] is a European study and the European experience with DCD transplantation is greater than in US. Results of this study indicate that a DBD/DCD strategy dominates the DBD only strategy. This information might be more applicable to the UK where rates of DCD usage are particularly high.

More generally, the information identified by this systematic review shows that, given that RCTs of LT vs no transplantation are neither practical nor ethical, the two most common methods of investigation in LT are decision analytic models and observational studies (prospective and retrospective). In the case of models, values for probabilities, costs and utilities are mainly derived from the literature (or expert opinion). In observational studies instead a hypothetical comparison group is created and values for this group estimated either from prognostic models or from the patients in the waiting list for transplantation. Advantages of modelling include the possibility of extending evidence to an appropriate time horizon and better quantification of uncertainty. On the other hand, both analytic models and observational studies show multiple sources of uncertainty because of the use of many assumptions.

Finally, most of the studies assumed the perspective of the health care provider or the transplant centre. We argue that studies assuming a societal perspective are better suited in this instance in order to capture productivity costs incurred by patients undergoing LT and associated carer burden.

5 Conclusions

This systematic review has identified three separate questions: 1) Cost-effectiveness of LT vs. no intervention; 2) LT vs alternative treatment for HCC and 3) type of LT (DBD vs. DCD). Whilst the available evidence suggests that LT vs no intervention provides value for money, there is not a clear answer to the other two questions.

In general, more research is needed into the cost-effectiveness of LT and the focus should be on modelling studies in order to better quantify uncertainty and to extend evidence on costs and benefits to a lifetime horizon. Finally, the perspective of LT cost-effectiveness analyses should include societal costs in order to include productivity losses incurred by LT patients and associated carer burden.

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Table 1 Data extraction table

Author	Country	Type of study and analysis	Comparison	Perspective	Patients population or underlying condition	Outcome measure	Sources of data	Horizon	Results	
									Base Case	Sensitivity analysis
Landman et al. (2011).	USA	Decision analytic model – Markov Model	Hepatic resection (HR) or Locoregional therapy (LRT) followed by salvage orthotopic liver transpl. (SOLT) VS primary orthotopic liver transpl. (POLT)	Societal	Hepatocellular Carcinoma	QALYs	Transition probabilities and costs were estimated from the literature; it is not clear the source of utility values	10 years	POLT dominates	PSA confirms POLT dominates at all clinically relevant values
Dageforde et al (2012).	USA	Decision analytic model – Markov Model	Liver transplantation using DBD VS Liver transplantation using DBD/DCD	Societal	ESLD. Base case, non-alcoholic steatohepatitis	QALYs	Transition probabilities, costs and utilities based on systematic reviews of the literature	10 years	DBD/DCD dominates DBD only	One and two-way SA and PSA confirm DBD/DCD dominates at all clinically relevant values
Longworth et al. (2003)	England and Wales	Prospective observational study. Economic evaluation alongside observational study + model based estimate for control group	Liver transplant VS no transplant	NHS	Primary biliary cirrhosis (PBC), alcoholic liver disease (ALD) and primary sclerosing cholangitis (PSC)	QALYs	Health resource use, survival rates and utility values from the patients who underwent transplantation. The same type of data for the comparator group were estimated by using validated	27 months	Mean gain in patient survival is greatest for ALD and lowest for PSC. Mean QALY gain: highest for PSC. ICERs: majority of bootstrap estimates fall in top-right	Estimates sensitive to use of alternative prognostic model. When cost of retrieval is included ICERs increase across groups. Results particularly sensitive to shadow costs.

							prognostic models.		quadrant, although PSC could also be cost-saving. CEACs: ALD lowest probability; PSC highest	
Lim et al (2014).	Singapore, USA, Switzerland	Decision analytic model – Markov Model	Liver Resection (LR) VS Cadaveric Liver Transplantation (CLT)	National health service	Early Hepatocellular Carcinoma	QALYS	Transition probabilities, costs and utilities were all estimated from the literature	Lifetime	ICERs of CLT vs LR ranged from \$111,821/QALY in Singapore to \$156,300 in Switzerland. CLT not cost-effective although it offers improve life expectancy	One-way sensitivity analysis, scenario and PSA Confirm results of the main analysis
Jay et al. (2012).	USA	Decision analytic model - Markov Model	Transplantation with a DCD livers VS remaining on the waitlist until DBD is available according to MELD-based allocation	Patient's/transplant centre	ESLD	QALYS	Transition probabilities data from a national registry, while costs and utilities are literature based	10 years	Results divided by MELD score bands: DCD is dominated except for patients in MELD 15-20, 21-30 and >30 for which DCD is not deemed cost-effective	PSA confirmed that for patients with MELD <15 DCD is dominated. For patients in MELD>20 there is an increase in effectiveness in all Monte Carlo iterations
Ouwens et al. (2003).	Netherlands	Economic evaluation based on a single observational study.	Liver transplant vs no intervention	Societal	Not given	QALYs	Costs and utility values from the patients who underwent transplantation. For the	lifetime	ICER not given	none

							comparator group (no intervention) these were estimated from patients put in the waitlist for transplant			
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Table 2 CHEERS Checklist

	Lim et al. 2014	Jay et al 2012	Longworth et al 2003	Dageforde et al. 2012	Ouwens et al. 2003	Landman et al. 2011
Title	Yes p. 227	x	Yes p. 1295	x	Yes p.123	Yes p.783
Abstract	x	Yes p. 1-2	x	Yes p.182	x	Yes p.783
Background and objectives	Yes p. 227-228	Yes p.2	Yes p. 1295-96	Yes p. 182-183	x	Yes p.783-84
Target population and subgroups	Yes p.228	Yes p. 3	Yes p. 1296	Yes p. 182	x	Yes p. 784
Setting and location	Yes p.231	x	Yes p. 1296	x	Yes p.123	Yes p. 784
Study perspective	Yes p. 230	Yes p. 2	Yes p. 1296	Yes p.183	x	Yes p. 784
Comparators	Yes p.228	Yes p. 2	Yes p. 1296	Yes p.183	Yes p.124	Yes p. 784
Time horizon	Yes p.228	Yes p.3	Yes p. 1296	Yes p.183	Yes p.125	Yes p. 784
Discount rate	Yes p. 231	Yes p.3	Yes p. 1297	Yes p.183	x	Yes p. 784
Choice of health outcomes	Yes p. 231	Yes p.4	Yes p. 1296	Yes p.184	Yes p.124	Yes p.785
Measurement of effectiveness (single study-based estimates)	x	x	x	x	Yes p.124	x
Measurement of effectiveness (synthesis-based estimates)	Yes p.229-30	Yes p.3	Yes p. 1296	Yes p.184	x	x
Measurement and valuation of preference-based outcomes	x	x	x	x	x	x

Estimating resources and costs(single study)	x	x	x	x	x	x
Estimating resources and costs(model based)	Yes p. 230-31	Yes p.4	Yes p. 1297	x	x	Yes p.785
Currency, price date and conversion	x	Yes p.4	x	Yes p. 183	Yes 125	Yes p.785
Choice of model	Yes p. 228	Yes p.2	x	Yes p. 183	x	Yes p.784
Assumptions	Yes p. 228-29	Yes p.2	x	Yes p. 183	x	Yes p.784
Analytic methods	x	x	Yes p. 1297	x	x	x
Study parameters	Yes p.231	Yes p. 15-16	x	Yes p. 183	x	Yes p.786
Incremental costs and outcomes	Yes p.231-232	Yes p.4-5	Yes p.1298-99	Yes p. 185	Yes p. 125	Yes p.786
Characterising uncertainty (single study)	x	x	Yes p. 1300	x	x	x
Characterising uncertainty (model based)	Yes p. 232	Yes p.5	x	Yes p. 184-186	x	Yes p.787-88
Characterising heterogeneity	Yes p.231-232	Yes p.4-5	Yes p. 1298-99	x	x	Yes p.788
Study findings, limitations, generalisability, and current knowledge	Yes 233-35	Yes p. 6-7	Yes p. 1301-05	Yes p. 187-188	x	Yes p.788-790
Source of funding	x	x	Yes p. 1295	x	x	x
Conflicts of interest	None declared	x	x	None declared	x	None declared
% checklist points met	19/24=79% High	18/24=75% High	17/24=71% Moderate	17/24=71% Moderate	8/24=33% Low	20/24=83% High

Appendix A

Search Strategies: Main Search

MEDLINE In-Process & Other Non-Indexed Citations and Ovid MEDLINE

via OvidSP <http://ovidsp.ovid.com/>

1946 – September 02 2015

Searched on 3rd September 2015. 2177 records were retrieved.

- 1 exp Liver Transplantation/ (46188)
- 2 (liver adj3 (transplant\$ or graft\$)).ti,ab. (49864)
- 3 (hepatic adj3 (transplant\$ or graft\$)).ti,ab. (2839)
- 4 1 or 2 or 3 (60500)
- 5 economics/ (26914)
- 6 exp "costs and cost analysis"/ (193294)
- 7 economics, dental/ (1885)
- 8 exp "economics, hospital"/ (20733)
- 9 economics, medical/ (8893)
- 10 economics, nursing/ (3938)
- 11 economics, pharmaceutical/ (2628)
- 12 (economic\$ or cost\$ or price or prices or pricing or pharmaco-economic\$).ti,ab. (553334)
- 13 (expenditure\$ not energy).ti,ab. (20717)
- 14 value for money.ti,ab. (1108)
- 15 budget\$.ti,ab. (20939)
- 16 (resource\$ adj2 (use\$ or utilis\$ or utiliz\$)).ti,ab. (19347)
- 17 Hospitalization/ (78012)
- 18 (hospitalis\$ or hospitaliz\$).ti,ab. (169474)
- 19 or/5-18 (879797)
- 20 ((energy or oxygen) adj cost).ti,ab. (3131)
- 21 (metabolic adj cost).ti,ab. (943)
- 22 ((energy or oxygen) adj expenditure).ti,ab. (18887)
- 23 or/20-22 (22174)
- 24 19 not 23 (874636)
- 25 4 and 24 (2315)
- 26 letter.pt. (949100)
- 27 editorial.pt. (394798)
- 28 historical article.pt. (325722)
- 29 or/26-28 (1653272)
- 30 25 not 29 (2241)
- 31 exp animals/ not humans/ (4109551)
- 32 30 not 31 (2177)

Key:

/ = indexing term (MeSH heading)

exp = exploded MeSH heading

\$ = truncation

.ti,ab. = terms in either title or abstract fields

adj3 = terms within three words of each other (any order)

adj = terms next to each other (order specified)

.pt. = publication type

Cumulative Index to Nursing & Allied Health (CINAHL Plus)

via EBSCO <https://www.ebscohost.com/>
Inception – 2nd September 2015

Searched on 3rd September 2015. 218 records were retrieved.

S23	S4 AND S22	218
S22	S20 not S21	200,890
S21	MH "Animal Studies"	69,254
S20	S18 not S19	201,272
S19	PT editorial or letter or commentary	491,408
S18	S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17	216,710
S17	TI (cost or costs or costing or costly or economic* or pharmaco-economic* or price or prices or pricing*) OR AB (cost or costs or costing or costly or economic* or pharmaco-economic* or price or prices or pricing*)	114,560
S16	TI (hospitalis* or hospitaliz*) OR AB (hospitalis* or hospitaliz*)	38,076
S15	(MH "Hospitalization")	19,953
S14	TI (resource* N2 (use* or utilis* or utiliz*)) OR AB (resource* N2 (use* or utilis* or utiliz*))	7,443
S13	MH "Health Resource Utilization"	12,003
S12	MH "Health Resource Allocation"	7,075
S11	S5 NOT S10	71,048
S10	S6 OR S7 OR S8 OR S9	582,887
S9	MH "Business+"	104,109
S8	MH "Financing, Organized+"	112,051
S7	MH "Financial Support+"	362,820
S6	MH "Financial Management+"	47,339
S5	MH "Economics+"	587,568
S4	S1 OR S2 OR S3	4,729
S3	TI (hepatic N3 (transplant* or graft*)) OR AB (hepatic N3 (transplant* or graft*))	137
S2	TI (liver N3 (transplant* or graft*)) OR AB (liver N3 (transplant* or graft*))	3,192
S1	(MH "Liver Transplantation")	3,852

Key:

MH = indexing term (CINAHL heading)

* = truncation

TI = words in the title

AB = words in the abstract

“ “ = phrase search

N3 = terms within three words of each other (any order)

PT = publication type

EconLIT

via OvidSP <http://ovidsp.ovid.com/>

1886-August 2015

Searched on 3rd September 2015. 15 records were retrieved.

- 1 (liver adj3 (transplant\$ or graft\$)).ti,ab. (15)
- 2 (hepatic adj3 (transplant\$ or graft\$)).ti,ab. (0)
- 3 1 or 2 (15)

Key:

\$ = truncation

.ti,ab. = terms in either title or abstract fields

adj3 = terms within three words of each other (any order)

EMBASE

via OvidSP <http://ovidsp.ovid.com/>
1974 – September 02 2015 (week 36 2015)

Searched on 3rd September 2015. 4500 records were retrieved.

- 1 exp liver transplantation/ (83412)
- 2 (liver adj3 (transplant\$ or graft\$)).ti,ab. (74232)
- 3 (hepatic adj3 (transplant\$ or graft\$)).ti,ab. (3845)
- 4 1 or 2 or 3 (93234)
- 5 Health Economics/ (34737)
- 6 exp Economic Evaluation/ (231633)
- 7 exp Health Care Cost/ (222766)
- 8 pharmacoeconomics/ (6128)
- 9 5 or 6 or 7 or 8 (416254)
- 10 (econom\$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic\$).ti,ab. (693247)
- 11 (expenditure\$ not energy).ti,ab. (27017)
- 12 (value adj2 money).ti,ab. (1575)
- 13 budget\$.ti,ab. (27020)
- 14 10 or 11 or 12 or 13 (719794)
- 15 9 or 14 (912551)
- 16 *health care utilization/ (11615)
- 17 (resource\$ adj2 (use\$ or utilis\$ or utiliz\$)).ti,ab. (27766)
- 18 *hospitalization/ (25717)
- 19 (hospitalis\$ or hospitaliz\$).ti,ab. (249566)
- 20 16 or 17 or 18 or 19 (293051)
- 21 15 or 20 (1155111)
- 22 letter.pt. (905673)
- 23 editorial.pt. (488963)
- 24 note.pt. (613892)
- 25 22 or 23 or 24 (2008528)
- 26 21 not 25 (1070901)
- 27 (metabolic adj cost).ti,ab. (1025)
- 28 ((energy or oxygen) adj cost).ti,ab. (3404)
- 29 ((energy or oxygen) adj expenditure).ti,ab. (22783)
- 30 27 or 28 or 29 (26332)
- 31 26 not 30 (1065125)
- 32 animal/ (1688436)
- 33 exp animal experiment/ (1880430)
- 34 nonhuman/ (4599433)
- 35 (rat or rats or mouse or mice or hamster or hamsters or animal or animals or dog or dogs or cat or cats or bovine or sheep).ti,ab,sh. (5147473)
- 36 32 or 33 or 34 or 35 (7484549)
- 37 exp human/ (16307893)
- 38 human experiment/ (342031)
- 39 37 or 38 (16309339)
- 40 36 not (36 and 39) (5760471)
- 41 31 not 40 (992681)
- 42 4 and 41 (4500)

Key:

/ = indexing term (EMTREE heading)

exp= exploded indexing term (EMTREE heading)

\$ = truncation

.ti,ab. = terms in either title or abstract fields

adj3 = terms within three words of each other (any order)

.pt. = publication type

.sh. = subject heading

IDEAS

via RePec <https://ideas.repec.org/>

Searched on 3rd September 2015. 36 records were retrieved.

"liver transplant"|"liver transplantants"|"liver transplantation"|"liver transplantations"
In whole records

Key:

" " = phrase search

| = OR

NHS Economic Evaluations Database (NHS EED)

<http://www.crd.york.ac.uk/CRDWeb/>

Inception – 31st March 2015

Searched on 3rd September 2015. 194 records were retrieved.

1	(((liver near3 transplant*)) OR ((liver near3 graft*)) IN NHSEED	192
2	(((transplant* near3 liver)) OR ((graft* near3 liver))) IN NHSEED	19
3	(((hepatic near3 transplant*)) OR ((hepatic near3 graft*))) IN NHSEED	9
4	(((transplant* near3 hepatic)) OR ((graft* near3 hepatic))) IN NHSEED4	
5	MeSH DESCRIPTOR liver transplantation EXPLODE ALL TREES IN NHSEED	76
6	#1 OR #2 OR #3 OR #4 OR #5	194

Key:

MeSH DESCRIPTOR = indexing term (MeSH heading)

* = truncation

near3 = terms within three words of each other (order specified)

PsycINFO

via OvidSP <http://ovidsp.ovid.com/>

1806 – August week 4 2015

Searched on 3rd September 2015. 29 records were retrieved.

1	liver/ (1182)	
2	exp liver disorders/ (3297)	
3	(liver or hepatic).ti,ab. (7569)	
4	1 or 2 or 3 (9423)	
5	organ transplantation/ (2627)	
6	4 and 5 (439)	
7	(liver adj3 (transplant\$ or graft\$)).ti,ab. (508)	
8	(hepatic adj3 (transplant\$ or graft\$)).ti,ab. (14)	
9	6 or 7 or 8 (560)	
10	exp "costs and cost analysis"/ (20657)	
11	"cost containment"/ (507)	
12	(economic\$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic\$).ti,ab. (158667)	
13	health care utilization/ (12774)	
14	(resource\$ adj2 (use\$ or utilis\$ or utiliz\$)).ti,ab. (5836)	
15	exp hospitalization/ (19063)	
16	(hospitalis\$ or hospitaliz\$).ti,ab. (35388)	

- 17 10 or 11 or 12 or 13 or 14 or 15 or 16 (218484)
- 18 9 and 17 (29)
- 19 (animal or animals or rat or rats or mouse or mice or hamster or hamsters or dog or dogs or cat or cats or bovine or sheep or ovine or pig or pigs).ab,ti,id,de. (289338)
- 20 18 not 19 (29)
- 21 (editorial or letter).dt. (50609)
- 22 20 not 21 (29)

Key:

/ = subject heading

exp = exploded subject heading

\$ = truncation

.ti,ab. = terms in either title or abstract fields

adj3 = terms within three words of each other (any order)

.dt. = document type

Appendix B

Search Strategies: Updated Search

CINAHL (EBSCO) 1981- present

via EBSCO <https://www.ebscohost.com/>

Inception – 11th August September 2017

Searched on 11th August 2017. 240 records were retrieved.

S23	S4 AND S22	240
S22	S20 not S21	191,079
S21	MH "Animal Studies"	411,844
S20	S18 not S19	191,435
S19	PT editorial or letter or commentary	405,247
S18	S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17	205,097
S17	TI (cost or costs or costing or costly or economic* or pharmaco-economic* or price or prices or pricing*) OR AB (cost or costs or costing or costly or economic* or pharmaco-economic* or price or prices or pricing*)	114,282
S16	TI (hospitalis* or hospitaliz*) OR AB (hospitalis* or hospitaliz*)	40,009
S15	(MH "Hospitalization")	15,749
S14	TI (resource* N2 (use* or utilis* or utiliz*)) OR AB (resource* N2 (use* or utilis* or utiliz*))	7,770
S13	MH "Health Resource Utilization"	10,982
S12	MH "Health Resource Allocation"	6,737
S11	S5 NOT S10	57,318
S10	S6 OR S7 OR S8 OR S9	525,022
S9	MH "Business+"	83,497
S8	MH "Financing, Organized+"	99,040
S7	MH "Financial Support+"	341,246
S6	MH "Financial Management+"	40,739
S5	MH "Economics+"	530,592

S4 S1 OR S2 OR S3 3,460
 S3 TI (hepatic N3 (transplant* or graft*)) OR AB (hepatic N3 (transplant* or graft*)) 107
 S2 TI (liver N3 (transplant* or graft*)) OR AB (liver N3 (transplant* or graft*)) 2,540
 S1 (MH "Liver Transplantation") 2,600

Database:

EconLit (EBSCO) 1886 – presentSearched on 11th August 2017. 19 records were retrieved.

S3 S1 OR S2 19
 S2 TI (liver N3 (transplant* or graft*)) OR AB (liver N3 (transplant* or graft*)) 0
 S1 TI (liver N3 (transplant* or graft*)) OR AB (liver N3 (transplant* or graft*)) 19

Embase Classic+Embase 1947 to 2017 August 10

Searched on 11th August 2017. 5650 records were retrieved.

1 exp liver transplantation/ (97922)
 2 (liver adj3 (transplant\$ or graft\$)).ti,ab. (88190)
 3 (hepatic adj3 (transplant\$ or graft\$)).ti,ab. (4416)
 4 1 or 2 or 3 (109731)
 5 Health Economics/ (35378)
 6 exp Economic Evaluation/ (264021)
 7 exp Health Care Cost/ (254608)
 8 pharmacoeconomics/ (6539)
 9 5 or 6 or 7 or 8 (471441)
 10 (econom\$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic\$).ti,ab. (851708)
 11 (expenditure\$ not energy).ti,ab. (33078)
 12 (value adj2 money).ti,ab. (1975)
 13 budget\$.ti,ab. (31911)
 14 10 or 11 or 12 or 13 (882704)
 15 9 or 14 (1091171)
 16 *health care utilization/ (14764)
 17 (resource\$ adj2 (use\$ or utilis\$ or utiliz\$)).ti,ab. (35640)
 18 *hospitalization/ (29760)
 19 (hospitalis\$ or hospitaliz\$).ti,ab. (316945)
 20 16 or 17 or 18 or 19 (369166)
 21 15 or 20 (1396549)
 22 letter.pt. (986100)
 23 editorial.pt. (543449)
 24 note.pt. (684615)
 25 22 or 23 or 24 (2214164)
 26 21 not 25 (1303117)
 27 (metabolic adj cost).ti,ab. (1275)
 28 ((energy or oxygen) adj cost).ti,ab. (3972)
 29 ((energy or oxygen) adj expenditure).ti,ab. (27324)
 30 27 or 28 or 29 (31555)
 31 26 not 30 (1296236)
 32 animal/ (1803984)
 33 exp animal experiment/ (2138527)
 34 nonhuman/ (5250895)
 35 (rat or rats or mouse or mice or hamster or hamsters or animal or animals or dog or dogs or cat or cats or bovine or sheep).ti,ab,sh. (5934392)
 36 32 or 33 or 34 or 35 (8613216)
 37 exp human/ (18957365)
 38 human experiment/ (391704)
 39 37 or 38 (18958956)
 40 36 not (36 and 39) (6535799)

- 41 31 not 40 (1204812)
 42 4 and 41 (5650)

IDEAS

via RePec <https://ideas.repec.org/>

Searched on 11th August 2017. 39 records were retrieved.

"liver transplant"|"liver transplantants"|"liver transplantation"|"liver transplantations"

In whole records

Key:

" " = phrase search

| = OR

Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

Searched on 11th August 2017. 2654 records were retrieved.

- 1 exp Liver Transplantation/ (50810)
- 2 (liver adj3 (transplant\$ or graft\$)).ti,ab. (56988)
- 3 (hepatic adj3 (transplant\$ or graft\$)).ti,ab. (3096)
- 4 1 or 2 or 3 (68303)
- 5 economics/ (27153)
- 6 exp "costs and cost analysis"/ (214834)
- 7 economics, dental/ (1899)
- 8 exp "economics, hospital"/ (22816)
- 9 economics, medical/ (9100)
- 10 economics, nursing/ (3986)
- 11 economics, pharmaceutical/ (2793)
- 12 (economic\$ or cost\$ or price or prices or pricing or pharmaco-economic\$).ti,ab. (677854)
- 13 (expenditure\$ not energy).ti,ab. (24903)
- 14 value for money.ti,ab. (1387)
- 15 budget\$.ti,ab. (25082)
- 16 (resource\$ adj2 (use\$ or utilis\$ or utiliz\$)).ti,ab. (24617)
- 17 Hospitalization/ (91664)
- 18 (hospitalis\$ or hospitaliz\$).ti,ab. (204842)
- 19 or/5-18 (1051631)
- 20 ((energy or oxygen) adj cost).ti,ab. (3723)
- 21 (metabolic adj cost).ti,ab. (1215)
- 22 ((energy or oxygen) adj expenditure).ti,ab. (22280)
- 23 or/20-22 (26278)
- 24 19 not 23 (1045357)
- 25 4 and 24 (2803)
- 26 letter.pt. (984555)
- 27 editorial.pt. (448046)
- 28 historical article.pt. (350161)
- 29 or/26-28 (1765089)
- 30 25 not 29 (2725)
- 31 exp animals/ not humans/ (4524451)
- 32 30 not 31 (2654)

NHS Economic Evaluations Database (NHS EED)

<http://www.crd.york.ac.uk/CRDWeb/>

Inception – 31st March 2015

Searched on 11th August 2017. 196 records were retrieved.

- 1 (((liver near3 transplant*)) OR ((liver near3 graft*))) IN NHSEED 194
- 2 (((transplant* near3 liver)) OR ((graft* near3 liver))) IN NHSEED 19
- 3 (((hepatic near3 transplant*)) OR ((hepatic near3 graft*))) IN NHSEED 9
- 4 (((transplant* near3 hepatic)) OR ((graft* near3 hepatic))) IN NHSEED4
- 5 MeSH DESCRIPTOR liver transplantation EXPLODE ALL TREES IN NHSEED 78
- 6 #1 OR #2 OR #3 OR #4 OR #5 196

PsycINFO 1806 to August Week 1 2017

Searched on 11th August 2017. 42 records were retrieved.

- 1 LIVER/ (1302)
- 2 exp Liver Disorders/ (3792)
- 3 (liver or hepatic).ti,ab. (8660)
- 4 1 or 2 or 3 (10782)
- 5 Organ Transplantation/ (2987)
- 6 4 and 5 (513)
- 7 (liver adj3 (transplant\$ or graft\$)).ti,ab. (608)
- 8 (hepatic adj3 (transplant\$ or graft\$)).ti,ab. (15)
- 9 6 or 7 or 8 (667)
- 10 exp "Costs and Cost Analysis"/ (23335)
- 11 "Cost Containment"/ (537)
- 12 (economic\$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic\$).ti,ab. (183822)
- 13 health care utilization/ (14084)
- 14 (resource\$ adj2 (use\$ or utilis\$ or utiliz\$)).ti,ab. (6769)
- 15 exp hospitalization/ (20723)
- 16 (hospitalis\$ or hospitaliz\$).ti,ab. (38837)
- 17 10 or 11 or 12 or 13 or 14 or 15 or 16 (249371)
- 18 9 and 17 (42)
- 19 (animal or animals or rat or rats or mouse or mice or hamster or hamsters or dog or dogs or cat or cats or bovine or sheep or ovine or pig or pigs).ab,ti,id,de. (323315)
- 20 18 not 19 (42)
- 21 (editorial or letter).dt. (60276)
- 22 20 not 21 (42)