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Cost and outcome of liver transplantation

van der Hilst, Christian

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Chapter 3

Costs of Liver Transplantation: A Systematic Review and Meta-Analysis Comparing the United States with other OECD Countries

Christian S. van der Hilst
Alexander J.C. IJtsma
Maarten J.H. Slooff
Elisabeth M. TenVergert

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ABSTRACT

Large cost variations of liver transplantation are reported. The aim of this study was to assess cost differences of liver transplantation and clinical follow-up between the United States and other Organization for Economic Cooperation and Development (OECD) countries. Eight electronic databases were searched, and 2000 citations published after 1990 with more than 10 transplantations, and with original cost data, were identified. A total of 30 articles included 5975 liver transplantations. Meta-analysis was used to derive a combined mean using a random-effects model to test for heterogeneity between studies. Estimated mean cost of a U.S. liver transplantation was US\$ 163 438 (US\$ 145 277 - 181 598) compared to US\$ 103 548 (US\$ 85 514 - 121 582) for other OECD countries. Patient characteristics, disease characteristics, quality of the health care provider, and methodology could not explain this cost difference. Health system characteristics differed between the United States and other OECD countries. Cost differences in liver transplantation between these two groups may be largely explained by health system characteristics.

1 INTRODUCTION

Total health care spending exceeded inflation in each of the 30 member countries of the Organization for Economic Cooperation and Development (OECD) during the period 1992 - 2006. Annual growth in health care spending per capita averaged 3.4% in the OECD¹. Therefore, health care is increasingly facing budget restraint; hence, optimal allocation of resources is imperative. Cost of health care differs between countries with the United States spending more on health care in absolute and relative terms than any other developed country². Concern about the increasing cost of health care has drawn special attention to expensive treatments benefiting only a relatively small group of patients³. Liver transplantation is one of those expensive treatments for the following reasons: (a) Patient selection requires an extensive diagnostic evaluation in a multidisciplinary team; (b) organ procurement generates high costs due to the deployment of expert teams and the need for transportation of the team and the donor liver over considerable distances; (c) the surgical procedure is complex requiring highly trained medical personnel, frequently working night and weekend shifts; (d) morbidity after transplantation is high with need for radiological and surgical reinterventions as well as prolonged use of medication; and finally (e) readmissions and even retransplantations are not uncommon^{4,5}. However, these high costs are offset by large gains in health and quality-adjusted life years for liver-transplant recipients^{5,6}. In 2007, the worldwide rate was 88% one-year patient survival and 74% five-year patient survival (European Liver Transplant Registry, Organ Procurement and Transplantation Network)^{7,8}. Due to this favorable outcome, liver transplantation has become the established therapy for patients with end-stage liver disease. These patients would otherwise survive only several weeks up to a few years because of absence of an alternative treatment.

The first article on the cost-effectiveness of liver transplantation was published in 1990⁹. Since then, several articles have been published in which costs relevant for liver transplantation were presented. Articles from the United States seemed to report higher cost of liver transplantation than articles from other countries. However, reasons for this cost difference are unexplored. Interestingly, survival after liver transplantation seemed similar between the United States and peer countries¹⁰.

The first aim of this study was to compare cost of liver transplantation between the United States and other countries from the OECD in a systematic review. The United States was chosen because of the high reported cost of liver transplantation, and the other OECD countries were chosen as a comparison because these countries have similar levels of development, economy, technology, and health care compared to the United States. The OECD consists of 30 democracies, most of which are considered to be the most economically advanced countries in the world.

The second aim of this study was to perform a meta-analysis on the cost data generated by the systematic review. This meta-analysis estimated whether the cost difference between the United States and the other OECD countries was a real difference. The choice of a model was based on the expected amount of heterogeneity¹¹.

The third aim of this study was to analyze the reasons for the difference in estimated costs between the United States and other OECD countries.

A systematic literature review written by Goeree et al. identified 77 unique factors that may potentially affect the transferability of economic evaluations from one country to another¹². They grouped these 77 factors into five broad categories enabling comprehensive comparison of costs between countries. These five broad categories were used in this study and comprised characteristics related to the patient, disease, quality of the provider of the treatment, health care system, and methodology used in the economic evaluation¹². For each of these five categories a comparison on cost of liver transplantation was made between the United States and the other OECD countries.

2 MATERIALS AND METHOD

2.1 Systematic review

All relevant prospective and retrospective studies that reported on cost, cost-effectiveness, or cost-utility of liver transplantation, published between 1990 and 2006, were identified. First, the following registers were searched for details of unpublished and ongoing systematic reviews or meta-analyses: National Research Register (NRR), Medical Research Council (MRC)-funded research database, Centre for Reviews and Dissemination (CRD) register of reviews, Center Watch Clinical Trials Listing Service, and National Institutes of Health (NIH) clinical trials databases. No unpublished or ongoing reviews or meta-analyses regarding cost of liver transplantation were indexed in these sources. As far as we know, no systematic reviews or meta-analyses on cost-effectiveness of liver transplantation have been conducted.

Second, the following electronic databases were searched: Medline, Embase.com, the Cochrane Central Register of Controlled Trials (CCTR), the Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Reviews of Effects (DARE), Health Technology Assessment (HTA) Database, National Health Service Economic Evaluation Database, and the Cumulative Index to Nursing & Allied Health Literature (CINAHL). Medical subject heading (MeSH) as well as free text searching was used to improve the sensitivity of the search. Search strings used were “liver transplantation” in combination with “cost,” “costs,” “cost-effectiveness,” or “cost-utility.” Searching took place between September 2006 and April 2007. No language restriction was applied on searching. The reference lists of selected articles were examined.

The potentially relevant citations were assessed according to title and abstract. From all citations that appeared relevant the full articles were retrieved and read in full. Articles based on patients undergoing combined organ transplantation were excluded, as were articles with costs based on less than 10 patients, and articles without complete information on the cost of transplantation and clinical follow-up. Articles from countries not belonging to the OECD were excluded. Finally, to allow for cost differences between patients within a study, articles without original cost data based on individual patients were also excluded, thereby eliminating articles using fixed fees for a liver transplantation. The search strategy was tested by hand searching two journals in which relevant articles were expected (articles of *American Journal of Transplantation* and *Liver Transplantation* published between 2002 and 2006).

Data were extracted using a standard extraction sheet including first author, year of publication, number of patients included, years of patient inclusion, country of transplantation, mean costs, method of cost assessment, professional fees, recipient indication, recipient age, adult or pediatric recipient, deceased or living donor, and primary or retransplantation. When two publications were based on a single group of patients, the most detailed publication was used to extract data. The other publication was used to provide additional information.

2.2 Meta-analysis

A meta-analysis was performed with all articles reporting measures of spread around the mean, such as standard deviation, standard error, or confidence intervals. Due to the expected heterogeneity, the random-effects model was chosen instead of the fixed-effect model. A 95% confidence interval (95% CI) around the mean was estimated for the pooled cost of the United States and the other OECD countries, respectively. Heterogeneity was assessed by the *Q* value with the corresponding *p*-value and the *I*² quantity¹¹.

A second meta-analysis was performed to include all articles selected in the systematic review. The standard deviation for studies without measures of spread was derived from the mean standard deviation of the United States and the other OECD countries, respectively. The random-effects model was applied to the data to assess the differences with the original model. The results from the second meta-analysis were used to further compare cost between the United States and other OECD countries. The meta-analysis was performed by using the software Comprehensive Meta Analysis (version 2.2.046, Biostat, Englewood, NJ).

2.3 Comparison of study characteristics

The reasons for the differences in cost of liver transplantation between the United States and other OECD countries were analyzed after the meta-analysis. This analysis was performed by comparing five broad categories: patient characteristics, disease characteristics, quality of the provider of treatment, health care system, and methodological characteristics of the economic evaluation¹².

Patient characteristics were examined by looking at the difference in age, gender, and the percentage of transplantations for adults and children between the United States and other OECD countries¹³.

Because the focus of this study was on the costs generated during the liver transplantation procedure and the clinical follow-up, patient characteristics, such as attitude toward treatment, lifestyle, socioeconomic status, and compliance, were not taken into account.

Disease characteristics were assessed by looking at differences in indication for transplantation and disease severity between the United States and the other OECD countries. Disease severity was assessed by the mean Model for End-Stage Liver Disease (MELD) score, United Network for Organ Sharing (UNOS) status, and Child-Pugh category depending on the available data.

As an indicator for the quality of the provider of the treatment, one-year patient survival rates after liver transplantation in the United States and other OECD countries were compared. As a second indicator for quality, the annual number of liver transplantations per center were compared. Centers were considered as having high volume when performing more than 20 transplantations annually¹⁴. As a third indicator for quality, the mean length of stay in the hospital after liver transplantation was compared between the United States and the other OECD countries.

The health care systems of the United States and other OECD countries were compared on structural differences. The most important difference between the health care systems of the United States and other OECD countries is the availability of resources; that is, richer countries have theoretically more resources available for health care. By adjusting costs to gross domestic product (GDP) per capita, differences in available resources were taken into account. GDP per capita, as reported by the OECD in 2006, is a measure of the average level of economic activity. GDP was separately adjusted for the United States and the other OECD countries, weighted by the number of patients included. Furthermore, cost of liver transplantation was also adjusted for GDP at purchasing power parity (PPP). GDP at PPP was reported by the International Monetary Fund (IMF) in 2006. PPP is a currency conversion rate taking into account differences in price levels between countries by using the prices of a basket of 3000 consumer goods and services, government services, and investment goods. Adjustment for GDP at PPP was done separately for the United States and the other OECD countries, weighted by the number of patients included. Health care system characteristics, such as alternative treatment options, were not compared because there are no alternatives for liver transplantation. Furthermore, availability of care and waiting lists were not compared because every health care system has a waiting list for liver transplantation due to the limited availability of donor livers.

Methodological characteristics of the economic evaluations were compared between the United States and the other OECD countries. Both the method of assessing cost of liver transplantation and the timing of the economic evaluation were considered relevant methodological characteristics. Concerning the method of assessing costs, a distinction was made between hospital charges, costs extracted from the hospital accounting system, costs calculated by using cost-to-charge ratios, microcosting, and Medicare fee. These five methods of assessing costs use different inclusion and valuation of cost components: (a) Hospital charges reflect the market price at which a hospital is willing to perform a service and may include profit; (b) cost-to-charge ratios are calculated by applying the ratio of the organization's costs to its charges preferably differentiated by department; (c) the hospital accounting system estimates costs by internal cost attribution; (d) microcosting is based on identification, measurement, and valuation of individual resources; and finally (e) Medicare fee represents the reimbursement paid by Medicare (the U.S. national social insurance program) to a health care provider and is only applicable to U.S. articles. Timing of the economic evaluation was also examined because developments, such as diagnostics, surgery, experience, and use of medication may alter cost over time. The year of publication of the article was used to assess timing of the economic evaluation.

2.4 Costing methods

In this study, only costs related to liver transplantation and initial hospital stay after transplantation were included. To enable comparison between the United States and other OECD countries, the overall mean cost of liver transplantations was used as an estimate. The arithmetic mean cost per liver transplantation was based on the mean cost per article, weighted by the number of patients included. Therefore, articles based on a large number of patients had a high impact on the arithmetic mean cost per liver transplantation. An estimated mean was calculated by the meta-analysis for the United States and other OECD countries. The estimated mean was used for cost comparison in this study.

Professional fees accounted on average for less than 10% of total costs in two large studies^{4,15}. Four U.S. articles excluded professional fees leading to a slight underestimation of costs. All the articles from other OECD countries included professional fees.

All costs were presented in 2005 U.S. dollar value. Due to the difference in time between reported articles, a correction for inflation was made. All reported costs were adjusted by year of patient inclusion for U.S. inflation to the year 2005 (<http://www.bls.gov/cpi/>). Conversions were made by using the exchange rates on July 1, 2005, because this was the most recent year in which published costs were determined. The resulting exchange rates were as follows: € 1 equals US\$ 1.1957, £ 1 equals US\$ 1.7708, and 1 CAD equals US\$ 0.805283. Euro zone currency before 2002, the year the Euro was introduced, was adjusted using the fixed conversion rates of the former national currencies. In this article inflation-corrected costs will be presented.

3 RESULTS

3.1 Results systematic review

From 2000 potentially relevant citations identified by our initial search strategy, 1829 were not included in the systematic review because these citations did not discuss cost of liver transplantation (Figure 1). Of the remaining 171 citations the full articles were retrieved. After applying the exclusion criteria specified earlier, 141 articles were excluded. The majority of these articles ($n = 120$) were excluded because of lack of information on individual patients. Other reasons for exclusion were the use of identical patient-level data in other included studies ($n = 11$), costs only focused on donor evaluation ($n = 4$), studies of non-OECD countries ($n = 3$), and cost data only available for fewer than 10 transplantations ($n = 3$). A list of excluded articles with reasons for exclusion is available on request from the authors. The selection process eventually led to 30 articles that were eligible for the systematic review^{4-6,9,13,15-39}. Among the selected articles, three of them were written in a non-English language. No additional articles on cost of liver transplantation were found by checking the references of the selected articles. Also, after hand searching the indicated two journals, no additional articles were found, confirming that the initial search was comprehensive.

In Table 1, all included articles are ordered on year of publication and name of the first author. Besides the United States, studies were performed in eight different OECD countries. Even though five institutions participated in multiple articles, patient populations were different and could, therefore, be included. The included articles were published between 1990 and 2006 and included patients between March 1979 and June 2005. The number of liver transplantations in the included articles ranged from 11 to 1621 per article (median: 100). A total of 15 U.S. articles included 4629 liver transplantations compared to 1346 liver transplantations as discussed in 15 articles from the other OECD countries. In total, this systematic review and meta-analysis included 5975 liver transplantations from 30 articles. U.S. articles reported weighted arithmetic mean cost of US\$ 174 490 per liver transplantation compared to US\$ 108 934 for the other OECD countries (Table 1).

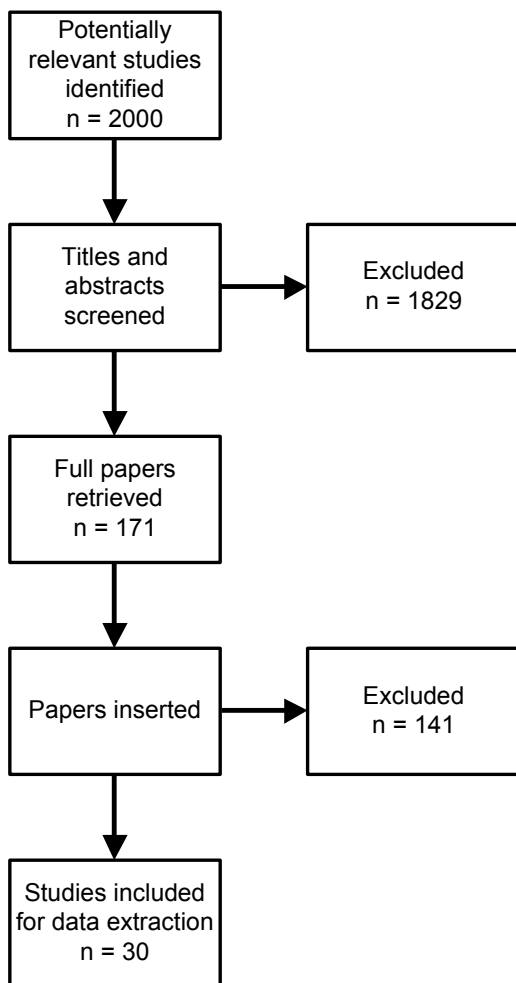


Figure 1. Flowchart of study inclusion.

Table 1. Articles on cost of liver transplantation included in the systematic review and meta-analysis.

Author	Year	N	Inclusion period	Country	Cost			Professional fees	Indication	Recipient age (mean, median)	Adult (%)	Deceased donor (%)	Primary LTx (%)	Additional re-LTx included (%)
					LTx & clinical follow-up (\$)	Inflation adjusted cost (2005 \$)	Method of cost assessment							
Englesbe	2006	240	Jul '02 - Jun '05	US	194 840	194 840	MC	incl	diverse	42	80	100	-	-
Ishida	2006	11	Jan '99 - Nov '01	JP	117 141	127 169	MC	incl	diverse	42	100	0	100	0
Kogure	2006	17	Sep '01 - Jan '05	JP	97 901	97 901	HC	incl	non-acute	48	100	0	100	0
Washburn	2006	222	Feb '02 - May '04	US	75 320	75 320	CC	incl	non-acute	53	100	97	100	1
Kraus	2005	38	Jun '03 - Sep '03	DE	58 589	62 187	MC	incl	diverse	-	100	-	-	-
Oostenbrink	2005	179	Jan '95 - Aug '01	NL	114 959	126 773	AS	incl	diverse	47	100	100	-	-
Brand	2004	26	Nov '96 - Dec '97	US	80 000	93 782	MF	incl	diverse	47	92	-	-	-
Cole	2004	47	Jan '97 - Jan '02	US	107 255	116 437	MC	incl	diverse	2	0	66	100	6
Filipponi	2003	252	Jan '97 - Dec '00	IT	93 552	106 101	MC	incl	diverse	51	100	100	93	0
Longworth	2003	208	Dec '95 - Dec '96	UK	105 551	123 734	MC	incl	ald, pbc,psc	52	100	100	100	0
Trotter	2003	67	Aug '97 - Jun '00	US	102 106	110 847	MC	excl	diverse	49	100	64	100	1
Azoulay	2002	139	Sep '86 - Sep '99	FR	103 946	117 890	HC	incl	diverse	39	-	100	0	0
Sagmeister	2002	51	Jan '95 - Oct '00	CH	141 639	166 039	MC	incl	diverse	48	100	100	100	0
Taylor	2002	119	Jan '91 - Dec '92	CA	56 283	67 436	MC	incl	diverse	45	100	0	100	0
Best	2001	1621	Jan '93 - Dec '99	US	144 017	163 336	MF	incl	diverse	57	100	-	-	-
Bucvalas	2001	83	Mar '94 - Apr '99	US	151 183	177 227	AS	incl	diverse	5	0	93	100	1
Fourquet	2001	38	Jan '94 - Apr '96	FR	62 387	82 215	MC	incl	diverse	46	100	100	100	0
Nair	2001	121	Jan '94 - Dec '96	US	110 555	137 613	HC	excl	diverse	48	100	100	100	4
Schnitzler	2001	683	Apr '90 - Jun '94	US	191 634	245 578	HC	-	non-acute	50	100	100	97	0
Van Agthoven	2001	100	Jan '93 - Nov '97	NL	79 686	99 189	MC	incl	diverse	46	100	100	91	0
Gilbert	1999	144	Jan '91 - Dec '96	US	153 343	190 872	HC	incl	diverse	44	-	100	100	0
Brown	1998	111	Jun '92 - Jun '93	US	201 727	258 512	HC	excl	diverse	44	90	100	100	0
Geevarghese	1998	100	Feb '91 - Mar '96	US	112 358	139 857	AS	-	diverse	46	-	-	-	10

Table 1. Articles on cost of liver transplantation included in the systematic review and meta-analysis (continued).

Author	Year	N	Inclusion period	Country	Cost LTx & clinical follow-up (\$)	Inflation adjusted cost (2005 \$)	Method of cost assessment	Professional fees	Indication	Recipient		Additional re-LTx included (%)		
										age (mean, median)	Adult (%)		Deceased donor (%)	Primary LTx (%)
Russo	1998	130	Sep '91 - Dec '96	US	108 407	134 938	CC	excl	diverse	37	82	100	91	0
Schulak	1997	935	Jul '84 - Jun '96	US	90 630	164 498	HC	-	diverse	39	80	100	100	10
Hoffmann	1996	56	Jun '93 - Sep '94	DE	72 571	93 000	HC	-	diverse	41	89	100	89	0
Smith	1996	91	Jan '90 - Dec '92	US	175 291	244 008	HC	incl	diverse	44	100	100	100	10
Pageaux	1993	39	Mar '89 - Dec '91	FR	76 236	106 172	MC	-	non-acute,non-hcc	50	100	100	-	-
Burroughs	1992	23	Oct '88 - Oct '89	UK	39 113	58 446	AS	incl	diverse	47	-	100	100	0
Bonsel	1990	76	Mar '79 - Sep '87	NL	72 088	123 933	MC	incl	diverse	34	80	100	89	0

Adult (%) = percentage of adult recipient versus pediatric recipients; deceased donor (%) = percentage of deceased donors versus living donors; primary LTx (%) = percentage of primary liver transplantations versus retransplantations; additional re-LTx included (%) = percentage of recipients with one additional retransplantation included in the total costs. Abbreviations: CA = Canada, CH = Switzerland, DE = Germany, FR = France, IT = Italy, JP = Japan, NL = Netherlands, UK = United Kingdom, US = United States, AC = accounting system of the hospital, CC = hospital charges converted by cost-to-charge ratios, HC = hospital charges, MF = Medicare fee, MC = microcosting, incl. = fees included, excl. = fees excluded, ald = alcoholic liver disease, pbc = primary biliary cirrhosis, psc = primary sclerosing cholangitis, non-hcc = non-hepatocellular carcinoma.

3.2 Results from meta-analysis

In the meta-analysis, eight U.S. articles (53%) and four OECD articles (27%) were included. The other articles did not report measures of spread. By applying a random-effects model, the estimated mean cost was US\$ 179 143 (US\$ 148 661 - 209 625) for the United States compared to US\$ 99 405 (US\$ 56 623 - 142 188) for the other OECD countries (Figure 2). High heterogeneity was observed in both groups¹¹. The Q value in the United States was 179 versus 45 for the other OECD countries (both $p < 0.001$) and the I^2 was 96% versus 93%, respectively. The high heterogeneity confirmed the choice for the random-effects model. The second analysis included all articles in the random-effects model. The mean cost was US\$ 163 438 (US\$ 145 277 - 181 598) compared to US\$ 103 548 (US\$ 85 514 - 121 582) for the United States and other OECD countries, respectively (Figure 2). High heterogeneity in both groups was also indicated in the second analysis. The Q value in the United States was 374 versus 138 for the other OECD countries (both $p < 0.001$) and the I^2 was 96% versus 90%, respectively. Sources of heterogeneity were explored by comparison of study characteristics.

3.3 Comparison of study characteristics

Cost differences according to patient characteristics

The mean age reported in the 15 U.S. articles and 10 OECD articles was 47.6 years and 45.2 years, respectively (Table 2). Four OECD articles reported only the median ages. The weighted mean of these median ages was 49.6 years. The majority of the recipients in the United States articles and the other OECD articles was male (57% vs. 59%). In the United States articles, 9% of the transplanted patients were pediatric recipients compared to 5% in the other OECD countries.

Cost differences according to disease characteristics

The indication for transplantation was reported in 12 U.S. articles (80%) and in 10 of the other OECD articles (67%). Table 2 shows that the U.S. articles reported more recipients with hepatitis C cirrhosis (26% vs. 18%), but less acute liver failure (3% vs. 9%) and primary biliary cirrhosis (4% vs. 15%) compared to the other OECD countries. One article reported higher costs for patients transplanted for alcoholic liver disease than patients transplanted for primary biliary cirrhosis and primary sclerosing cholangitis⁵. Another article reported that patients with acute liver failure had higher costs than patients with chronic liver failure³⁸.

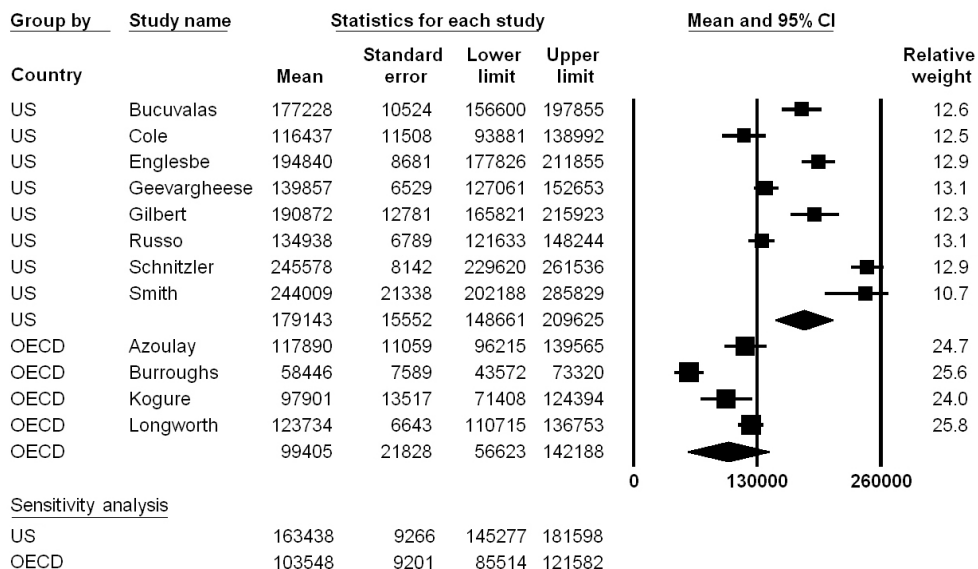


Figure 2. Meta-analysis of cost of liver transplantation with random effects model. **Abbreviations:** CI = confidence interval, US = United States, OECD = Organization for Economic Cooperation and Development.

Information on disease severity before liver transplantation, as measured by the MELD score, UNOS status, or Child-Pugh category, was reported in 58% and 39% of the United States and other OECD articles, respectively. However, in both categories of articles, disease severity of recipients before transplantation was similar (Table 2).

Cost differences according to quality of the provider of the treatment

One-year patient survival rates between the United States and the other OECD countries were compared. Furthermore, 13 U.S. articles and 8 other OECD articles reported one-year patient survival. In addition, only one U.S. article and two other OECD articles reported two-year patient survival rates, and these rates were used as well^{6,33,36}. The 14 U.S. articles reported mean one-year patient survival of 84%, and the other 10 OECD articles reported mean one-year patient survival of 80%.

All United States and other OECD liver transplantations were performed in high-volume centers¹⁴. During the study period of the included studies, 100% and 99% of liver transplantations were performed in high-volume centers in the United States and other OECD countries, respectively.

Mean length of hospital stay for liver transplantation could be assessed for 82% and 53% of the cases in the United States and the other OECD countries, respectively. The mean length of stay after liver transplantation was 30.4 days compared to 62.4 days for the United States and the OECD countries, respectively (Table 2).

Table 2. Characteristics of articles of cost of LTx in the United States and other OECD countries.

<i>Patient characteristics</i>	US	Other OECD countries
Gender (male %)	57%	59%
Age (mean, years)	47.6	45.2
Pediatric recipients (%)	9%	5%
<i>Disease characteristics</i>		
Diagnosis		
acute liver failure	3%	9%
chronic liver failure	83%	80%
<i>of which: alcoholic liver disease</i>	17%	14%
<i>of which: hepatitis C cirrhosis</i>	26%	18%
<i>of which: primary biliary cirrhosis</i>	4%	15%
tumor	1%	3%
metabolic and other	12%	8%
MELD (mean)	21.6	22.1
UNOS status 1	19%	22%
UNOS status 2	31%	27%
UNOS status 3/4	51%	51%
Child-Pugh category A	13%	0%
Child-Pugh category B	51%	44%
Child-Pugh category C	35%	56%
<i>Quality of the provider</i>		
One-year patient survival rate	84%	80%
Centers > 20 LTx annually (%)	100%	99%
Length of stay after LTx (mean, days)	30.4	62.4
<i>Different health care systems</i>		
GDP	\$ 41 900	\$ 35 480
PPP index (other OECD countries = 100)	126	100

Other OECD countries: Canada, France, Germany, Italy, Japan, Switzerland, the Netherlands, and United Kingdom. Abbreviations: US = United States, OECD = Organization for Economic Cooperation and Development, GDP = gross domestic product, PPP = purchasing power parity, MELD = model for end-stage liver disease, UNOS = United Network for Organ Sharing.

Cost differences according to different health care systems

The GDP of the United States is US\$ 41 900 compared to the weighted mean GDP of the other OECD countries of US\$ 35 480. A liver transplantation performed in the United States would cost an estimated US\$ 138 396 if the GDP was the same as the GDP of the other OECD countries. This reduces the cost difference between the United States and the other OECD countries from 58% to 34% (Table 3). The PPP of the United States is 126% of the weighted mean PPP of the other OECD countries. Cost of a U.S. liver transplantation would be reduced to US\$ 129 425 if the PPP was equal to the other OECD countries. This reduces the cost difference between the United States and other OECD countries even further to 25% (Table 3).

Table 3. Impact on mean cost per liver transplantation by correcting for GDP and GDP at PPP.

Mean cost of liver transplantation	US	Other OECD countries
Inflation-corrected	\$ 163 438	\$ 103 548
GDP per capita-corrected	\$ 138 396	\$ 103 548
GDP at PPP per capita-corrected	\$ 129 425	\$ 103 548

Other OECD countries: Canada, France, Germany, Italy, Japan, Switzerland, the Netherlands, and United Kingdom. Abbreviations: US = United States, OECD = Organization for Economic Cooperation and Development, GDP = gross domestic product, PPP = purchasing power parity.

Cost differences according to methodology used in the economic evaluation

Figure 3 shows the mean cost per liver transplantation for the five different methods of cost assessment. The preferred method to calculate costs of transplantation in the United States was by using hospital charges, whereas the other OECD countries preferred microcosting. However, note that in all U.S. articles, cost of liver transplantation was similar, notwithstanding the method of cost assessment used. Only cost-to-charge ratios led to lower U.S. costs. The articles from the other OECD countries showed only a small difference between costs estimated by hospital charges, the hospital accounting system, and microcosting.

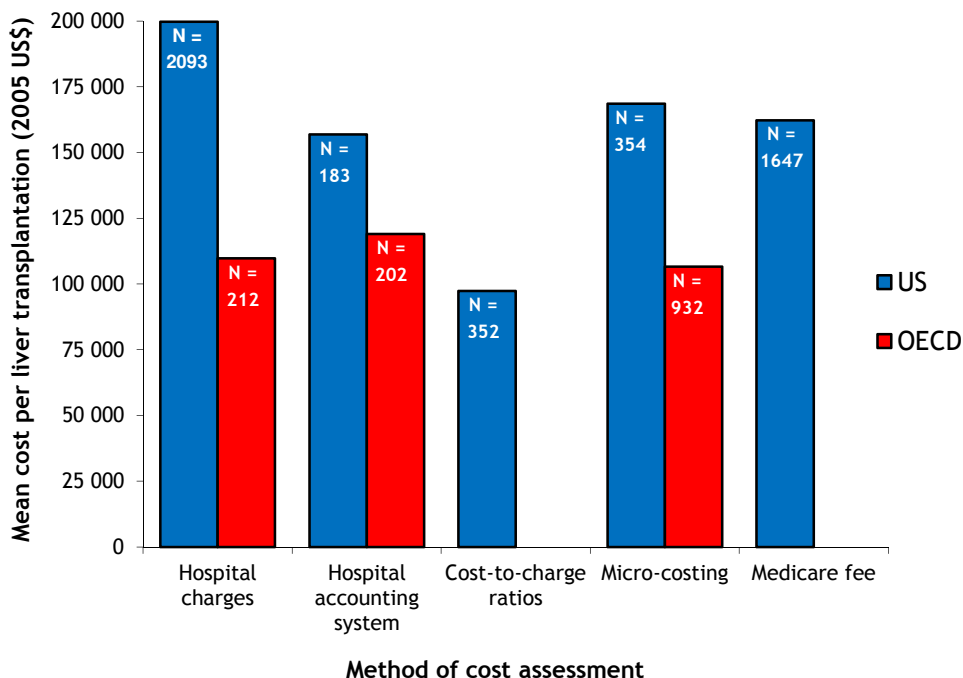


Figure 3. Mean cost per liver transplantation for different methods of cost assessment. Numbers within bars represents number of patients used to estimate the mean. Abbreviations: US = United States, OECD = Organization for Economic Cooperation and Development.

The timing of the economic evaluation differed slightly between the United States and the other OECD countries. The first U.S. article was published in 1996³⁵ compared to 1990 for the other OECD countries⁹. The most recent articles included in this meta-analysis for the United States^{4,39} and the other OECD countries^{26,27} were published in 2006. Figure 4 shows the mean arithmetic cost per transplantation for the 30 articles with the size of the circle depicting the number of transplantations. Both in the United States and in the other OECD countries, cost of liver transplantation showed a decline of US\$ 500 and US\$ 690 per year, respectively. The difference in cost of liver transplantation between the United States and the other OECD countries remained quite stable in the past two decades.

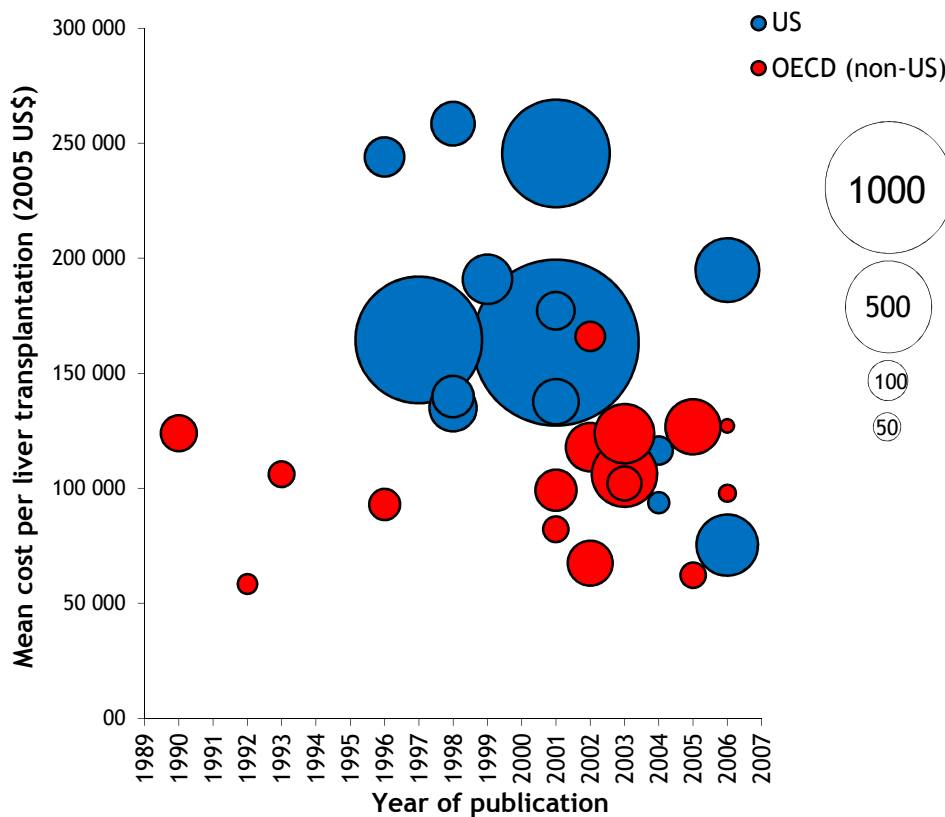


Figure 4. Mean cost per liver transplantation in different health care systems. *The size of the circle depicts the number of patients in the study. Abbreviations: US = United States, OECD = Organization for Economic Cooperation and Development.*

4 DISCUSSION

This comprehensive review and meta-analysis were conducted to summarize the research to date and to examine the differences in cost of liver transplantation between the United States and other OECD countries. An insight into these cost differences may assist health care decision makers in not only gaining an insight into the cost of liver transplantation in different health systems, but critically scrutinize their own policy as well. Furthermore, insight into cost of liver transplantation may not only support increased allocation of health care resources to existing transplant programs but also may aid in the discussion about the introduction or expansion of this effective therapy in emerging and developing countries and regions.

So far, the economical consequences of liver transplantation were explored scarcely. Available articles concerned heterogeneous groups of patients, varied widely in the included number of patients, used different methods of cost assessment, and considered different eras in liver transplantation. This heterogeneity leads to difficulties in the interpretation of cost differences between U.S. articles and articles from the other OECD countries. The present study is the first meta-analysis comparing the United States with the other OECD countries by combining a total of 5975 liver transplantations. Our study revealed that a liver transplantation performed in the United States was more expensive than a liver transplantation performed in other OECD countries.

The results of the meta-analysis show that the pooled estimate cost of US\$ 163 438 (US\$ 145 277 - 181 598) for liver transplantations in the United States differs significantly from the pooled estimate of US\$ 103 548 (US\$ 85 514 - 121 582) from the other OECD countries. In addition to a difference between the United States and other OECD countries, there is also large heterogeneity within the United States and among the other OECD countries. The random-effects model on the selection of articles with primary data on measures of spread led to the same conclusions as the all-inclusive model that included all articles. While the estimated mean was similar, the confidence interval of the model that included all articles was smaller due to the higher number of included articles. The mean costs of transplantations as incurred in the United States and in the other OECD countries were still significantly different from each other, even with all articles included. Thus, the liver transplantation cost difference between the United States and the other OECD countries can be considered significant, despite the large variation within both groups.

Recipient characteristics showed similar gender and age distribution between the United States and the other OECD countries. The 4% difference between the proportion of pediatric recipients in the United States and other OECD countries could be explained by the two U.S. articles that exclusively examined pediatric recipients^{13,20}. However, reported mean cost of liver transplantation in pediatric recipients in these two articles was similar to mean costs in other U.S. articles. Therefore, it was unlikely that age, gender, or the difference between adult and pediatric recipients caused a higher transplantation cost as reported in the United States articles.

Disease characteristics were slightly different when assessing the indication for liver transplantation. In a recent article comparing the United States with the United Kingdom and Ireland¹⁰, a similar distribution of indications was presented. Higher costs were reported for alcoholic liver disease⁵ and for acute liver failure³⁸. However, the U.S. articles included in this review reported only slightly more alcoholic liver disease than that reported in the articles from the other OECD countries (17% vs. 14%) while acute liver failure was reported less often as an indication (3% vs. 9%). Since mean MELD score, UNOS status, and Child-Pugh class were also similar between the United States and other OECD countries, it was not likely that disease characteristics were an explanation for the higher cost in the United States.

The quality of the provider of the treatment was assessed by the results after transplantation and the volume of transplantations. Unfortunately, the majority of articles reported no graft survival rates or quality-adjusted life years. Therefore, only patient survival rates could be assessed. A small difference between the one-year patient survival rates of the United States and the other OECD countries was found (84% vs. 80%). The small difference may be explained by the inclusion of the three OECD articles published between 1990 and 1993, which reported lower survival^{9,19,31}. In literature, a similar one-year patient survival after liver transplantation has been reported in the United States, Canada, and the United Kingdom^{2,10}. The majority of liver transplantations of the United States and other OECD countries was performed in a high-volume center. The U.S. articles reported approximately half the length of stay in comparison to that mentioned in articles from the other OECD countries, probably due to a different discharge policy (Table 2). However, the shorter length of stay of U.S. patients did not translate to lower costs. Furthermore, it is difficult to derive quality differences from length of stay without information on the required care after discharge. In conclusion, a cost difference arising out of the quality of the provider of the treatment was not likely due to similar one-year patient survival, a similar number of high-volume centers, and an inverse relationship between costs and length of stay in the United States compared to other OECD countries.

Health care system characteristics turned out to be the most important explanation for the cost differences in liver transplantation. Corrections for GDP per capita and PPP led to major reduction of the cost difference between the United States and other OECD countries. According to a report of the World Health Organization⁴⁰, the United States spends 15.2% of GDP on health care, compared to a weighted mean of 9.4% of GDP for the other OECD countries. Therefore, the higher cost of liver transplantation in the United States compared to other OECD countries was in line with overall differences in cost of health care. The higher cost of health care in the United States consisted primarily of higher prices of hospital stay, physician services, and pharmaceuticals^{1,41}. Other explanations such as administrative complexity, malpractice litigation, and absence of supply constraints also added to the higher cost of health care in the United States, but to a lesser extent^{1,41}. These explanations for higher cost of health care were reflected in GDP and PPP as well as in the proportion of GDP spent on health care. Health care system explanations being exclusively related to organ transplantation could be attributed to differences in costs as well.

A policy in the allocation of organs leading to transplantation of severely affected patients may lead to worse outcome, with more complications and reinterventions eventually leading to higher costs. Since February 2006, the United States has been using the MELD score for allocation of donor livers. Half of the OECD countries included in this study have recently adopted the MELD system as well. However, allocation systems were different between countries at the time of publication of the articles. In addition, changes in donor liver allocation within countries makes it very difficult to assess the impact of allocation systems on costs.

Methodology used in the economic evaluation was assessed by looking at the method of cost assessment and timing of the publication. Different methods of cost assessment were used within the articles from the United States and other OECD countries. Regardless of using hospital charges, hospital accounting system, microcosting, or Medicare fee, U.S. articles reported higher costs than other OECD articles. Two U.S. articles used cost-to-charge ratios and due to a mean cost-to-charge ratio of 0.56, these costs were clearly lower. Converting charges into hospital costs is becoming more commonplace in U.S. studies but should still be used with caution⁴². In addition, mean cost of liver transplantation seemed to slightly decrease over time for both the United States and for the other OECD countries. Possible explanations for these slightly decreasing costs were increased experience leading to a decline in morbidity-related costs and a higher efficacy of the transplant-related procedures resulting in less resource utilization¹⁵. Important to note, however, is that by combining slightly declining costs over time with increased patient survival after liver transplantation, cost-effectiveness improves leading in turn to better value for money. Methodology used in the economic evaluation was not an explanation for the cost difference between the United States and the other OECD countries. A limitation of this review was the unavailability of primary data. Therefore, meta-analysis was not straightforward. Another limitation of this review was the restricted scope of costs included. Costs of all phases of the liver transplantation process were retrieved from articles. However, information on cost of the donor, recipient selection, recipient waiting, and outpatient follow-up were absent or too limited to be of any use for a sensible comparison. Costs related to these other phases will add to the total cost, even though the costs of liver transplantation and clinical follow-up will comprise the majority of total costs. A concern for future comparisons is the impact of the current decline in value of the US dollar compared to other major currencies. The studies included in this meta-analysis were performed between 1990 and 2005 with relatively stable exchange rates between the currencies. However, the impact of a decline in value of the US dollar may alter the cost difference between health care interventions performed in the United States and other OECD countries.

Correcting costs for GDP per capita and PPP may reduce variation due to exchange-rate volatility. Future studies are needed to quantify the evolving cost-effectiveness of liver transplantation to start or expand this effective therapy in new regions and centers across the world. More information is needed on the impact of incentives for physicians and hospitals to provide such therapies. With future studies reporting on cost of liver transplantation, stratification might become possible regarding indication for liver transplantation or regarding different donor sources. More information is also needed to specify costs of the other phases of liver transplantation, such as costs incurred for recipient screening, on the waiting list, and during long-term follow-up of the recipient. The prospective Dutch COLT study (Cost and Outcome of Liver Transplantation) is gathering this information.

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