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Is living donor liver transplantation cost-effective?

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Deceased donor (DD) liver transplantation has been accepted as the standard of care for patients with end stage liver disease. With the growing discrepancy between the numbers of donors and recipients, the median waiting time for liver transplantation has increased dramatically, exceeding in some countries one to two years [1]. Strategies to expand the donor pool include increasing the donor consent rate, the use of marginal donors, split liver and most recently living donor liver transplantation (LDLT) [2]. Initial studies focused on the efficacy and safety of LDLT compared to DD liver transplantation. While multiple studies have now demonstrated excellent patient and graft survival rates with LDLT, the first studies on cost and cost-effectiveness are only emerging. In addition to ethical concerns, there is an ongoing debate in the medical community about the ability to afford expensive life saving techniques such as cadaveric and living donor liver transplantation and there is concern about a gap between scarce financial resources in medicine and a growing availability of expensive health related interventions. Therefore studies on cost and cost-effectiveness are increasingly important in this era of financial pressures.

This article focuses on economic aspects of liver transplantation and aims to give an insight into the financial aspects of liver transplantation. First the most recent data for

DD liver transplantation will be reviewed and finally the data for LDLT. An economic assessment of liver transplantation should include the costs of the pretransplant care including the initial work-up, the transplantation itself and the posttransplant care. However, the study design of the published studies and the follow-up period considered in the cost analysis is highly variable and comparisons are therefore difficult. Nevertheless it gives the reader some ideas about the cost and cost-effectiveness of DD liver transplantation and LDLT. A glossary of the most important economic definitions is given in Table 1. For easier comparisons the different national cost are compared in Euro (exchange rate November 2004; 1 USD = 0.76€).

1. Cost studies

Early assessment of the costs of liver transplantation in the late 1980s and early 1990s probably overestimated the costs of liver transplantation (Table 2). As reviewed by O'Grady in a retrospective cost (charges) analysis of DD liver transplantation in the UK there is a variance of 40–45% per unit charge between the different centers [3]. The average charges for one liver transplantation ranged from 45'780–64'350€. High costs were observed at the beginning of a new program, followed by a trend towards reduced cost as the number of transplants increased. Several factors such as cytomegalovirus (CMV) disease, the number of units of blood products administered during transplantation, bacteraemia, pretransplant renal dysfunction, and

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Abbreviations: DD, deceased donor liver transplantation; LDLT, living donor liver transplantation; QALY, quality adjusted life years gained.

Table 1
Glossary of the most important economic terms

Costs: value of all resources that are consumed caused by an intervention
 Charges: hospital charges are used as a proxy for costs
 Cost-effectiveness analysis: costs and effects of a program and an alternative are calculated and presented in a ratio of incremental costs to incremental effect [13]

re-transplantation were identified in these early studies as independent variables associated with higher costs in a multiple linear regression model [4].

In recent years waiting times progressively increased which may lead to transplantation at more advanced and, thus, less cost-effective stages of the disease. These additional costs could either be due to an increase of the costs for the transplant procedure itself and/or for pretransplantation care. This question was addressed by Gilbert et al. who retrospectively analyzed the charges of DD liver transplantation for the periods 91–93 (group A) and 94–96 (group B) in a total of 144 DD liver transplantations in the US [5]. The median charges of group B amounted to 147'079€ and were higher than for group A (132'930€). Surprisingly the higher charges were mostly due to higher pretransplant cost, which almost doubled during the study period and not by higher expenses for the transplant procedure itself. Showstack et al. performed a prospective multicenter (three centers) US cohort study of 711 patients receiving a DD liver transplantation between 1991 and 1994 [6]. Mean costs for the transplantation procedure until hospital discharge amounted to 154'610€. Donor and recipient age, advanced liver disease, alcoholic liver disease, death in the hospital after transplantation, and re-transplantation were independently associated with higher resource utilization. In addition the resource utilization also differed significantly among the transplant centers.

A similar study was performed by Rufat et al. who evaluated in a prospective study the costs of DD liver transplantation from 1994 to 1998 in France (38 transplantations) [7]. The mean costs (1 year) after transplantation including recipient evaluation amounted to 85'515€. Again, older age (>40 years) and severity of liver disease were associated with higher costs. In addition, acute rejection and postoperative renal failure led to a significant increase in costs during the first year after transplantation, but not CMV infection. A limitation of this study might be the small sample size and the low number of emergency DD liver transplantation compared to other studies.

Filipponi and al. analyzed in a retrospective Italian study the yearly costs of DD liver transplantation in 252 patients [8]. The average costs were fairly constant over 4 years (1997–2000) amounting to 77475€ in 2000. Preoperative impairment of renal function was an important factor determining the costs after transplantation. In contrast to the study by Showstack non-viral (mostly alcoholic) hepatitis was associated with lower costs, whereas higher costs were

caused by fulminant hepatic failure, rare indications of liver transplantation (such as cholangiocarcinoma, HCC, sclerosing cholangitis etc.) and by patients with portal vein thrombosis. In contrast to other studies, severity of liver disease (Child-Pugh score) was not associated with higher costs. Preoperative renal function was also identified in the study of Brown et al as the most important factor for higher cost is liver transplantations together with fulminant liver failure, whereas the degree of liver impairment seemed less important [9]. Renal insufficiency together with preoperative respirator dependence were again the major contributing factors to costs of liver transplantation in the study by Markmann et al [10].

Most studies included patients with fulminant liver failure into the cost analysis [5,7–11] or focused only on patients with chronic liver disease [6]. Only one study analyzed the costs for chronic liver disease and acute liver failure separately including pretransplant cost and the costs up to one year after transplantation [12]. In this study the total overall costs for patients with chronic liver failure amounted to 107'675€ compared to 90'792€ for patients with acute liver failure. This difference was largely due to higher cost before liver transplantation, whereas the cost for the transplant procedure and the first year follow-up are almost identical.

Trotter et al. recently published the first comprehensive cost study comparing DD liver transplantation (43 transplantations) with LDLT (24 transplantations) in the US from 1997 to 2000 [11]. The analysis included the donor evaluation (rejected donors included), donor hepatectomy and donor follow-up for one year. Total costs for one year amounted to 102'220€ for DD liver transplantation and to 123'600€ for LDLT. The authors emphasize that pretransplant costs were almost twofold higher in LDLT patients, whereas the costs for transplantation (LDLT: 90'136€, DD liver transplantation: 70'605€) were only slightly higher and for posttransplant care slightly less than DD liver transplantation (both not significant). The reason for the higher pretransplant costs in LDLT is explained by the fact that these patients had more advanced liver disease as indicated by more frequent clinical decompensations. Surprisingly the mean cost for the acquisition of a cadaveric liver is only 1% less than the total mean cost for a live donor (evaluation of the living donor, hepatectomy and medical care of the donor in the first year). The authors stress the fact that the LDLT series included 4 re-transplantations during the first 10 procedures at the centre and that the re-transplantation rate was lower after gaining experience. Therefore the actual costs of LDLT are likewise lower.

A comparison of these studies is difficult because the patient populations included and the study designs are different, some studies use charges other costs and the time period for the cost analysis are different. With all these limitations in mind the mean costs per transplantation in Europe tend to be lower than in the US. However more recently the costs in the US decreased significantly,

Table 2
Cost studies

Author	Country	Design	Number of transplantations	Time	Cost elements ^a	DD ^b or LDLT	Costs (Euro)	Risk factors for higher costs
Gilbert (5)	US	Retrospective	144	91–96	Charges including pretransplantation charges and charges until hospital discharge	DD	132'930–147'079	n.r.
Showstack (6)	US	Prospective	711	91–94	Charges only for the transplant procedures until hospital discharge, excluding professional fees	DD for patients with chronic liver disease	154'610	Donor and recipient age Advanced liver disease Alcoholic liver disease Death in the hospital after DD
Rufat (7)	France	Prospective	38	94–95	Costs from transplantation until 1 year after transplantation including recipient evaluation	DD	86'515	Re-transplantation Older age (>40years) Severity of liver disease Acute rejection Postoperative renal failure
Brown (9)	US	Retrospective	109	92–93	Charges from transplantation until first hospital discharge	DD Including liver kidney transplantation	116'866	Pretransplant kidney function Fulminant liver failure (UNOS Status 1)
Markmann (10)	US	Retrospective	1148	92–98	Charges from transplantation until first hospital discharge	DD	n.r.	Pretransplant kidney function Ventilator dependence
Agthoven (12)	Netherland	Retrospective	100	93–97	Costs including: pretransplant work-up and up to one year after transplantation	DD	107'675 for chronic liver disease 90'792 for acute liver failure	n.r.
Filipponi (8)	Italy	Retrospective	252	97–00	Costs from transplantation until one year after transplantation	DD	75'747–83'846	Pretransplant kidney function Non-alcoholic liver disease Fulminant hepatic failure Portal vein thrombosis
Trotter (11)	US	Prospective	67	97–01	Costs (expressed as cost unit which could be roughly valued at \$1000) including pretransplant work-up and up to one year after transplantation	DD and LDLT	102'220–123'600	n.r.

DD liver transplantation, nr, not reported.

^a If not specified professional fees are included.^b If not specified patients with chronic liver disease and acute liver failure are included in the analysis.

approaching figures in Europe. These differences can easily be explained by the different health care system. Also the factors associated with higher costs vary widely, only renal insufficiency, either pre or postoperatively is consistently associated with higher costs.

Data regarding the costs of LDLT are still scarce with only one full paper published so far. Clearly more studies are needed in the future, to analyze in more detail the cost differences between DD liver transplantation and LDLT. It will be interesting to analyze whether the new organ allocation system in the United States, prioritizing patients with more advanced disease, will lead to decreased cost for the pretransplant care but increased costs for the transplantation procedure.

2. Studies on cost effectiveness

A cost effectiveness analysis assesses the costs of an intervention in relation to its benefits expressed in life years gained or QALYs (quality adjusted life years gained). The cost effectiveness analysis makes it possible to compare different interventions by its cost effectiveness ratio [13] (Table 3). A cost effectiveness ratio below 38'000€ (\$ 50'000) per life year gained is usually regarded as cost effective [14].

Ouwens et al. compared the cost effectiveness of lung, heart and liver transplantation in the Netherlands [15]. Data were based on three Dutch technology assessment studies and included 81 liver transplantations between 1978 and 1987. Survival and costs without a transplantation program were estimated based on an analysis of the waiting list. Costs per liver transplantation amounted in the first year to 63'156€ and resulted in a survival benefit per patient of 11.5 QALYs. The cost effectiveness ratio of liver transplantation was 19'760€ per life year gained. The authors discuss a favorable cost effectiveness ratio of liver transplantation compared to lung and heart transplantation, which was mainly caused by the remarkable survival gains of liver transplantation.

Longworth et al. [16] analyzed the costs and survival for patients on the waiting list for liver transplantation over 27

months in England and Wales. Costs and survival of a control group were estimated by observed patients waiting for transplantation and data from the literature. The analysis compared three disease groups (primary biliary cirrhosis, alcoholic liver disease and primary sclerosing cholangitis). Costs for liver transplantation ranged from 75'110 to 94'450€. The mean costs per QALY gained were between 30'030 (primary sclerosing cholangitis) and 68'640€ (alcoholic liver disease). Cost effectiveness for alcoholic liver disease was poor in comparison to the other two disease groups because a higher number of patients with alcoholic liver disease were evaluated for transplantation, without being accepted for it. The authors discuss that the poor cost effectiveness ratio of 68'640€ per QALY gained for alcoholic liver disease should improve over time if the estimated survival gain would be calculated over a longer time period (longer than 27 months).

We conducted the first cost effectiveness study using a Markov model where we compared the effectiveness (life years and QALYs gained), the lifetime costs and the cost-effectiveness of DD liver transplantation alone and DD liver transplantation in combination with LDLT to the conservative management of patients with endstage liver disease [17]. If patients had the possibility of being transplanted their survival increased by an average of 6.2 QALYs compared to patients treated conservatively. The addition of LDLT further increased the survival by an additional 1.3 QALYs compared to DD liver transplantation alone. Both strategies, using either DD liver transplantation alone or the combination of DD liver transplantation and LDLT, therefore, significantly increased the survival of patients with endstage liver disease. As expected both strategies were however also associated with higher costs (LDLT and DD liver transplantation=222'215€ and DD liver transplantation alone=191'139€) compared to conservative treatment (51'506€). However the high effectiveness of LDLT and DD liver transplantation or DD liver transplantation alone in improving the survival of patients with endstage liver disease still lead to a marginal cost effectiveness of either 23'530€/QALY for the combination of DD liver

Table 3
Studies on cost effectiveness

Author	Country	Design	Number of transplantations	Time	Cost elements	DD or LDLT	Costs per DD (Euro)	Cost effectiveness of DD or LDLT (Euro/outcome)
Ouwens (15)	Netherlands	Retrospective	81	78–87	costs	DD	63'156 (1 year)	19'760 per year
Longworth (16)	UK	Retrospective	208	95–96	costs	DD		30'030–68'640 per QALY
Sagmeister (17)	Switzerland	Retrospective	51	95–00	costs	DD and LDLT	118'457	22'451–23'530 per QALY

DD liver transplantation.

transplantation and LDLT or 22'451€/Qaly for DD liver transplantation alone. Both procedures can therefore be considered as highly cost-effective compared to other widely accepted therapies in medicine. Although it is difficult to transfer national cost data to other countries with different health care systems, sensitivity analysis showed that our data are very robust and the marginal cost effectiveness remained below 38'000€ even if we significantly increased the costs for the transplantation procedure. Therefore we believe that our data are also valid for other European countries as well as the US.

The comparison of the published studies demonstrates similar cost effectiveness ratios for the Swiss and the Dutch study (19'760–23'451€). The study of England and Wales shows a poorer cost effectiveness ratio between 30'030 and 68'640€ but this study measured cost effectiveness of liver transplantation only up to 27 months, which is not ideal, and it is likely that the cost effectiveness ratio will improve if a longer time frame would be considered.

3. Cost effectiveness of LDLT for HCC

Liver transplantation is an excellent treatment option for small hepatocellular cancers (HCC), because it not only offers cure for the tumor but also the underlying cirrhosis. However, the results of cadaveric liver transplantation for HCC largely depend on the waiting time. Both in Europe and the United States waiting times are increasing and therefore patients might develop contraindication for transplantation while waiting and might become ineligible for transplantation. This was confirmed in a recent study analyzing the effects of an increasing waiting on patient survival [18]. In this study 2 years mortality increased from 16 to 46% while the waiting time increased from 62 days to 162 days. In this situation LDLT has the advantage to decrease waiting time, allowing patients to be transplanted before they show tumor progression and develop metastasis. It is therefore not surprising, that the cost effectiveness of LDLT for the treatment of HCC has received special attention. Sarasin et al used a decision analytic model to predict the average life expectancy and cost effectiveness of DD liver transplantation and LDLT for patients with cirrhosis and early HCC [19]. Although LDLT was more expensive than DD liver transplantation for all scenarios considered, the marginal cost effectiveness of LDLT per Qaly decreased from 128'212€ for a waiting time of 2 months to 27'664€ for a waiting of one year, reaching the cost effectiveness threshold of 38'000€ when the waiting time exceeded 7 months. LDLT was therefore estimated to gain up to 2,8 years at cost under 38'000€ when the waiting time for a cadaveric organ exceeded 7 months [19].

4. Conclusion

Liver transplantation is an expensive intervention in medicine with costs up to 154'620€ [6]. Based on the published studies LDLT is about 20% more expensive than DD liver transplantation with a similar survival benefit for the recipient. Nevertheless liver transplantation shows a remarkable survival gain compared with conservative treatment [15,17]. Therefore the marginal cost effectiveness ratio (incremental costs per incremental survival benefit) is still in a range that is considered as cost effective. LDLT is especially attractive for patients with HCC, allowing to perform the transplant procedure in a timely fashion before patients develop contraindications. Also from a cost perspective LDLT is more cost-effective in this situation compared to DD liver transplantation if waiting times exceeds certain limits. However, this might change if patients with HCC are prioritized such as in the new UNOS allocation system. There are still a number of unanswered questions remaining [20]: Who pays for the income loss of the donor during hepatectomy? What is the impact of living donation concerning future disability? Is there a donor risk concerning future health insurability? These are important questions that should be addressed in future studies and taken into account by health care providers and payers.

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Should living donor liver transplantation be part of every liver transplant program?

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The critical shortage in donor organs is generally proffered as the main impetus behind the development of living donor liver transplantation (LDLT), and although the procedure has significantly impacted since its initial development approximately 17 years ago on the pediatric waiting list mortality and morbidity, the same cannot be stated with reference to the adult population of potential liver transplant recipients [1,2]. The picture which emerges is complex and is affected by a variety of factors such as geographic variability in the availability of deceased donor (DD) organs, differences in institutional commitments, surgical expertise, the availability of ancillary support services, emerging data on donor and recipient outcomes and complications, anatomic as well as psychosocial limiting factors in both potential donors and recipients,

and ethical considerations as well as conflicting viewpoints within the transplant community. In addressing the question ‘Should LDLT be part of every liver transplant program?’ all of the issues listed need to be discussed. Although the transplant community has been developing a number of guidelines as to who should or should not perform LDLT, the question of level of need for LDLT and donor/recipient risk are constantly being weighed against the required threshold of surgical and institutional expertise. In addition, to further add complexity to this situation, we are concomitantly re-evaluating and extending our accepted indications for liver transplantation within the context of LDLT, with changes in our perceptions of minimal outcome limits in specific oncologic diseases. Ultimately, the question as to who should be performing LDLT should also enter into the realm of ‘Who oversees innovative practice?’ and ‘Do we have a structure to monitor the development and evolution of innovative techniques such as LDLT?’ The dichotomy which has developed with LDLT between our rule as physicians to ‘primum non nocere’: first do no harm, and our desire to help an ever-increasing population of patients with end stage liver disease places us in urgent need of structure and guidelines.

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Abbreviations: ACOT, US Department of Health and Human Services Advisory Committee on Organ Transplantation; DD, deceased donor; ELTR, European Liver Transplant Registry; ESLD, end stage liver disease; LDLT, living donor liver transplantation; MELD, Model for end stage liver disease.

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