prospectively measured. Medical costs were calculated in Japanese yen for the years 1999-2002 and converted to US dollars (US$) for the year 2009 using PPP and CPI.

The health utility scores of 19 participants were determined using a general instrument, the EQ-5D Japanese version [69,70]. EQ-5D was self-administered by participants before LDLT and at 3, 6, 12, and 24 months post-LDLT. Survival rates were determined in 79 patients with LDLT between September 1997 and April 2004 in the First Division of Surgery, Hokkaido University Hospital. Data yielded a 1-year survival rate of 79.5% and a 3-year survival rate of 76.2%. Interpolated values were substituted for missing health utility scores and survival rates.

Medical costs per QALY ratio (MCQR) was derived as a result of cost-utility analysis. An annual discount rate of 0% was adopted, as recommended by Drummond *et al.* [71], and a societal perspective was used for both analyses.

One-way sensitivity analysis was implemented to assess the robustness of MCQR at 24 months post-LDLT. The variables were total medical costs, the 3 most expensive categories of all 19 categories in cost analysis, health utility score, survival rate, and discounted rate. Totals medical costs, the 3 most expensive categories, and health utility score were calculated within the 25th to 75th percentiles. Survival rate was calculated as ±10% of baseline values, and discounted rates of cost and utility analyses were determined as 0-10%.

5.3. Results of Cost-Utility Analysis of LDLT

The median age of the 11 participants in the cost analysis was 42 yr (range, 27-58 yr). The median duration of hospitalization was 119 days (range, 73-306 days). The indications for LDLT were fulminant hepatic failure (n = 4), primary biliary cirrhosis (n = 3), liver cirrhosis type B (n = 1), liver cirrhosis type C (n = 1), alcoholic liver diseases (n = 1), and liver cirrhosis type B plus liver cancer (n = 1). The cumulative medical costs from pre-LDLT to 24 months post-LDLT are shown in Table 8. During follow-up, medical costs were highest (US$136,176) at 1-3 months post-LDLT, whereas the increment during the late follow-up period (13-24 months post-LDLT) was only US$16,189.

Table 8. Medical costs for patients with LDLT

	Mean	Percentiles		
		25th	50th	75th
Medical costs pre- and post-LDLT (number of cases)				
Pre-LDLT (n=7)	8,962	5,359	9,122	12,568
1-3 months post-LDLT (n=9)	139,695	112,017	136,176	154,965
1-3 months post-LDLT (n=10)	12,264	5,453	10,295	13,615
1-3 months post-LDLT (n=10)	15,963	7,843	12,615	22,528
1-3 months post-LDLT (n=11)	22,609	14,025	16,189	27,682
Cumulative medical cost				
Pre- to 12 months post-LDLT	176,885	130,673	168,207	203,675
Pre- to 24 months post-LDLT	199,494	144,697	184,397	231,358

LDLT; living donor liver transplantation
US$, 2009

The median age of the 19 participants in the utility analysis was 46 yr (range, 27-58 yr). The indications for LDLT were fulminant hepatic failure (n = 6), primary biliary cirrhosis (n = 5), liver cirrhosis type B (n = 1), liver cirrhosis type C (n = 1), liver cirrhosis type B plus liver cancer (n = 2), alcoholic liver disease (n = 1), epithelioid hemangioendothelioma (n = 1), acute exacerbation of chronic hepatitis B (n = 1), and primary sclerosing cholangitis (n = 1). The median health utility score [25th-75th percentiles] was 0.66 at pre-LDLT (range, 0.64-0.75; n = 13), compared with 1.00 at 3 months (range, 0.67-1.00; n = 9), 1.00 at 6 months (range, 0.86-1.00; n = 11), 1.00 at 12 months (range, 0.92-1.00; n = 8), and 1.00 at 24 months post-LDLT (range, 1.00-1.00; n = 2). The median health utility scores were improved at post-LDLT compared with pre-LDLT values. However, after adjusting for survival, no significant difference was observed in health utility score between pre- and post-LDLT.

Cumulative QALYs were 0.85 at 12 months post-LDLT and 1.60 at 24 months post-LDLT (Table 9). MCQR thus decreased from US$721,640/QALY at 3 months post-LDLT to US$112,300/QALY at 24 months post-LDLT (Table 9)

Table 9. QALYs for patients with LDLT, and medical costs per QALY

Months post-LDLT	QALY	Cumulative QALY	Medical cost per QALY
3	0.20	0.20	721,640
6	0.23	0.43	360,063
12	0.42	0.85	196,676
24	0.75	1.60	112,300

US$, 2009

MCQR was relatively stable for health utility scores and survival rate. However, considerable variation in MCQR was observed with changes in medical cost (Table 10).

Table 10. One-way sensitivity analysis of MCQR at 24 months post-LDLT

Variables	Low value (US$)	High value (US$)	Range of analysis
Total medical cost	79,581	124,042	25th to 75th percentile
Administration	110,610	118,973	25th to 75th percentile
Operation	103,818	117,200	25th to 75th percentile
Injection	103,815	129,605	25th to 75th percentile
Health utility scores	111,258	125,995	25th to 75th percentile
Survival rates	92,200	142,291	+10% to -10%
Discount rates	107,013	112,300	10% to 0%

US$, 2009

5.4. Interpretation, Limitation and Conclusion

Ishida *et al.*[8] showed that cost-effectiveness for LDLT increased progressively for patients with ESLD. The medical costs were highest at 1-3 months post-LDLT, and the costs after 1-3 months post-LDLT came to less than 10% of the costs during those 1-3 months. Health utility score as measured in terms of QALY was not markedly different between pre- and post-LDLT.

To the best of our knowledge, cost-utility analysis of LDLT has rarely been performed to measure both medical costs and health utility. In this study, MCQR for LDLT (US$112,300/QALY) was comparable to published MCQRs for organ transplantations such as DDLT versus the absence of DDLT in patients with alcoholic liver disease in England and Wales (US$89,348/QALY: 95% bootstrap confidence intervals, US$22325-US$154,499) [17]. Results were also consistent with MCQR for heart transplantation versus optional conventional treatment in patients needing heart transplants (US$91,314/QALY) [72], and for lung transplantation versus standard care in patients with end-stage pulmonary disease in the Netherlands (US$210,860/QALY) [73]. Furthermore, the present results are within the standard range suggested by Laupacis *et al.* [60] (US$20,000 – US$100,000/QALY), although the panel on cost-effectiveness in health technologies notes that no absolute standards exist for deciding whether an intervention is cost-effective [74].

Several limitations need to be considered when interpreting the present findings. First, cost analysis did not include donor-related medical costs. The national fee schedule did not list the donor-related fee at the beginning of this survey, although the schedule did list the fees for some ESLDs in 2000. The addition of these costs (e.g., national fee for surgery of US$3,536 since 2000) should increase MCQR. Furthermore, cost analysis did not include indirect costs. For example, costs involving factors such as travel and suspended economic activity were not taken into account, thus underestimating the results. Conversely, the resumption of economic activities may exert a different impact. The influence of relevant indirect costs on MCQR must therefore be considered. Second, the subjects were derived from patients in a single center. Nevertheless, Ishida *et al.* [8] believe that the subjects were an approximately representative LDLT population in Japan, as medical costs of hospitalization ranged widely for subjects (US$83,120-US$259,973) and resembled those in the populations of other Japanese representative centers (US$38,996-US$310,059) [75-77], whereas survival rates (79.5% at 1 year and 76.2% at 3 years) mirrored those in 49 centers in Japan (80.8% at 1 year and 78.5% at 3 years). Finally, they were unable to set alternative treatments, owing to the relatively small number of DDLTs performed in Japan and the difficulty in measuring health utility for patients with ESLD not receiving LDLT, owing to ethical consideration.

In conclusion, this study indicates that LDLT becomes progressively more cost-effective over time. The procedure also improves HRQOL of post-LDLT survivors. LDLT appears to represent a cost-effective medical technology.

6. DISCUSSION

Advances in medical technologies have made the treatment of previously untreatable conditions possible. However, these same advances in technologies have also resulted in escalating medical expenditures, resulting in a dilemma in which it is economically unfeasible to have limitless utilization of these technologies. HEA represents a tool to support the scientific decision-making process involved in maximizing the healthcare outcomes of the public with limited resources. The use of QALY as an outcome measure that can be potentially applied to all types of medical technologies allows evaluations for selecting the most cost-effective technology available. However, these evaluations require the following

two factors: the costs are appropriately estimated using standardized estimation methods, and the cost effectiveness and specific thresholds for evaluations have been determined.

6.1. Subjects of Cost Estimation in HEA in Liver Transplantations

The liver transplantation process can be divided into 3 different stages: pretransplantation, transplantation admission, and post-transplantation. It is consequently necessary to conduct cost estimations for each of these 3 stages in HEA of liver transplantation. The various costing items for the cost estimations in each stage are discussed below.

The notable costing items that contribute to the costs incurred in the pretransplantation period include the evaluation of recipient, maintenance of the recipient while on the waiting list, and pretransplantation admission. A specific consideration for evaluations of the pre-transplant period is that costs incurred during this period are not limited to patients who have successfully undergone the transplantation procedure, but must also include the costs of candidate patients who were unable to have the procedure. This is due to the fact that the majority of hospitals that conduct transplantations admit and treat both transplantation patients as well as patients who ultimately do not undergo the transplantations owing to insufficient donor organs, organ rejection, or death. In addition to conducting transplantation therapy, such aforementioned patients are consistently increasing in number. Additionally, it is essential to obtain information on the patients' whereabouts during the waiting period, because whether these patients are in their own homes, hospitals, or ICUs has been shown to have a heavy influence on the costs incurred during the pretransplant period [39]. Furthermore, in the case of LDLT, costing items associated with testing to ensure donor safety, donor evaluation costs, and costs of failed donor evaluation should also be taken into consideration.

In the transplant admission period, costing items that should be included in cost evaluations should include organ acquisition costs, management of complications, hospital stay, and professional fees. However, many liver transplantation cost estimation studies have included general estimates of these costing items. Additionally, the costs of donor hepatectomies should be included for studies involving LDLT.

As there may be abrupt changes in recipient patient conditions approximately two years after the transplantation, post-transplantation follow-up care and patient visits should be conducted for as long as possible. The cost of immunosuppressive drugs administered during this period may be considered to be a costing item that has a major influence on overall costs. Although the dosage of immunosuppressive drugs may be reduced in liver transplant recipients after stabilization, the fact that these drugs are in principle administered for life results in heavy accumulated drug expenditures. Additionally, a portion of patients have to be administered with costly pharmaceuticals such as preventive drugs against the recurrence of hepatitis B or interferons against hepatitis C for lengthy durations.

Next, liver transplantation costs can be categorized on the basis of perspectives, namely, "costing items that directly involve the patient" and "costing items related to departments that have no specific or direct involvement with the patient". The costing items as presented above belong in the former category, but in reality there are also numerous costs that belong in the latter. As the costing items in the latter category involve activities that are essential for the liver transplantation process, they should be included in cost estimates.

As the indirect costs associated with loss in labor productivity for liver transplant recipients are not an essential costing item for estimating the costs of the transplantation process, these costs have essentially not been included in the cost estimation studies reviewed in this chapter.

In addition to utilizing the aforementioned costing items in cost estimation studies of liver transplantation, it is strongly desired for researchers to report the detailed breakdown of costs by each costing item. This would improve the transferability of cost estimates, and increase the value of the estimate as information to support the decision-making process in third parties.

6.2. What is the Value of One QALY?

Although it is extremely difficult to clearly establish the value of a single QALY, the evaluation of insurance listings for new health technologies utilizes a value of £20,000-£30,000 per QALY in the UK [78]. Published studies from the US frequently appear to use a standard value of US$50,000 per QALY. However, these thresholds have not been supported by any scientific basis.

The first study that proposed specific thresholds for evaluating whether a medical technology is cost-effective or not was conducted by Kaplan and Bush in 1982 [79]. The guidelines for the adoption of medical technologies as recommended by Kaplan and Bush are presented in Table 11, with "cost effective", "controversial", and "questionable" evaluated at ICER < US$20,000, ICER = US$20,000 – US$100,000, and ICER > US$100,000, respectively. However, the bases for these calculations are not transparent. Furthermore, a Canadian research team led by Laupacis *et al.* [60] produced the following grades of recommendation for the evaluation to support the adoption of new technologies in 1992: "strong evidence", "moderate evidence", and "weak evidence" were evaluated at ICER < CA$ 20,000/QALY, ICER = CA$20,000 – CA$100,000/QALY, and ICER > CA$100,000/QALY (Table 12). As the 1982 value of the US dollar was more than twice that of the 1992 value of the Canadian dollar, it is important to note the large differences in thresholds between both sets of guidelines.

Table 11. Guidelines for adoption of medical technologies

Cost per well-year	Policy implication
Less than $20,000 per well-year	Cost-effective by current standards
$20,000 to $100,000 per well-year	Possibly controversial, but justifiable by many current examples
Greater than $100,000 per well-year	Questionable in comparison with other health care expenditure

Source: Kaplan and Bush 1982 [79]

Table 12. Grades of recommendation for adoption of appropriate utilization of new technologies

Grade	Recommendation
A.	Compelling evidence for the adoption and appropriate utilization. The new technology is as effective as or more effective than the existing one and is less costly.
B.	Strong evidence for adoption and appropriate utilization The new technology is more effective than the existing one and costs less than $20,000 per quality adjusted life year (QALY) gained. The new technology is less effective than the existing one, but its introduction would save more than $100,000/QALY gained.
C.	Moderate evidence for adoption and appropriate utilization. The new technology is more effective than the existing one and cost $20,000 to $100,000/QALY gained. The new technology is less effective than the existing one, but its introduction would save $20,000 to $100,000/QALY gained.
D.	Weak evidence for adoption and appropriate utilization The new technology is more effective than the existing one and costs more that $100,000/QALY gained. The new technology is less effective than the existing one, but its introduction would save less than $20,000/QALY gained.
E.	Compelling evidence for rejection The new technology is less effective than or as effective as the existing one and is more costly.

Source: Laupacis *et al.* [60]

In a study using samples from Japan, South Korea, Taiwan, Australia, the UK and the US, Shiroiwa *et al.* [80] have utilized a standardized method (double-bound dichotomous choice and analysis by nonparametric Turnbull method) to contemporaneously estimate the WTP value of one QALY. The WTP estimates for a single QALY by country were as follows: Japan, JPY 5 million; South Korea, KWN 68 million; Taiwan, NT$ 2.1 million; Australia, AU$ 64,000; UK, £23,000, and the US, US$62,000.

Although the differences in estimation methodologies and intrinsic differences among countries do not allow for precise comparisons, the fact that the estimates for the value of life as produced by Kaplan and Bush in 1982 [79], Laupacis *et al.* in 1992 [60], and Shiroiwa *et al.* in 2010 [80] are very similar is of great interest. However, owing to the large differences in monetary value, the more recently reported estimates show a lower value of life. The reasons for this remain unclear.

6.3. Ethical Issues Associated with Fairness of Resource Allocation in Liver Transplantation

Although liver transplantation is an effective treatment for ESLD, the short supply of organ donors and the protraction of the waiting period for ESLD patients are becoming a social problem. The issue of selecting liver transplantation recipients from a large body of ESLD patients, all of whom require the procedure for survival, is an extremely important issue from the ethical perspective of fairness in resource allocation.

The US and the UK implemented an organ allocation system based on the model for end-stage liver disease (MELD) score, which places an emphasis on the disease severity of each

patient, in February, 2002 and December, 2006, respectively. MELD score is calculated from the following three parameters to objectively evaluate the disease severity of each patient: serum bilirubin level, serum creatinine level, and the international normalized ratio for prothrombin time (INR). However, does this use of MELD score to prioritize patients for receipt of a donor liver actually ensure fairness in resource allocation in liver transplantation?

In the evaluation of the actual operational situation in the US, there are problems that still prevent the actualization of safe and fair resource allocation. There are two aspects wherein factors of inequities remain. The first of these, as shown in the review conducted in this chapter, is that liver transplantation requires immense healthcare costs. In the US, where there is no national public insurance system, it is possible that doctors and hospitals may not place a patient in need of a liver transplant on the waiting list if they do not appear to have the means to pay for the procedure. This possibility arises owing to the fact that these actions are deemed legal under the current laws, and these issues were even highlighted in the 2002 motion picture "John Q", in which Denzel Washington played a father whose son needed a heart transplant but was not placed on a recipient list as it was not covered by HMO insurance. As such, there exists an inequity in which patients with poor economical strength are unable to receive the benefits of new medical technologies. (However, this problem is not limited to organ transplants, but is a widespread problem in all aspects of healthcare.)

The second inequity is that in the US, it is not illegal for a single patient to be simultaneously placed on waiting lists in numerous different regions. In general, the specifics of when and where an organ donor may emerge are unknown, and it may be impossible for patients in normal circumstances to reach the appropriate hospital within the short timeframe where the donor organ is still viable for transplantation. However, patients with a sufficient economical clout may possess private jets or other various modes of transportation that allows them fast access to hospitals located in distant locales for medical procedures. A notable example of someone who could actualize this situation is Steve Jobs, the CEO of Apple Inc. Only four months after he took a leave of absence from his work, he was the recipient of a new liver. However, this transplantation was not conducted in the state of California, where he resides, but in Methodist University Hospital, Tennessee. This inequity, in which wealthy patients have a higher chance of benefiting from new medical technologies, is therefore shown to exist.

7. CONCLUSIONS

In this chapter, using the theme of Cost-Effectiveness Analysis of Liver Transplantation, we have highlighted the issues presented in the existing literature as well as elucidated the problems that need to be addressed in the future in the aspects of cost, effectiveness and cost-effectiveness.

Presently, there are approximately 40 studies of cost estimates of liver transplantations in the scientific literature, and comparative analyses have progressed. However, we have shown that due to differences in research subjects, scope of costing items, and cost estimation methodologies, it is extremely dangerous to directly use the published cost estimates in the decision-making process. It is therefore required for researchers who conduct cost estimation research to ensure the transparency of the estimation results. Readers should also conduct

detailed examinations of the possible applications and suitability of these published cost estimates before applying them to settings in their own institutions and countries.

Despite the first cost-effectiveness analysis of liver transplantation being conducted 20 years ago, it has become clear that there is a scarcity of such studies up to the present. Liver transplantations are an established treatment for ESLD patients. However, although the procedure can help achieve desirable health outcomes, the extremely high costs involved highlight the need for more cost-effectiveness analyses of liver transplantation. The scope of costing for cost-effectiveness analyses generally includes costing items from the pretransplantation period until the post-transplantation period. If there are insufficient costing items included in the cost estimation, the costs of liver transplantations may be severely underestimated, which may in turn distort decision-making concerning medical resource allocation. Therefore, efforts must be made to improve the quality of cost estimation studies. In the case of studies that have not reported the detailed breakdown of costing items, it becomes impossible to determine if similar results would be obtained when applied to other jurisdictions even if these costs have been utilized in cost-effectiveness analyses. Therefore, details in the scope of costing and costing methodologies should be reported in studies that estimate the costs of liver transplantations, as this would enhance the transferability of resulting estimates. In this way, the value of the determined cost-effectiveness can be expected to increase.

Although there are no standardized and absolute criteria with which the cost-effectiveness of a technology can be determined, the scientific literature up to the present has largely determined that liver transplantation is in fact a cost-effective treatment.

REFERENCES

[1] United Network for Organ Sharing. http://www.unos.org/ Access: August 31, 2010.

[2] European Liver Transplant Registry. http://www.eltr.org/ Access: August 31, 2010.

[3] Japanese Liver Transplantation Society. Liver transplantation in Japan: registry by the Japanese Liver Transplantation Society. *Japanese Journal of Transplantation* 2009;44(6):559-571.

[4] Buchanan P, Dzebisashvili N, Lentine KL, Axelrod DA, Schnitzler MA, Salvalaggio PR. Liver transplantation cost in the model for end-stage liver disease era: looking beyond the transplant admission. *Liver Transpl* 2009;15(10):1270-1277.

[5] Markley ET, Cooil B, Rubin JE, Chari RS. Cost prediction in liver transplantation using pretransplant donor and recipient characteristics. *Transplantation* 2008;86(2):238-244.

[6] Passarani S, De Carlis L, Maione G, Alberti AB, Bevilacqua L, Baraldi S. Cost analysis of living donor liver transplantation: the first Italian economical data. *Minerva Anestesiol* 2007;73(10):491-499.

[7] Englesbe MJ, Dimick J, Mathur A, *et al.* Who pays for biliary complications following liver transplant? A business case for quality improvement. *Am J Transplant* 2006;6(12):2978-2982.

[8] Ishida K, Imai H, Ogasawara K, *et al.* Cost-utility of living donor liver transplantation in a single Japanese center. *Hepatogastroenterology* 2006;53(70):588-591.

[9] Kogure T, Ueno Y, Kawagishi N, *et al.* The model for end-stage liver disease score is useful for predicting economic outcomes in adult cases of living donor liver transplantation. *J Gastroenterol* 2006;41(10):1005-1010.

[10] Washburn WK, Pollock BH, Nichols L, Speeg KV, Halff G. Impact of recipient MELD score on resource utilization. *Am J Transplant* 2006;6(10):2449-2454.

[11] Kraus TW, Mieth M, Schneider T, *et al.* Cost distribution of orthotopic liver transplantation: single-center analysis under DRG-based reimbursement. *Transplantation* 2005;80(1 Suppl):S97-S100.

[12] Oostenbrink JB, Kok ET, Verheul RM. A comparative study of resource use and costs of renal, liver and heart transplantation. *Transpl Int* 2005;18(4):437-443.

[13] Reed A, Howard RJ, Fujita S, *et al.* Liver retransplantation: a single-center outcome and financial analysis. *Transplant Proc* 2005;37(2):1161-1163.

[14] Brand DA, Viola D, Rampersaud P, Patrick PA, Rosenthal WS, Wolf DC. Waiting for a liver: hidden costs of the organ shortage. *Liver Transpl* 2004;10(8):1001-1010.

[15] Cole CR, Bucuvalas JC, Hornung R, *et al.* Outcome after pediatric liver transplantation impact of living donor transplantation on cost. *J Pediatr* 2004;144(6):729-735.

[16] Filipponi F, Pisati R, Cavicchini G, Ulivieri MI, Ferrara R, Mosca F. Cost and outcome analysis and cost determinants of liver transplantation in a European National Health Service hospital. *Transplantation* 2003;75(10):1731-1736.

[17] Longworth L, Young T, Buxton MJ, *et al.* Midterm cost-effectiveness of the liver transplantation program of England and Wales for three disease groups. *Liver Transpl* 2003;9(12):1295-1307.

[18] Trotter JF, Mackenzie S, Wachs M, *et al.* Comprehensive cost comparison of adult-adult right hepatic lobe living-donor liver transplantation with cadaveric transplantation. *Transplantation* 2003;75(4):473-476.

[19] Azoulay D, Linhares MM, Huguet E, *et al.* Decision for retransplantation of the liver: an experience- and cost-based analysis. *Ann Surg* 2002;236(6):713-721.

[20] Sagmeister M, Mullhaupt B, Kadry Z, Kullak-Ublick GA, Clavien PA, Renner EL. Cost-effectiveness of cadaveric and living-donor liver transplantation. *Transplantation* 2002;73(4):616-622.

[21] Taylor MC, Greig PD, Detsky AS, McLeod RS, Abdoh A, Krahn MD. Factors associated with the high cost of liver transplantation in adults. *Can J Surg* 2002;45(6):425-434.

[22] Skeie B, Mishra V, Vaaler S, Amlie E. A comparison of actual cost, DRG-based cost, and hospital reimbursement for liver transplant patients. *Transpl Int* 2002;15(9-10):439-445.

[23] Best JH, Veenstra DL, Geppert J. Trends in expenditures for Medicare liver transplant recipients. *Liver Transpl* 2001;7(10):858-862.

[24] Bucuvalas JC, Ryckman FC, Atherton H, Alonso MP, Balistreri WF, Kotagal U. Predictors of cost of liver transplantation in children: a single center study. *J Pediatr* 2001;139(1):66-74.

[25] Nair S, Cohen DB, Cohen MP, Tan H, Maley W, Thuluvath PJ. Postoperative morbidity, mortality, costs, and long-term survival in severely obese patients undergoing orthotopic liver transplantation. *Am J Gastroenterol* 2001;96(3):842-845.

[26] Schnitzler MA, Woodward RS, Brennan DC, Whiting JF, Tesi RJ, Lowell JA. The economic impact of preservation time in cadaveric liver transplantation. *Am J Transplant* 2001;1(4):360-365.

[27] van Agthoven M, Metselaar HJ, Tilanus HW, *et al.* A comparison of the costs and effects of liver transplantation for acute and for chronic liver failure. *Transpl Int* 2001;14(2):87-94.

[28] Freeman R, Tsunoda S, Supran S, *et al.* Direct costs for one year of liver transplant care are directly associated with disease severity at transplant. *Transplant Proc* 2001;33(1-2):1436-1437.

[29] Gilbert JR, Pascual M, Schoenfeld DA, Rubin RH, Delmonico FL, Cosimi AB. Evolving trends in liver transplantation: an outcome and charge analysis. *Transplantation* 1999;67(2):246-253.

[30] Rufat P, Fourquet F, Conti F, Le Gales C, Houssin D, Coste J. Costs and outcomes of liver transplantation in adults: a prospective, 1-year, follow-up study. GRETHECO study group. *Transplantation* 1999;68(1):76-83.

[31] Showstack J, Katz PP, Lake JR, *et al.* Resource utilization in liver transplantation: effects of patient characteristics and clinical practice. *JAMA* 1999;281(15):1381-1386.

[32] Brown RS Jr, Lake JR, Ascher NL, Emond JC, Roberts JP. Predictors of the cost of liver transplantation. *Liver Transpl Surg* 1998;4(2):170-176.

[33] Geevarghese SK, Bradley AE, Wright JK, *et al.* Outcomes analysis in 100 liver transplantation patients. *Am J Surg* 1998;175(5):348-353.

[34] Russo MW, Sandler RS, Mandelkehr L, Fair JH, Johnson MW, Brown RS Jr. Payer status, but not race, affects the cost of liver transplantation. *Liver Transpl Surg* 1998;4(5):370-377.

[35] Schulak JA, Ferguson RM, Hanto DW, Ryckman FC, Vogt DP, Bohnengel A. Liver transplantation in Ohio. *Surgery* 1997;122(4):842-848

[36] Brown RS Jr, Ascher NL, Lake JR, *et al.* The impact of surgical complications after liver transplantation on resource utilization. *Arch Surg* 1997;132(10):1098-1103.

[37] Smith DG, Henley KS, Remmert CS, Hass SL, Campbell DAJr, McLaren ID. A cost analysis of alprostadil in liver transplantation. *Pharmacoeconomics* 1996;9(6):517-524.

[38] Pageaux GP, Souche B, Perney P, *et al.* Results and cost of orthotopic liver transplantation for alcoholic cirrhosis. *Transplant Proc* 1993;25(1 Pt 2):1135-1136.

[39] Evans RW, Manninen DL, Dong FB. An economic analysis of liver transplantation: costs, insurance coverage, and reimbursement. *Gastroenterol Clin North Am* 1993;22(2):451-473.

[40] Burroughs AK, Blake J, Thorne S, Else M, Rolles K. Comparative hospital costs of liver transplantation and the treatment of complications of cirrhosis. A prospective study. *Eur J Gastroenterol Hepatol* 1992;4:123-128.

[41] Bonsel GJ, Essink-Bot ML, de Charro FT, van der Maas PJ, Habbema JD. Orthotopic liver transplantation in The Netherlands. The results and impact of a medical technology assessment. *Health Policy* 1990;16(2):147-161.

[42] Sculpher MJ, Pang FS, Manca A, *et al.* Generalisability in economic evaluation studies in healthcare: a review and case studies. *Health Technol Assess* 2004;8:1-192.

[43] O'Brien BJ. A tale of two (or more) cities: geographic transferability of pharmacoeconomic data. *Am J Manag Care* 1997;3:S33-S39.

[44] Goeree R, Burke N, O'Reilly D, Manca A, Blackhouse G, Tarride JE. Transferability of economic evaluations: approaches and factors to consider when using results from one geographic area for another. *Curr Med Res Opin* 2007;23(4):671-682.
[45] Cronbach LJ. Beyond the two disciplines of scientific psychology. *Am Psychol* 1975;30(2):116-127.
[46] Sherman KE, Sherman SN; Chenier T, Tsevat J. Health values of patients with chronic hepatitis C infection. *Arch Intern Med* 2004;164(21):2377-2382.
[47] Longworth L, Bryan S. An empirical comparison of EQ-5D and SF-6D in liver transplant patients. *Health Econ* 2003;12(12):1061-1067.
[48] Ratcliffe J, Longworth L, Young T, *et al.* Assessing health-related quality of life pre- and post-liver transplantation: a prospective multicenter study. *Liver Transpl* 2002;8(3):263-270.
[49] Ratcliffe J, Young T, Longworth L, Buxton M. An assessment of the impact of informative dropout and nonresponse in measuring health-related quality of life using the EuroQol (EQ-5D) descriptive system. *Value Health* 2005;8(1):53-58.
[50] Chong CA, Gulamhussein A, Heathcote EJ, *et al.* Health-state utilities and quality of life in hepatitis C patients. *Am J Gastroenterol* 2003;98(3):630-638.
[51] Siebert U, Sroczynski G, Rossol S, *et al.* Cost effectiveness of peginterferon alpha-2b plus ribavirin versus interferon alpha-2b plus ribavirin for initial treatment of chronic hepatitis C. *Gut* 2003;52(3):425-432.
[52] Bryan S, Ratcliffe J, Neuberger JM, Burroughs AK, Gunson BK, Buxton MJ. Health-related quality of life following liver transplantation. *Qual Life Res* 1998;7(2):115-120.
[53] Lewis MB, Howdle PD. Cognitive dysfunction and health-related quality of life in long-term liver transplant survivors. *Liver Transpl* 2003;9(11):1145-1148.
[54] Ishida K, Imai H, Ogasawara K, Tamashiro H. A review of health economic assessment for liver transplantation: toward social acceptance of liver transplantation in Japan. *Nippon Koshu Eisei Zasshi* 2004;51(4):233-239. (in Japanese)
[55] Kankaanpaa J. Cost-effectiveness of liver transplantations: how to apply the results in resource allocation. *Prev Med* 1990;19(6):700-704.
[56] Bonsel GJ, Klompmaker IJ, Essink-Bot ML, Habbema JD, Slooff MJ. Cost-effectiveness analysis of the Dutch liver transplantation programme. *Transplant Proc* 1990;22(4):1481-1484.
[57] Hisashige A, Katayama T, Mikasa H. Technology assessment of organ transplantation in Japan: economic evaluation of liver transplantation from a living donor. *Joint Conference on Medical Informatics* 1997; 400-401. (in Japanese)
[58] Northup PG, Abecassis MM, Englesbe MJ, *et al.* Addition of adult-to-adult living donation to liver transplant programs improves survival but at an increased cost. *Liver Transpl* 2009;15(2):148-162.
[59] Ouwens JP, van Enckevort PJ, TenVergert EM, *et al.* The cost effectiveness of lung transplantation compared with that of heart and liver transplantation in the Netherlands. *Transpl Int* 2003;16(2):123-127.
[60] Laupacis A, Feeny D, Detsky AS, Tugwell PX. How attractive does a new technology have to be to warrant adoption and utilization? Tentative guidelines for using clinical and economic evaluations. *CMAJ* 1992;146(4):473-481.
[61] Seek AL, Sullivan MA, Pomfret EA. Transplantation of the right hepatic lobe. *N Engl J Med* 2002;347(8):615-618.

[62] Fan ST, Lo CM, Liu CL, Yong BH, Chan JK, Ng IO. Safety of donors in live donor liver transplantation using right lobe grafts. *Arch Surg* 2000;135(3):336-340.

[63] Chisuwa H, Hashikura Y, Mita A, *et al.* Living liver donation: preoperative assessment, anatomic considerations, and long-term outcome. *Transplantation* 2003;75(10):1670-1676.

[64] Singer PA, Siegler M, Whitington PF, *et al.* Ethics of liver transplantation with living donors. *N Engl J Med* 1989;321(9):620-622.

[65] Malago M, Testa G, Marcos A, *et al.* Ethical considerations and rationale of adult-to-adult living donor liver transplantation. *Liver Transpl* 2001;7(10):921-927.

[66] Colardyn F. Organizational and ethical aspects of living donor liver transplantation. *Liver Transpl* 2003;9(9):S2-S5.

[67] de Villa VH, Lo CM, Chen CL. Ethics and rationale of living-donor liver transplantation in Asia. *Transplantation* 2003;75(3 Suppl): S2-S5.

[68] Finkler SA. The distinction between cost and charges. *Ann Intern Med* 1982;96(1):102-109.

[69] The Japanese EuroQol Translation Team. The development of the Japanese EuroQol instrument. *J Health Care Soc* 1998;8:109-117. (in Japanese)

[70] Ikeda S, Ikegami N. Health status in Japanese population. Results from Japanese EuroQol study. *J Health Care Soc* 1999;9:83-91. (in Japanese)

[71] Drummond MF, O'Brien B, Stoddart GL, Torrance GW. *Methods for the Economic Evaluation of Health Care Programmes*. 2nd Edition. Oxford: Oxford University Press, 1997.

[72] van Hout B, Bonsel G, Habbema D, van der Maas P, de Charro F. Heart transplantation in the Netherlands; costs, effects and scenarios. *J Health Econ* 1993;12(1):73-93.

[73] Ramsey SD, Patrick DL, Albert RK, Larson EB, Wood DE, Raghu G. The cost-effectiveness of lung transplantation. A pilot study. *Chest* 1995;108(6):1594-1601.

[74] Evans C, Tavakoli M, Crawford B. Use of quality adjusted life years and life years gained as benchmarks in economic evaluations: a critical appraisal. *Health Care Manag Sci* 2004;7(1):43-49.

[75] Matunami H, Kawasaki S, Hashikura Y, *et al.* Cost of living-related liver transplantation. *Kan Tan Sui* 1996;33:95-98. (in Japanese)

[76] Yagi T, Urushihara N, Oishi M, *et al.* Problems in living donor liver transplantation in adults: postoperative management, complications, and costs. *Transplant Proc* 2000;32(7):2156-2157.

[77] Nakata S, Umeshita K, Ueyama H, *et al.* Cost analysis of operative procedure for transplant patients. *Transplant Proc* 2001;33(1-2):1904-1906.

[78] NICE. *Guide to the Methods of Technology Appraisal.* 2008. (Available from: http://www.nice.org.uk/ [31 August 2010].)

[79] Kaplan RM, Bush JW. Health-related quality of life measurement for evaluation research and policy analysis. *Health Psychology* 1982;1:61–80.

[80] Shiroiwa T, Sung YK, Fukuda T, Lang HC, Bae SC, Tsutani K. International survey on willingness-to-pay (WTP) for one additional QALY gained: what is the threshold of cost effectiveness? *Health Econ* 2010;19(4):422-437.