Cost and outcome of liver transplantation

van der Hilst, Christian

Chapter 9

Summary, Discussion, and Future Perspectives

SUMMARY

In this chapter the thesis is summarized.

Chapter 1 provided a general introduction to this thesis. An outline was presented of the complexity of the liver transplantation procedure and the large amount of medical professionals involved. A brief history was given of the 50 years in which liver transplantation has become a standard, albeit complex, procedure for end-stage liver disease in most developed countries including the Netherlands[1,2,3]. An overview was given on the most important developments in liver transplantation; the introduction of the immunosuppressants cyclosporin A[4] and tacrolimus[5] and developments in preservation fluids, such as the University of Wisconsin solution[6]. Several technical innovations, such as the veno-venous bypass[7,8], piggyback technique[9,10], reduced-size liver transplantation[11,12], split liver transplantation[13], domino liver transplantation[14,15], and living related liver transplantation[16] were highlighted as well. The improvement in outcome of this complex procedure in terms of patient and graft survival has increased dramatically. One-year and five-year patient survival of 86% and 72% and one-year and five-year graft survival of 82% and 65% were presented. The different indications for liver transplantation were stated with non-cholestatic cirrhosis and cholestatic diseases as the most common diagnosis for liver transplantation in adults and children, respectively. The selection of suitable recipients for the scarce donor organs was discussed in combination with the timing of liver transplantation. Because the demand for organs is greater than the supply, waiting lists exist. The Eurotransplant system, in which the three Dutch liver transplant centers participate, utilize the Model for End-Stage Liver Disease (MELD) and Pediatric End-Stage Liver Disease (PELD) score for organ allocation by means of a national waiting list[17,18]. For high urgency patients a supra-national waiting list exists. The availability of liver transplantation as a treatment modality in developed countries was highlighted. A short description of a liver transplant operation including post-transplant treatment and follow-up was given and the importance of immunosuppression in liver transplantation was addressed.

The Dutch health care environment in which this study has taken place was described and the Dutch health system, which performs very well on international benchmarks, was discussed. The Netherlands were compared on health spending vs GDP per capita with other countries. The Netherlands has one of the highest GDP per capita in the world and total health spending per capita is also very high[19]. The Dutch insurance system, where everyone has health insurance for a wide range of healthcare interventions, including liver transplantation and all follow-up, was explained.

The last part of the introduction elaborated on the costs associated with liver transplantation and the minor national budget impact due to the small amount of liver transplantations annually.

In **chapter 2** the aim and outline of the thesis was explained.
At the introduction of living donor liver transplantation in the Netherlands, a nation-wide study, named the CVZ study was initiated. Part of this study was the *Cost and Outcome of Liver Transplantation (COLT)* study to get insight into cost variation in different types of liver transplantation. The twofold aim of the thesis was explained. The first aim of the thesis was to analyze cost-effectiveness of the use of donor livers from the expanded donor pool for liver transplantation. Second aim of the thesis was to analyze the economic consequences of initiatives to improve the outcome of liver transplantation.

Summary Part A: Cost-Effectiveness of Extended Criteria Donors in Liver Transplantation

In **chapter 3** of this thesis the cost differences of liver transplantation and clinical follow-up between the United States and other Organization for Economic Cooperation and Development (OECD) countries were described[20]. 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 almost 6000 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 PPP) compared to US$ 103 548 (US$ 85 514 - 121 582 PPP) for other OECD countries. Patient characteristics, disease characteristics, quality of the health care provider, and methodology could not explain this cost difference. However, health system characteristics differed between the United States and other OECD countries. Cost differences in liver transplantation between these two groups were largely explained by health system characteristics.

Chapter 4 contained a detailed prospective observational multicenter cost-effectiveness study that compared liver transplantations with donation after brain death (DBD) and donation after cardiac death (DCD) grafts[22]. DCD is one of the major extended criteria groups and an important part in the calculation of the donor risk index. All liver transplantations in adults in the Dutch liver transplant centers between 2004 and 2009 were included with one-year follow-up. Primary outcome parameter was cost per life year after transplantation. Secondary outcome parameters were one-year patient and graft survival, complications, and patient-level costs. From 382 recipients that underwent 423 liver transplantations, 293 were primarily transplanted with DBD and 89 with DCD organs. Baseline characteristics were not different between both groups. The donor risk index was significantly different as were cold and warm ischemic time. Ward stay was significantly longer in DCD transplantations. Patient and graft survival were not significantly different. DCD livers had more and more severe complications, more reinterventions and consequently higher costs than DBD livers. The cost per life year for DBD was € 88 913 compared to € 112 376 for DCD. This difference was statistically significant. However, patient and graft survival was not different in this study. The advice was given that reimbursement should be differentiated to better accommodate DCD transplantations.

Chapter 5 described an analysis of the Eurotransplant donor risk index (ET-DRI) score on costs and outcome of DBD liver transplantation[21]. An observational, national, multicenter study including all primary DBD liver transplantations from 2004 to 2009 was conducted. The risk of the DBD graft was defined by using the ET-DRI. Patients were divided into quartiles based on the ET-DRI. Primary outcome was total hospital costs in the first year after transplantation. Secondary outcome included five-year patient and graft survival, cost per life year saved and cost-effectiveness. A total of 277 adult patients with DBD liver transplantation were divided into four groups. This resulted in a median ET-DRI of 1.26 (range 1.00 – 1.43) in the first quartile, 1.49 (range 1.43 - 1.63) in the second quartile, 1.70 (range 1.63 - 1.87) in the third quartile, and 2.03 (range 1.88 - 3.63) in the fourth quartile. Total mean (standard deviation) one-year costs were € 92 900 (€ 55 100), € 89 800 (€ 52 900), € 89 800 (€ 60 500), and € 101 700 (€ 64 300) in the four groups with increasing ET-DRI (p = 0.579). The incidence and costs for biliary complications were significantly higher in the fourth quartile. Five-year patient and graft survival and cost-effectiveness were not different between the four groups. This chapter demonstrated that the ET-DRI from DBD donors did not affect the costs and cost-effectiveness of liver transplantation. A separate DRI-score for DBD and DCD should be developed.

Summary Part B: Economic Evaluation of Initiatives to Improve Outcome of Liver Transplantation

Peri-operative blood loss is related to survival and the occurrence of complications and therefore influences costs. **Chapter 6** focused on the impact and risk factors for blood loss in liver transplantation[23]. Blood loss and associated blood products were important predictors for outcome. This chapter evaluated the impact of various blood products on outcome after liver transplantation. Twenty-nine variables, including blood product transfusions, were studied in relation to outcome in 433 adult patients undergoing a first orthotopic liver transplantation between 1989 and 2004. Data were analyzed using univariate and multivariate stepwise Cox's proportional hazards analyses, as well as propensity score-adjusted analyses to control for selection bias in the use of blood products.

The proportion of patients receiving transfusion of any blood component decreased from 100% in the period 1989 – 1996 to 74% in the period 1997 – 2004. In univariate and multivariate analyses, the indication for transplantation, transfusion of platelets and red blood cells (RBC) were dominant in predicting one-year patient survival. These risk factors were independent from well-accepted indices of disease, such as the MELD score. The effect on one-year survival was dose-related with a hazard ratio of 1.377 per unit of platelets (p = 0.01) and 1.057 per unit of RBC (p = 0.001). The negative impact of platelet transfusion on survival was confirmed by propensity score-adjusted analysis.

This chapter indicated that, in addition to RBC, platelet transfusion was an independent risk factor for survival after OLT. This finding has important implications for transfusion practice in liver transplant recipients.

The subsequent **chapter 7** studied implications of different transfusion practices[24]. In particular a restrictive transfusion protocol was compared with a conventional transfusion protocol. A total of 433 patients undergoing primary liver transplantation in three Dutch transplant centers between 2004 and 2009 were included. Two centers used a conventional transfusion protocol (n=291 patients), and one center used a restricted transfusion protocol (n=142 patients). Data on patient and graft survival as well as recipient-related costs and complications were collected. Preoperative characteristics differed on donor type, warm ischemia time, graft type, cardiac history and pulmonary history. The restricted transfusion protocol was associated with the use of significantly less blood products and a higher percentage of patients that were transplanted without the use of any blood products. Thirty-day and one-year patient and graft survival were not different between the restricted transfusion protocol and the conventional transfusion group. Costs for blood product transfusions were significantly less in the restricted transfusion group, but overall hospital costs were not different. This chapter concluded that the use of a restricted transfusion protocol in liver transplantation is as safe as a conventional transfusion protocol with similar overall hospital costs.

Chapter 8 assessed one of the most severe complications in liver transplantation; hepatic artery thrombosis[25]. Early hepatic artery thrombosis (eHAT) after liver transplantation occurs in 3% of adults and 8% of children and often results in retransplantation. eHAT is initially asymptomatic and arterial patency is monitored with percutaneous Doppler ultrasound screening (pDUS). The aim of this chapter was to analyze the diagnostic accuracy of 'continuous' Doppler registration (CONDOR) using an implantable miniature Doppler and to compare costs between pDUS and CONDOR.

This prospective observational study was conducted in 102 liver transplant recipients. Hepatic arterial signal was checked by CONDOR at least six times per day for the first 10 days after transplantation with comparison of diagnostic accuracy of CONDOR versus pDUS. The study protocol was approved by the Medical Ethics Committee of the University Medical Center Groningen.

Extra investigations were performed after 48 (11%) regular pDUS when arterial patency was questioned resulting in 32 extra pDUS, 14 computed tomography (CT) angiographies, and 2 reoperations. CT scan confirmed eHAT in 4 cases. In 10 cases of pDUS-suspected eHAT, subsequent CT showed an open artery, the CONDOR signal was clearly pulsatile. In 2 of 4 patients with five eHATs, a weak arterial signal was inadvertently interpreted as an open artery (sensitivity of 60%). The accuracy for detection of eHAT increased from 93% (pDUS) to 99% (CONDOR). Using CONDOR, additional CT angiographies may be prevented in 10% of cases. Mean cost per patient for pDUS were € 392 while CONDOR had mean costs of € 677 for the 10-day monitoring period.

CONDOR was a useful adjunct to pDUS because it reduced the false-positive rate of pDUS. Further development of the technique and analysis of the signal generated by CONDOR is needed to improve the sensitivity before CONDOR can replace pDUS as a reliable screening method for detection of eHAT. The additional costs for CONDOR were limited and might even be negative if CONDOR is able to replace pDUS completely.

DISCUSSION AND FUTURE PERSPECTIVES

Nowadays clinical research cannot examine clinical outcome alone. Since healthcare spending is under pressure in most countries of the world, costs need to be taken into account as well. Cost-effectiveness analysis in healthcare is a valuable tool that gives complementary information about medical interventions. The combination of clinical outcome and cost studies ought to support the decision whether or not a particular intervention is applicable for funding within the available budget. Only by applying a combination of both analytic tools we will be able to obtain the most out of the available budget. Therefore cost-effectiveness analysis alongside clinical outcome studies should be a standard part of the introduction of new diagnostics and treatments. Cost-effectiveness studies cost a fraction of the budget impact of new medical technology it assesses. In the Netherlands, before new pharmaceuticals become eligible for reimbursement, a cost-effectiveness analysis is mandatory. Other medical technology does not have to be subjected to cost-effectiveness analysis[26]. The Non Departmental Public Body, called NICE, is set up to reduce variation in the availability and quality of National Health Service treatments and care in England (and to a lesser extent in Wales, Scotland and Northern Ireland). NICE uses cost-effectiveness analysis for new pharmaceuticals but also for medical interventions and public health interventions[27].

Cost-effectiveness studies are useful in several domains. Health professionals operate in a health care sector with financial constraints. Cost-effectiveness studies may allow them to optimize their added value to patients by choosing cost-effective diagnostics, interventions and care. Insurance companies could embrace such studies to decide whether or not a particular intervention will be part of an insurance policy. Also the health care authorities and hospitals can use these tools to allocate available resources in an optimal way. For society as a whole the utilization of cost-effectiveness studies will eventually lead to better value for money in healthcare.

In most clinical research, frequentist statistics, such as statistical hypothesis testing and confidence intervals, is used[28]. For cost-effectiveness analysis Bayesian statistics, like a cost-effectiveness plane, may give additional insight because it allows a combined visual presentation of the difference in clinical effects and costs in one graph[29].

Cost analysis should always present both mean costs and median costs since this is relevant for policymakers. Since cost distributions are usually right-skewed with (high cost) outliers, median costs have less value when assessing the total economic impact for individuals, hospitals, insurers or governments.

Discussion and Future Perspectives Part A: Cost-Effectiveness of Extended Criteria Donors in Liver Transplantation

Liver transplantation is a complex medical intervention with good short- and long-term results albeit at considerable costs. A well-functioning hospital infrastructure is required to ensure adequate performance of this complex procedure including the patient selection process, donor and implantation operations, post operative care and follow-up which nowadays comprises decades. Due to global pressure on expenditures for health care, value for money is needed and such expensive treatments, like liver transplantation, are under scrutiny. Although liver transplantation is a relatively rare intervention and the total budget impact on a national level is limited, the impact on hospital resources, including staff, is high and cost and outcome variability between different types of liver transplantations is large. Therefore cost-effectiveness studies, such as presented in this thesis, are warranted.

To provide a background for this thesis, overall costs were compared in an international setting of OECD countries (chapter 3). The mean costs of liver transplantations are especially high in the United States because of specific health system characteristics. Higher administrative costs due to different requirements from multiple insurers, higher drug and equipment costs due to the government being denied to use negotiation power for Medicare (the U.S. national social insurance program), defensive medical practices due to the risk of being sued, and higher wages for specialists all contribute to higher costs in the United States[30,31]. These findings indicate that the health care environment in which liver transplantation is performed is an important driver of the costs of this treatment modality. This will have implications for less developed countries lacking the facilities and funds for liver transplantation. Often patients from these countries are referred to large centers in well developed host countries. The cost for liver transplantation in such host countries is often high because of health system characteristics. For these less developed countries it may be worthwhile to develop a liver transplantation program in their own country within their local framework and according to their own design in order to be able to reduce total costs. Well-developed countries could provide training for medical specialists from the lesser developed countries. This way high tech medical care can be exported to countries with a lower cost health care system.

In chapters 4 and 5 some interesting conclusions in relation to cost-effectiveness can be drawn. The ET-DRI is used as an instrument to assess graft quality. This parameter has been validated in a population of 5732 liver transplantations performed in the Eurotransplant region[32]. Even though an increasing ET-DRI is associated with an increasing risk of graft failure, it was unknown whether it is associated with higher costs for liver transplantation. In chapter 4 we analyzed 382 primary liver transplantations in a national multicenter study with five-year clinical follow-up. Four groups were made, each with an increasing ET-DRI-score. The fourth quartile of the ET-DRI had significantly higher costs than the other three quartiles. Five-year graft survival was significantly worse for the fourth quartile of the ET-DRI as well.

However, one-year graft survival and one-year and five-year patient survival was not significantly different between the groups. The use of DCD grafts appeared to be an important component in higher costs[33] as well as a higher ET-DRI[31]. When calculating the ET-DRI separately for DCD and for DBD liver transplantation, costs between quartiles was not different for both groups. This indicates that higher costs for the highest quartile of the ET-DRI actually are a proxy for higher costs of DCD liver transplantation, compared to DBD transplantation. It appears that the ET-DRI score has limited predictive value for the combination of DCD and DBD grafts. Therefore it should be adapted. Two separate scores should be calculated, one for DCD and one for DBD liver transplantation. Both scores should be based on the increased risk compared to an optimal donor. Another matter of consideration might be to include a factor for macrovesicular steatosis, an established risk factor for graft failure[34].

A more general shortcoming of ET-DRI and other known scoring systems for quality of donor livers is the lack of information on the condition of the recipient, intended to receive an (expanded) donor graft. This should include recipient variables with a known impact on outcome, such as the MELD score. The interaction between patient and graft condition is known and influences transplantation success[35]. The mechanism by which the surgeon and hepatologist decide on accepting or declining a donor graft for a given recipient also includes logistic considerations. The complicated, multifactorial decision on acceptance or decline of a graft for transplantation needs to be researched. Combining a scoring system for the (interaction between) quality of donor livers and the condition of the patients, might create a new model predicting transplantation success at the pre-transplantation phase.

In chapter 5, liver transplantations with grafts from DCD donors were found to result in more complications and generated significantly higher costs, compared to transplantations with grafts from DBD donors. There is one tariff for reimbursement for liver transplantation in the Netherlands. This tariff is on average too low for transplantations with a DCD donor liver graft, and too high for a liver transplantation with DBD grafts. The mix of DBD and DCD livers grafts is different between hospitals and may also change over time. This is an argument to introduce a differentiated reimbursement for livers from DBD and DCD donors.

Discussion and Future Perspectives Part B: Economic Evaluation of Initiatives to Improve Outcome of Liver Transplantation

In the second part of this thesis, costs of liver transplantation were assessed on the micro-level of individual transplantations. We concentrated on two established cost generators during and after liver transplantation; peri-operative blood loss and hepatic artery thrombosis (HAT). To assess the influence of new techniques to improve the outcome of liver transplantation we used different statistical techniques, propensity score analysis as well as randomization.

The number of peri-operative RBC transfusions and platelet transfusions were identified as independent risk factors for survival after liver transplantation (chapter 6). More blood products correlated negatively with survival. However, a reduction in the use of blood products by a restrictive protocol, as shown in chapter 7, had no significant effect on clinical outcome in terms of patient and graft survival and morbidity. A restrictive transfusion protocol resulted in significantly lower costs for blood product transfusion but total hospital costs were not different. A logical assumption is that the impact on total costs is not discernable, probably due to overshadowing of other relevant cost generating factors, such as longer recipient operation and hospital stay.

In chapter 8 we examined a second large cost generator in liver transplantation; early hepatic artery thrombosis (eHAT). This complication frequently leads to biliary complications, including multiple abscesses in the graft and ultimately graft loss if not treated. Often multiple reinterventions like abscess drainage and even retransplantation are needed. This means a heavy burden for patients and high associated costs. Early detection of HAT is of paramount importance because the graft might be saved by urgent thrombectomy, a less invasive and cheaper intervention than retransplantation. The conventional detection of HAT has an inherent delay because of the time interval between diagnostic tests. Therefore, we have studied a newly designed implantable continuous Doppler monitoring device. The monitoring device was not sensitive enough compared to conventional monitoring with percutaneous Doppler ultrasound screening. In addition, the implantable device itself was associated with higher costs. Cost reduction therefore was not possible with this new device. A similar device with better sensitivity and specificity might be cost-effective if it is able to detect HAT more accurate and earlier than conventional monitoring.

Both the restrictive blood transfusion protocol and implantable continuous Doppler monitoring device are examples of initiatives to lower costs at a micro level by improving clinical outcome through a reduction in the number and severity of complications. The complexity of liver transplantation makes it challenging, but attainable to assess the added value of new interventions.
The effect on costs of both the restrictive blood transfusion protocol and implantable continuous Doppler monitoring device was less positive than was estimated at the start of the studies. However, other initiatives for prevention of adverse effects or early detection or treatment of life-threatening complications in (liver) transplantation should be carefully researched since the clinical outcome and costs of graft failure are very high and, when retransplantation is performed, have impact on other patients on the waiting list as well. A step-by-step approach should be taken to identify the largest cost-driving factors in liver transplantation and consequently try to reduce these costs.

Nowadays, survival in the first year after liver transplantation is high, approximately 90%, which is an achievement for a major surgical operation in patients with predominantly poor health. Therefore, major increases in survival in the first year can not be expected.

In this thesis outcome variables during the first year after liver transplantation were considered. Cost-effectiveness studies of events and interventions during long-term follow up after liver transplantation are unexplored areas in literature. These studies are needed because increasingly more patients survive longer after liver transplantation and generate costs. Currently, five-year and ten-year patient survival after liver transplantation is 72% and 60% respectively[36,37]. The clinical end points for long-term outcome need to be different from clinical end points for short term follow-up due to different events and interventions. Long-term events mostly concern complications of immunosuppression, recurrent disease, and the prevention of secondary health problems, such as obesity, cardiovascular disease, and malignancies[38]. Treatment strategies for long-term complications and secondary health issues are of a different nature compared to those in the first year.

For long-term outcome, survival is still a relevant parameter. An alternative outcome measure is health-related quality of life measured in QALY's (Quality Adjusted Life Years). It measures perceived well-being of patients besides survival. In long-term outcome, non-medical issues become important, such as social reintegration and return to work, which contribute to quality of life but not necessarily to an increase in survival. For long-term outcome, non-medical experts like psychologists, social workers and physiotherapists need to be involved in treatment and can be incorporated in cost effectiveness research.

The cost-effectiveness of interventions to identify, treat or even prevent secondary health problems after transplantation need to be determined. Getting patients back to full societal engagement[39], school, study or work should be new long-term targets in liver transplantation.

Two domains of the liver transplant procedure are not investigated in this thesis. The transplantation process usually starts with a patient with end-stage liver disease that is placed on a waiting list. First, the cost of handling patients on the waiting list was not part of the COLT study. Analysis could be worthwhile to define determinants for a successful transplantation or failure defined as death or removal from the waiting list because the patient is too ill to be transplanted. Factors such as timing of listing, urgency classification, and pre-transplant care could be investigated. This may lead to adaptation of current management of patients on the waiting list and ultimately to a higher success rate of the transplantation program as a whole. This might contribute to increasing cost-effectiveness on a societal level.

The second domain is organ allocation, procurement and preservation. Cost-effectiveness of liver transplantation still needs to be determined for the donation part of the transplantation process. The cost-effectiveness of different ways of organizing organ donation and of initiatives to improve the use of available donor organs is largely unknown. The recent introduction of organ machine perfusion technology enables improving the quality of existing organs and resuscitate otherwise discarded organs. Organ machine perfusion may improve and expand the donor pool. This is also interesting from a cost-effectiveness perspective.

REFERENCES

1. Starzl TE, Marchioro TL, Von Kaulla KN, Hermann G, Brittain RS, and Waddell WR. Homotransplantation of the liver in humans. Surg Gynecol Obstet. 1963;117:659–676.
2. Starzl TE, Groth CG, Brettschneider L, Penn I, Fulginiti VA, Moon JB, Blanchard H, Martin AJ, and Porter KA. Orthotopic homotransplantation of the human liver. Ann Surg 1968;168:392-414.
3. Krom RAF, Gips CH, Houthoff HJ, Newton D, van der Waaij D, Beelen J, Haagsma EB, and Slooff MJH. Orthotopic liver transplantation in Groningen, The Netherlands (1979-1983). Hepatology 1984;4:S1:61S-65S.
4. Calne RY, Rolles K, Thiru S, McMaster P, Craddock GN, Aziz S, White DJG, Evans DB, Dunn DC, Henderson RG, and Lewis P. Cyclosporin A initially as the only immunosuppressant in 34 recipients of cadaveric organs: 32 kidneys, 2 pancreases, and 2 livers. Lancet 1979;2:1033–1036.
5. Warty V, Diven W, Cadoff E, Todo S, Starzl T, and Sanghvi A. FK506: a novel immunosuppressive agent. Characteristics of binding and uptake by human lymphocytes. Transplantation 1988;46:453-455.
6. Southard JH and Belzer FO. Organ preservation. Annu Rev Med 1995;46:235-247.
7. Shaw BW Jr., Martin DJ, Marquez JM, Kang YG, Bugbee AC Jr., Iwatsuki S, Griffith BP, Hardesty RL, Bahnson HT, and Starzl TE. Venous bypass in clinical liver transplantation. Ann Surg 1984;200:524-533.
8. Griffith BP, Shaw BW Jr., Hardesty RL, Iwatsuki S, Bahnson HT, and Starzl TE. Veno-venous bypass without systemic anticoagulation for transplantation of the human liver. Surg Gynecol Obstet 1985;160:270-272.
9. Tzakis A, Todo S, and Starzl TE. The anterior route for arterial graft conduits in liver transplantation. Transpl Int 1989;2:121.
10. Belghiti J, Panis Y, Sauvanet A, Gayet B, and Fékété F. A new technique of side to side caval anastomosis during orthotopic hepatic transplantation without inferior vena caval occlusion. Surg Gynecol Obstet 1992;175:270-272.
11. Bismuth H and Houssin D. Reduced-sized orthotopic liver graft in hepatic transplantation in children. Surgery 1984;95:367-370.
12. Broelsch CE, Emond JC, Thistlethwaite JR, Rouch DA, Whitington PF, and Lichtor JL. Liver transplantation with reduced-size donor organs. Transplantation 1988;45:519-523.
13. Pichlmayr R, Ringe B, Gubernatis G, Hauss J, and Bunzendahl H. Transplantation einer Spenderleber auf zwei Empfanger (Splitting-Transplantation) - Eine neue Methode in der Weiterentwicklung der Lebersegmenttransplantation [Transplantation of one donor liver to two recipients (splitting transplantation) A new method for further development of segmental liver transplantation]. Langenbecks Arch Chir 1988;373:127-130. German.
14. Furtado A, Tomé L, Oliveira FJ, Furtado E, Viana J, and Perdigoto R, Sequential liver transplantation. Transpl Proc 1997;29:467-468.
15. Hemming AW, Cattral MS, Chari RS, Greig PD, Lilly LB, Ashby P, and Levy GA. Domino liver transplantation for familial amyloid polyneuropathy. Liver Transpl and Surgery 1998;4:236-238.
16. Strong RW, Lynch SV, Ong TH, Matsunami H, Koido Y, and Balderson GA. Succesful liver transplantation from a living donor to her son. New Eng J Med 1990;322:1505-1507.
17. Kamath PS, Wiesner RH, Malinchoc M, Kremers W, Therneau TM, Kosberg CL, D'Amico G, Dickson ER, and Kim WR. A model to predict survival in patients with end-stage liver disease. Hepatology 2001;33:464-470.
18. Wiesner RH, McDiarmid SV, Kamath PS, Edwards EB, Malinchoc M, Kremers WK, Krom RAF, and Kim WR. MELD and PELD: Application of Survival Models to Liver Allocation. Liver Transpl 2001;7:567-580.
19. Fuchs VR, The gross domestic product and health care spending, New Engl J Med 2013;369:2-4.
20. Van der Hilst CS, IJtsma AJC, Slooff MJH, and Ten Vergert EM. Cost of liver transplantation: a systematic review and meta-analysis comparing the US with other OECD countries. Med Care Res Rev 2009;66:3-22.
21. Van der Hilst CS, Van Rijn R, Bottema JT, Van Hoek B, Metselaar HJ, Van den Berg A, Slooff MJH, and Porte RJ. Cost-effectiveness in liver transplantation with extended criteria grafts from donation after brain death donors. Submitted.
22. Van der Hilst CS, IJtsma AJ, Bottema JT, van Hoek B, Dubbeld J, Metselaar HJ, Kazemier G, Van den Berg AP, Porte RJ, and Slooff MJ. The price of donation after cardiac death in liver transplantation: a prospective cost-effectiveness study. Transpl Int. 2013;26:411-418.
23. De Boer MT, Christensen MC, Asmussen M, Van der Hilst CS, Hendriks HGD, Slooff MJH, and Porte RJ. The impact of intraoperative transfusion of platelets and red blood cells on survival after liver transplantation. Anesth Analg 2008;106:32-44.

24. Van der Hilst CS, Slooff MJH, Kazemier G, Ringers J, Hendriks HGD, De Boer MT, Lisman T, and Porte RJ. Outcome and costs of conventional versus restricted blood product transfusion policy in liver transplantation. *Submitted*.
25. De Jong KP, Bekker J, Van Laarhoven S, Ploem S, Van Rheenen PF, Albers MJIJ, Van der Hilst CS, Groen H. Implantable continuous doppler monitoring device for detection of hepatic artery thrombosis after liver transplantation. Transplantation, 2012;94:958-964.
26. IJzermans MJ (ed.). Guidelines for conducting economic evaluations in healthcare. Zorginstituut Nederland. 2015. Dutch.
27. National Institute for Health and Care Excellence. Developing NICE guidelines: the manual. Process and methods. 2014 [updated 2016 Apr; cited 2016 Nov 22]. Available from: http://nice.org.uk/process/pmg20/.
28. Bland JM and Altman DG. Bayesians and frequentists. BMJ 1998;317:1151.
29. Black WC. The CE plane: a graphic representation of cost-effectiveness. Med Decis Making 1990;10:212-214.
30. Lorenzoni L, Belloni A, and Sassi F. Health-care expenditure and health policy in the USA versus other high-spending OECD countries. Lancet 2014;384:83-92.
31. Blumenthal D, Stremikis K, and Cutler D. Health care spending – A giant slain or sleeping? NEJM 2013;369:2551-2557.
32. Braat AE, Blok JJ, Putter H, Adam R, Burroughs AK, Rahmel AO, Porte RJ, Rogiers X, and Ringers J. The Eurotransplant donor risk index in liver transplantation: ET-DRI. Am J Transpl 2012;12:2789-2796.
33. Jay CL, Lyuksemburg V, Kang R, Preczewski L, Stroupe K, Holl JL, Abecassis MM, and Skaro AI. The increased costs of donation after cardiac death liver transplantation. Ann Surg 2010;251:743-748.
34. Zamboni F, Franchello A, David E, Rocca G, Ricchiuti A, Lavezzo B, Rizzetto M, and Salizzoni M. Effect of macrovescicular steatosis and other donor and recipient characteristics on the outcome of liver transplantation. Clin Transplant 2001;15:53-57.
35. Schoening W, Helbig N, Buescher N, Andreou A, Schmitz V, Bahra M, Puhl G, Pascher A, Pratschke J, and Seehofer D. Eurotransplant donor–risk-index and recipient factors: influence on long-term outcome after liver transplantation – a large single-center experience. Clin Transpl 2016;30:508-517.
36. Jain A, Reyes J, Kashyap R, Dodson F, Demetris AJ, Ruppert K, Abu-Elmagd K, Marsh W, Madariaga J, Mazariegos G, Geller D, Bonham CA, Gayowski T, Cacciarelli T, Fontes P, Starzl TE, and Fung JJ. Long-term survival after liver transplantation in 4,000 consecutive patients at a single center. Ann Surg 2000;232:490-500.
37. Adam R, Karam V, Delvart V, O'Grady J, Mirza D, Klempnauer J, et al. Evolution of indications and results of liver transplantation in Europe. A report from the European Liver Transplant Registry (ELTR), Journal of Hepatology, 2012;57:675-688.
38. Sheiner PA, Magliocca JF, Bodian CA, Kim-Schluger L, Altaca G, Guarrera JV, Emre S, Fishbein TM, Guy SR, Schwartz ME, and Miller CM. Long-term medical complications in patients surviving ≥ 5 years after liver transplant. Transplantation. 2000;69:781.
39. Avison WR, McLeod JD, and Pescosolido BA. Mental Health, Social Mirror. Berlin: Springer; 2007. p. 333.