Costing Study of Liver Transplantation in Adults

by

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A thesis submitted in conformity with the requirements for the degree of Masters of Science, Subspecialization in Clinical Epidemiology Graduate Department of Community Health University of Toronto

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ABSTRACT
COSTING STUDY OF LIVER TRANSPLANTATION IN ADULTS
MSc in Clinical Epidemiology 1999
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The direct cost of liver transplantation from the perspective of the Ontario government was determined in a retrospective analysis of data from hospital charts and databases. A consecutive series of 119 adult patients from 1991-92 was followed from the date of listing to the second anniversary of the transplant. Patient-specific in-hospital services during the pre-transplant, transplant and post-transplant phases were compiled and costed. The primary outcome was the impact of complications on the cost of liver transplantation. The overall mean measured cost of liver transplantation was C$89066.44 (range 30505.19-690431.10). The multivariate logistic regression model for overall costs revealed that severe liver disease (OR=11.97), CMV infection (OR=6.12), additional operative procedure (OR=4.22), and biliary complications (OR=5.00) were associated with an increased likelihood of high cost. To reduce the cost of liver transplantation, consideration should be given to performing the procedure earlier in the course of disease, eliminating CMV infection, and reducing biliary complications.
INTRODUCTION

The factors that impact on the cost of liver transplantation are largely unknown. To what extent preoperative and postoperative factors could be used to predict costs is relevant to the appropriate allocation of healthcare resources. The cause and severity of liver disease, as well as postoperative complications, may be predictive of overall costs. The present analysis is an attempt to determine the overall direct cost of liver transplantation in adults, from the perspective of third party payers, primarily the government of Ontario.

The cost of liver transplantation has not been established in Canada. Most of the world literature on the topic refers to transplant charges, with very little consideration of actual costs of the procedure. The factors associated with improved prognosis following liver transplantation have been documented by several studies in this area. However, it is not known how these factors impact on the cost of treatment. Liver transplantation is currently the accepted treatment for end-stage liver disease. Between 200 and 300 liver transplants are carried out per year in Canada. The identification of groups in whom liver transplantation is particularly expensive may permit more informed decision making, especially when combined with survival data. The determination of the cost of complications will permit the commitment of resources to identifying strategies to eliminate those complications that are particularly expensive. In addition, the data on costs as they relate to severity of liver disease will aid decision making with regard to timing of transplantation. The ultimate goal will be to improve resource allocation.

The study was a retrospective analysis using existing data from hospital charts and existing databases. A consecutive series of patients undergoing liver transplantation was followed longitudinally from the date of listing to the second anniversary of the transplant. Data were obtained on all adult patients who underwent primary liver transplantation at The Toronto Hospital in 1991 and 1992. Since some of these patients were listed for transplantation in 1990, and the two-year follow-up period was not complete until 1994, it was necessary to accumulate costing data from 1990, 1991, 1992, 1993 and 1994.
CHAPTER 1

EFFECTIVENESS OF LIVER TRANSPLANTATION

Liver transplantation is the only form of treatment available for endstage liver disease <6>. Initially liver transplantation results were poor, with a one year survival rate of 30 percent prior to 1980. Advances in immunosuppression and standardization of surgical techniques led to dramatic improvements in the early 1980s <23>. A review of survival rates following liver transplantation in 1985 revealed one year survival rates of between 26 and 79 percent, and three year survival rates of between 12 and 60 percent <1>. The overall survival of adult liver transplant patients in the United States in 1992 was 80% at one year <24>. In 1992, transplant patients with alcohol related cirrhosis were found to have a one year survival of 78 percent, and a two year survival of 73 percent <18>. For non-alcoholic cirrhosis, the one year survival was 70 percent, and the two year survival 65 percent. An Austrian group examined their results in alcoholic patients, and found one, two and five year survival rates of 71%, 66% and 63% <22>. More recently, one year survival rates as high as 93% <10>, 88% <20>, and 83% <21> have been reported following liver transplantation. Recent results from the University of Alberta have shown a one year survival of 88% and a five year survival of 78% <73>. One year survival for patients with primary biliary cirrhosis or primary sclerosing cholangitis was as high as 95%.

The potential list of indications for transplantation now includes virtually every serious disease process affecting the liver <17>. The appropriate timing for listing for transplantation is a subject of ongoing research. Many authors have advocated early referral and listing for transplantation due to evidence that in most disease processes prognosis following transplantation worsens with disease progression, and chronic organ donors shortages make long waits inevitable <28>.

Investigators from the Mayo Clinic have studied preoperative predictors of increased resource utilization in liver transplantation. They concluded that a Karnofsky score of 40 or less, poor nutritional status, and renal failure independently predicted increased utilization <26>. The
Pittsburgh group evaluated the efficacy of liver transplantation in primary biliary cirrhosis by comparing the survival of 161 patients who had undergone transplants to that of a control group who had been treated conservatively <25>. The control group were simulated controls developed using the Mayo model, which is a Cox regression model for predicting the probability of survival in patients with primary biliary cirrhosis treated conservatively <27>. At one year following transplantation, the actual survival probability was .76, compared to an averaged Mayo model survival probability of .45, and at two years, the figures were .74 and .31. At five years, the transplanted group had a stable probability of survival of .72, while that of the control group had continued to decline to .12. This group concluded that liver transplantation markedly improves long term survival in patients with primary biliary cirrhosis.

Investigators from the Mayo Clinic have also analysed survival for primary sclerosing cholangitis (PSC), and produced a mathematical model to predict survival using serum bilirubin, histological stage on liver biopsy, age and the presence of splenomegaly <29>. The survival function for these patients produced a probability of survival at five years of .779 for a patient with an average level of severity at presentation. The analysis was based on 426 patients from five centres, with a full spectrum of disease severity. Those patients who underwent transplantation were censored at the date of transplantation. Presumably these patients had worse disease, and would have been more likely to die if they had not been transplanted. Farges et al analysed survival in French patients with PSC <30>. Twenty-three patients treated with steroids and or portal hypertension surgery between 1976 and 1985 were compared to 28 patients treated with transplantation between 1986 and 1992. Indications for transplantation were jaundice unrelated to acute cholangitis, repeated bouts of acute cholangitis not controlled by medical treatment, cirrhosis with portal hypertension and liver failure. Patients treated without transplantation had an actuarial survival rate of 74% at five years, compared to 89% for those treated with transplantation. At ten years, the non-transplant survival was 56%, and actual patient numbers for the transplant group were not yet available.

In 1994, a French group published an evaluation of the efficacy of liver transplantation in alcoholic cirrhosis <19>. They performed a case-control study in addition to an analysis using
simulated controls. A cohort of patients with alcoholic cirrhosis was used to construct a proportional-hazards prognostic model. This model was applied to a population of patients with alcoholic cirrhosis who underwent liver transplantation. Actual survival after transplantation was compared with simulated survival using the model. A case-control study was also done, in which each transplanted patient was matched to a control patient for age, severity of cirrhosis, and bleeding history. The constructed proportional-hazards model combined serum bilirubin, albumin, age and encephalopathy to predict survival. Comparison of actual and predicted survival showed that the model accurately predicted outcome. There was no significant difference between transplanted patient survival at two years (73%) and that of matched controls (67%) or simulated controls (67%). When analyzed according to severity of cirrhosis at time of transplantation, there was no difference in two year survival for the low and medium risk group. The high risk group demonstrated a two year survival of 64% for the transplanted group, compared to 41% (p=.1) for the matched controls, and 23% for the simulated controls (p<.01). The observation that patients with less than severe liver disease did not benefit from transplantation appears counterintuitive. This may have been due to the fact that only two years of follow-up were considered, or may suggest that alcoholic cirrhosis is not as strong an indication for transplantation as other chronic liver diseases. It is also possible that another outcome, such as quality of life, would be a more meaningful basis on which to consider efficacy of liver transplantation.

Recently, a number of studies have addressed the quality of life of patients following liver transplantation. Levy et al studied 210 patients undergoing transplantation over an eight year period<31>. The instrument they employed was the National Institute of Arthritis, Diabetes, Digestive and Kidney Diseases liver transplantation Quality of Life form. The core questions were taken from the Karnofsky Performance Status Scale, the Sickness Impact Profile, the Index of Well-Being, the Medical Outcome Survey, and the Nottingham Health Profile. The questionnaire explored patient demographics, occupation, symptom distress/frequency, activities of daily living, and impact of health on daily life. Questions were grouped into four categories, comprising self-image, health perception, ability to function, and ability to work. No
information is provided on validation of the questionnaire. Patients were questioned pretransplant, and at one, two and five years post-transplant. There were striking improvements in self-image, functioning ability, and perception of health status as early as one year following transplantation. However, at one year only 39.2% were working compared to 62.2% preoperatively. At two years this had improved to 57.5%, and five years following transplantation 69.7% were working for pay.

A second American group evaluated 50 liver transplant patients using the Karnofsky Performance Status <32>. The mean pretransplant score was 55, compared to 72 at three months, 79 at six months, 84 at one year, 88 at two years, and 95 at three years post-transplant. These results demonstrate improved general health, and functional rehabilitation. The Psychosocial Adjustment to Illness Scale was also used in this study, and scores demonstrated significant improvement after transplantation, specifically in the vocation, environment, domestic environment, and sexual relationship domains.

Collis et al undertook a cross-sectional study of liver transplantation, with a longitudinal subgroup <33>. Thirty post-liver transplant patients were studied, 11 of whom were also studied pre-operatively. The main outcome measures were the Clinical Interview Schedule (CIS), the General Health Questionnaire (GHQ), the Nottingham Health Profile (NHP), and the Mini-Mental State Examination (MMSE). NHP scores demonstrated lower levels of impairment after transplant than before. MMSE scores ranged from 24 to 30, indicating no significant cognitive impairment. Median GHQ score was 7.0 before operation and 1.0 after operation, and most of the difference was accounted for by differences in subscales for somatic symptoms and social functioning. There was no significant change in CIS score, suggesting no alteration in overall psychiatric morbidity. This group concluded that liver transplantation improves quality of life, but not up to the level of the general population.

A German group assessed the quality of life of 45 liver transplant recipients using a series of questionnaires addressing physical and psychological status, physical complaints, capability to participate in daily life, social support, and global quality of life <74>. The questionnaires used were standardized instruments well established in the German literature. Physical complaints
were more common than in the general population, mostly on the basis of drug side effects. Participation in daily life activities was comparable to the general population, 80% reported very good social support, and 60% rated their quality of life as very high. The authors concluded that during the first post-transplant year, patients reported a high quality of life in important areas of living.

The quality of life (QoL) of patients who were transplanted has been compared to that of a group who were assessed for, but not transplanted <34>. The main outcome measures were QoL as assessed by the Nottingham Health Profile and survival. Of the 109 patients assessed over a two year period, 27 patients were transplanted, 71 were not transplanted during the study period, and 11 were rejected for transplantation. Marked improvement in quality of life was found in transplant survivors, but it did not change in those not transplanted. Interpretation of these findings is problematic, since there were clear differences between those transplanted and those not transplanted. This study has been criticised as well for the use of the Nottingham Health Profile, since the scores are often skewed, sometimes bimodal, and troublesome to summarize <35>. A subsequent comment on this study emphasized the importance of using a disease specific quality of life instrument <36>. While the Nottingham Health Profile contains relevant generic QoL domains, questions concerning problems volunteered by the patients themselves are needed to produce an instrument that will be sufficiently sensitive to detect important changes in the patients’ quality of life.

Investigators from the University of Pittsburgh have studied the QoL of 346 adults before and after liver transplantation in three US centres <83>. Five domains were evaluated with standardized questionnaires. At follow-up, recipients had fewer disease-related symptoms, and lower levels of distress overall, but distress due to excess appetite, headaches, and poor vision were increased after surgery. All measures of personal functioning improved significantly, and 58% of those who could not work before surgery had returned to work following transplantation.

The available quality of life studies are not useful for cost-effectiveness analysis. In order to adjust improvements in length of survival for quality of the time gained, a numerical adjustment factor must be generated <62>. Simply summing up numerical weightings generated
from health assessment scales such as those employed in previous studies does not guarantee that changes in scores will be perceived as improvements by the patients. Individuals are unlikely to give equal weights to all components of a health state. Also, for purposes of resource allocation, it is important that steps are taken to deliver outcomes that are desired and that this is done as efficiently as possible. Nonpreference-weighted measures such as those employed in existing studies are therefore viewed as inappropriate for use in cost-effectiveness analysis. Preference-weighted health related quality of life methods assign weights to health states by evaluating individual and population preferences for particular health states. The methods used for gathering preferences have been derived from utility theory. Decision-analytic methods incorporating economic and psychological methods have also been used for preference assignment <62>. Appropriate preference-weighted scores allow the determination of utilities of various health states, which are used to calculate quality-adjusted life years.
CHAPTER 2

COSTING ISSUES IN TRANSPLANTATION

Mitchell et al <6> have raised the question of whether or not organ transplantation is an affordable intervention. Transplant programs appear to consume considerable resources, and many of these costs are difficult to quantify since they are often subsumed in the general running expenses of the hospital. Organ transplantation is performed for end-stage organ failure. For kidney transplantation, there is an alternative treatment for which costs can be compared. In Australia, it was found that the first year cost of renal transplantation was virtually identical to the first year cost of home hemodialysis, at Aust$20,000-25,000. However, in subsequent years the cost of maintaining a transplant patient fell to Aust$5,000, and the annual cost of home hemodialysis was significantly higher at Aust$14,000 <6>. As early as 1986, it was widely accepted that kidney transplantation had been proven to be cost-effective <1>. For other organ transplants, including heart, lung and liver, there is no alternative other than death, which is likely to be considerably less costly <1>. While this is probably true from the standpoint of direct costs to third party payers, it may not be true when all indirect costs to the family and society as a whole are taken into account. In conditions such as primary biliary cirrhosis, which often leads to liver failure in young women in the most productive years of their lives, liver transplantation has resulted in up to 94% returning to the workforce on either a full or part-time basis <25>.

The Cost of Non-Transplant Treatment

The costs associated with the treatment of end-stage liver disease have not been determined. In 1980, the cost of medical and surgical therapy for patients with an episode of acute variceal bleeding was found to average US$35,000 per case <16>. This must be interpreted with caution, since these patients were not being considered for transplantation. Also, dramatic changes in the management of variceal bleeding in the last two decades will have
made these values meaningless. A group in Tennessee examined the charges for patients who would have met candidacy requirements for liver transplantation but died without a transplant <4>. The mean hospital charges for 20 of these patients during the last twelve months of their lives was US$45,643 in 1984, compared to charges of US$92,866 for the first year following a liver transplant. The hospital costs associated with the medical management of the last year of life for alcoholic cirrhotics was found by another group to be US$31,000 in 1993 <8>.

The cost of dying of end-stage liver disease (ESLD) in Hawaii has been examined <38>. 153 patients treated between 1991 and 1995 were studied with respect to mean inpatient hospital charges and length of stay. The mean charge for 129 patients admitted with esophageal varices was US$30980. Seven patients admitted to the liver team died of ESLD with a mean charge of US$110576. Transjugular intrahepatic portosystemic shunts were performed in 17 patients with a mean charge of US$43209. Surgical shunts were undertaken in six patients with a mean charge of US$53994. Seven liver transplants were performed at a mean charge of US$222968. These values included only inpatient hospital charges, were not expressed in constant dollars, and no discounting was done.

Existing Studies on Liver Transplant Costing

A number of studies have addressed the issue of liver transplantation costing. In 1986, Evans <1> estimated the total first year cost of a liver transplant to be between US$68,000 and US$238,000, with a cost per year of life gained of US$38,000. Unfortunately, no information was provided on the source of these estimates. An analysis from the University of Pittsburgh in 1986 determined the cost of the preoperative workup to be US$5705, and the postoperative tests to be US$46,585 <2>. It is difficult to tell whether these values refer to the actual costs of performing the tests, or to the charges made to payers for the tests. Since charges are often determined by market forces, they may bear very little relevance to actual costs. The authors of this study claimed it to be a cost-benefit analysis, but the determination of costs was inadequate,
since no hospital stay, operating room, personnel or physical plant costs were considered. In addition, there was no adequate comparison to an alternative treatment, and benefits were not expressed in monetary units.

A slightly more thorough attempt at determining costs was carried out on 32 University of Pittsburgh patients transplanted between 1981 and 1986 <3>. The “Direct Costs” of the immediate transplant phase were found to be on average US$260,128, including US$36,982 in professional fees and US$223,146 in hospital costs. Some of the figures used in these calculations were based on charges, and some were estimated opportunity costs and transfer payments. The “Indirect Costs”, including travelling, lodging and rehabilitation, were found to be on average US$27,305. This was based on best-guess estimates for opportunity costs. The total cost of the period immediately surrounding the transplant was found to be on average US$287,432. The cost of one actuarial life-year saved was found to be US$51,000, excluding the costs for those who died in the first year following the procedure. The methodology for costing was deeply flawed in this analysis, since many of the “costs” were actually charges, and most of the other costs appear to be simple guesses.

In 1987 investigators from the University of Tennessee <4> assessed the hospital charges made for 55 liver transplants carried out between 1982 and 1985. They also assessed follow-up costs by sending questionnaires to postoperative patients. The mean hospital charges for the preoperative investigation phase was US$3,953. The mean hospital charges for the perioperative period were US$93,257. The mean charges for the medical care provided for the first one-year follow-up period was estimated to be US$20,556, based on the 48% of patients who returned the questionnaires. They found that the mean total charges for transplantation were US$174,220 in 1982, US$71,976 in 1983, and US$81,338 in 1984. Charges were found to vary greatly with the pre-transplant status of the patient. Those patients waiting for their transplant at home prior to transplantation generated charges of US$63088, compared to US$90212 for unstable hospitalized patients and US$149591 for patients in intensive care for management of liver failure. These charges were not expressed in constant dollars.

A study from the Netherlands attempted a cost-effectiveness analysis of 81 liver
transplants <5>. This appears to have been the first attempt at rigorous cost analysis. Cost volume data were obtained from a detailed system recording actual numbers of services provided, including time of medical personnel. Capital hospital costs were estimated on an annual program basis from the hospital financial administration. Undiscounted costs were calculated for each phase of treatment. The transplant date was chosen as the point at which to assign present value of costs for each patient. A negative discount rate of 5% was assigned to costs before transplantation. The 1987 cost of the pretransplant phase was US$13,276. The perioperative phase cost US$66,430, and the post-transplant cost to the end of the second year was US$25,398. The total cost in 1987 from the pretransplant phase to the end of the second year of follow-up was US$105,104.

An Australian group has looked at the costs of the entire spectrum of transplant procedures <6>. The per patient operating expenses of the three existing liver transplants programs ranged from A$116,000 to A$123,000 for the first year. Labour, fixed capital, drugs, and overhead costs were included, but the methods of determining these costs were not specified. In a subsequent letter, the methodology used by this group was criticized <15>. It was claimed that the reported costs did not include equipment used less than seventy percent of the time, building space, or patient management before referral or beyond six months from the transplant.

The cost of pediatric liver transplantation was assessed in a small number of patients in Georgia <7>. The total hospital costs for the first ten pediatric transplants were US$2,220,351, for an average of US$206,375 for the eight survivors. Once again, no information was provided on how these figures were calculated. Pageaux et al <8> found that the first year hospital costs for liver transplantation for alcoholic patients averaged US$86,000, compared to US$63,000 in non-alcoholic patients. A second Dutch study analysed costs for 152 liver transplants performed between 1979 and 1990 <9>. The costs for patients with biliary cirrhosis were estimated at approximately US$131,500, including costs incurred during ten years of follow-up. The method of cost determination was not specified.

Recently, a multicentre trial compared the cost of transplantation using two different immunosuppressant regimens <10>. Charges were recorded for all patients from the date of
transplant to the end of the first year. 529 patients were randomized to receive either tacrolimus (FK-506) or cyclosporine A. The total average charge for the tacrolimus group was US$156,993 compared to US$170,113 for the cyclosporine group. A similar comparison has been done in Pittsburgh, where 20 patients receiving FK506 immunotherapy were compared to 20 patients who had received cyclosporine <44>. While many costs were not different, a dramatic decrease in length of stay for the FK506 group resulted in a reduction in transplantation procedure charges of US$110694.

An American group reported decreasing liver transplant charges over time <32>. The average total hospital, organ procurement, and physician charges for the transplantation hospitalization for fifty transplants was US$165,000. The hospital charges declined from an average of US$154,000 in 1991-92 to US$103,000 in 1993-95. Another US group found that hospital charges in constant 1985 US dollars declined from a median of US$71922 in 1985-86 to US$49970 in 1995-96 <39>. A multihospital study from Boston explored the impact of a series of variables on the first post-transplant year costs of liver transplantation, including costs of the admission for transplantation <40>. Cost data were collected prospectively on 66 patients enrolled in a randomized controlled trial of cytomegalovirus immune globulin prophylaxis <41>. Costs were followed using Transition I-Clinical Cost Manager (Transition Systems, Inc., Boston, MA), which tracks all individual expenses related to each hospitalization by category. Beginning with the admission for transplantation, all expenses were followed for one year, including organ acquisition, operating room, intensive care and regular hospital room, nursing care, laboratory and radiologic tests, and pharmacy costs. Costs were incurred between Jan 1988 and June 1990. All costs were assumed to have occurred in 1989, and were adjusted to 1994 US dollars using a cumulative inflation rate of 45.1% based on the US Consumer Price Index. Using univariate analysis, there was a strong correlation between hospital length of stay and cost. Length of stay was found to increase with, age <16, higher pre-transplant prothrombin time, donor seropositivity for CMV, higher number of platelet transfusions, greater number of units of blood products transfused, abdominal reexploration, vascular complications, invasive fungal disease, bacteremia, and CMV infections. In a multivariate analysis, bacteremia, CMV disease,
abdominal reexploration, age <16, and the number of units of blood products transfused were found to be independently associated with longer post-transplant first year of stay. The derived model, including five independent predictors, accounted for 41.1% of the variability of hospital length of stay. The median first posttransplant year cost was US$1994$66665. The cost was higher for patients who died within the first year of transplantation compared to those who were alive at one year, US$99503 vs. US$63094.

Evans et al have examined the issues involved in the economics of liver transplantation <42>. These authors believe it is useful to distinguish between components and elements of cost in transplantation. Components refer to the treatment phase being analyzed, such as pretransplantation, evaluation, candidacy, transplantation, and post-transplantation. Most analyses focus on the transplantation period, due to the difficulty in obtaining data for the other components. The three primary elements of transplantation costs are considered to be hospital charges, professional fees and organ acquisition costs. As has been noted previously, charges are considerably higher than costs because they include mark-up. After noting that costs and charges are considerably different, these authors used the two terms interchangeably. These authors have outlined a number of other costing estimates. The US Department of Health and Human Services estimated first-year costs of US$240000 in 1983, while an earlier review in Massachusetts placed the average total first year cost at US$230000. Massachusetts Blue Cross and Blue Shield estimated liver transplant costs at US$270000 assuming a postoperative stay of 61 days. The Massachusetts General Hospital estimated the average charge per patient to be US$38000 in 1984, compared to an estimate of US$60000 from the Boston Centre for Liver Transplantation.

The variation from year to year in the cost of liver transplantation hospital charges has been examined at the Children's Hospital of Pittsburgh <43>. Charges increased from US$60864 to US$99737 between 1981 and 1985. Unpublished data from this hospital, quoted by Evans <42>, breaks down estimated charges by category. Laboratory charges were estimated to be US$52304, compared to organ procurement charges of US$26456, room and board
charges of US$39353, operating room charges of US$17394, pharmacy charges of US$14035, and professional fees of US$36000.

Evans <42> analyzed data collected in conjunction with the US National Co-operative Transplantation Study on 1680 liver transplants performed in 74 US centres in 1988. Hospital billing information was requested, and was received on 416 patients. The median procedure charges totalled US$1988145795.30. Median hospital stay charges were US$104048, median professional fees were US$25466, and median donor acquisition charges were US$16280.50. Charges were analyzed by a series of prognostic variables. Increased cost was associated with age under 50, nonwhite racial status, retransplants, intensive care unit admission prior to transplant, death at under one year. Nonteaching hospitals had lower costs than teaching hospitals, as did less active transplant programs. The latter is somewhat counterintuitive, and may be explained by higher retransplant rates in busier programs. Actual levels of reimbursement by third party payers varied greatly. Reimbursement exceeded 80% of billed charges for only 69.9% of the transplants analyzed, and 78.3% of these patients had private insurance. Of those patients in whom reimbursement was less than 60% of billed charges, 52.3% did not have private insurance. American transplant programs may be inclined to offer the service to privately insured patients in preference to those without such coverage.

An abstract from a Canadian transplant centre in Halifax briefly outlined a costing of the initial transplant admission <37>. Actual costs of 48 consecutive transplants from 1993 to 1995 were determined. Total donor costs were divided by the number of organs transplanted (including hearts, livers and kidneys) to give a procurement cost of C$4521 per organ. Cost centre annual budgets and productivity were used to calculate the costs of all services provided to recipients. The mean total recipient cost of each transplant was C$31,692 +/- 9,366 in 1993-94 and C$25,253 +/- 20,329 in 1994/95. These costs did not include physician services costs. Details of this analysis were requested from the authors but not received.

In 1988, the Province of Ontario funded liver transplants at a cost of C$47600. Toronto General Hospital carried out a detailed costing exercise using care maps and hypothetical patients in 1990 (unpublished data, July 17, 1990). The costs of nursing, professional services, diagnostic
services, procedures, medications, clerical and other support systems and supplies were considered for all phases of the transplant including numbers of patients assessed, those waiting, transplanted, followed up and readmitted. The overall costs per liver transplant were estimated to be C$90,000.

The Toronto Hospital has reported a comparison of the costs for the three month period immediately following liver transplantation between two different regimens for immunosuppression <14>. Hospitalization costs were determined using hospital per diem rates for specified care levels, and the costs of acute rejection episodes were calculated using a case costing model. The mean cost of these two components for immunosuppression using induction with intravenous cyclosporine A in 1997 was C$21,600, while the cost using induction with Neoral cyclosporine was C$17,929.

In Ontario, the Joint Policy and Planning Committee created a Transplantation Working Group, which in July, 1998 submitted a report entitled, "A Methodology for Costing and An Approach for Funding Transplantation" <60>. The JPPC is a partnership of the Ontario Ministry of Health and the Ontario Hospital Association, and was given a mandate in September, 1997 to recommend a costing methodology for transplantation. This group divided the transplant process into four phases: assessment and waiting period, donor procurement, peri-operative phase, and one year post-discharge. Where possible, patient-specific costs were used for the peri-operative phase. For the other phases, chart reviews were done to create a template of activities, which were then costed out. The costs included in the JPPC study were the direct costs of all care and services provided to the patient which could be traced directly to the transplant services provided to the patient. Patients who were assessed for transplantation but found to be ineligible were included in the analysis. For the peri-operative phase, costs were determined using the Ontario Case Cost Project methodology from hospitals that had implemented a case-costing methodology. The Toronto Hospital and London Health Sciences Centre submitted unaudited data for 1994/95. Transplant centres were then asked to provide estimated costs based on chart reviews for the assessment phase, waiting period, and post-discharge phase. Templates of care were developed for each phase of the transplant, and
validated by the other transplant centres.

The JPPC study estimated the assessment and waiting period to cost C$11170 in London, and C$9150 in Toronto. For the peri-operative period, patient-specific costs were only available from London, which found a mean cost of C$51084. The Toronto Hospital provided average direct inpatient costs of C$31500. The estimated one-year post-discharge follow-up cost was C$34371 in Toronto. The average direct cost of liver transplants in 1998 was estimated to be C$85749, not including organ procurement. Organ procurement costs after the pronouncement of brain death were estimated to be C$6869.71. No donor air transportation costs appear to have been considered in the JPPC analysis. Potentially more significant is the fact that no professional fees were included.

**Existing Studies on Kidney and Pancreas Transplant Costing**

Costing issues in renal transplantation are somewhat different than for other organs in that an alternative treatment is available. Long-term management of renal failure is possible with dialysis, but no such alternative is available for end-stage liver, heart or lung disease. There is a widely held perception that transplantation is the most cost-effective option in the treatment of end-stage renal disease. While for some patients dialysis may provide more benefits at a lower cost, many find that enhanced quality of life makes transplantation a more attractive option <45>. US Medicare payments in 1996 for patients with ESRD averaged US$36900. Annual expenses for dialysis patients averaged US$43700, compared to US$17600 for transplant patients, exclusive of the costs of the transplant procedure. Mean hospital charges for renal transplant operations carried out in 1994 (adjusted to 1996$) were US$74069, with a median of US$63710, exclusive of professional charges. These charges varied depending on age of the patient, region of the country, teaching status of the hospital, and the payer source <45>.

Actuarial evaluation of renal transplant charges in 1996 in the US has estimated the procedure to cost US$81900, the first year of follow-up to cost US$116100, and subsequent years to cost US$15900 <46>. The 1995 charges from US centres varied dramatically, from a low of US$49500 to a high of US$90500 <45>. Cost-effectiveness of renal transplantation has
been calculated for both the initial operation and retransplantation <47>. The cost of the first transplant operation was estimated to be US$64660. The quality-adjusted life expectancy was found to be 6.94 years, at a lifetime medical care cost of US$250917.

Hospital charges for simultaneous pancreas-kidney transplants have been estimated using a critical pathway model <48>. Total charges in 1991 were US$112261, compared to US$110950 in 1995 (unadjusted). An Italian group has calculated the actual cost of a kidney transplant between 1987 and 1995 to be US$30090, compared to US$46085 for a simultaneous pancreas-kidney transplant <49>. Evans et al have reviewed charges for pancreas transplants in the US in 1988 <76>. Data were obtained from 66.7% of the pancreas transplant centres, and the charges for 133 randomly selected patients were assessed. The median charge for a pancreas transplant with or without a kidney was US$66917.

**Existing Studies on Heart and Lung Transplant Costing**

In 1991, the Ministre de la Sante et des Services sociaux du Quebec commissioned a report on the survival, costs and cost-effectiveness of cardiac transplantation <50>. The direct cost to the health care system, including hospital, laboratory, professional fees and drugs were estimated in 1991 Canadian dollars. The average cost of evaluation of patients for consideration of transplant was C$10464, surgical cost up to the first hospital discharge was C$5774, and the cost of donor organ procurement was C$4330. The cost of the first year of follow-up was C$25016, compared to C$12909 for the second year. Salary costs were estimated to average C$7272, and co-ordination costs averaged C$1000. The average total costs over 13 projected years of survival were C$189960. Discounted at 5%, average survival was 9.39 years and average costs were C$149106. The costs generated by a heart transplant candidate who was not transplanted were estimated to be on average C$4962. The incremental cost-effectiveness of heart transplantation was found to be C$14553 per year of life gained.

An American group has retrospectively studied the charges from 107 heart transplants carried out between 1988 and 1993 <51>. Total charges in 1992 dollars for patients requiring
ICU care prior to transplantation averaged US$239,375, compared to US$128,593 for patients at home or on a general hospital ward prior to transplantation. The major components were room charges, supplies, pharmacy, laboratory, organ procurement and professional fees. An economic analysis has been undertaken of heart-lung transplantation <52>. In 1989, 27 US heart-lung transplant programs were asked to provide hospital billing data, and data were received on 42 patients. Median total charges for these procedures was US$13,488.

The cost-effectiveness of lung transplantation has been estimated for the first 25 transplants carried out at the University of Washington <53>. Compared with traditional therapy, lung transplantation cost US$176,817 per QALY. On the other hand, an abstract of a Canadian study placed the cost in 1993 dollars at Can$62,860 per life year gained <54>. In this study, the average cost of the initial hospitalization for lung transplantation was Can$114,953. Another American centre found the mean charges for surgery and postoperative care to be US$164,989. Follow-up charges were US$11,917 per month in the first year, and US$4,525 per month subsequently <55>. A third US study looking at costs from 1989 to 1992 found that initial hospitalization mean charges were US$137,234 <56>. The University of Pittsburgh has published a cost-utility study of lung transplantation <57>. The direct cost of care was estimated from adjusted charges for the surgical admission plus physician fees. Utilities were determined from a quality of well-being scale. The mean charges for the transplant admission were US$153,921. Cost-utility ratios were calculated for various survival gains, and it was concluded that 2.7 years of life must be gained to justify the surgery on social grounds.

**Summary of Existing Transplant Costing Studies**

Liver transplantation costs have not been assessed in Canada in a manner which permits evaluation of the contribution that patient-specific factors make to overall costs. While the JPPC study analyzed data from individual patients for parts of its costing procedure, too few patients were studied to comment on differential costs. The patient-specific determinants of costs were unknown, and the public policy implications were unclear. In addition, professional fees and donor organ transportation fees were not included.
Most of the remaining studies have been incomplete analyses from the US that used charge data in place of true costs. In a detailed discussion of cost issues in transplantation, Eggers and Kucken <11> pointed out that a major problem with using charge data is that they may bear little relationship to costs and may vary greatly across hospitals. Charges are set by hospitals based on factors such as estimated costs, market conditions, payer mix, and revenue maximization strategies. Typically, hospital charges are substantially above actual costs. In the US Medicare system, overall Diagnosis Related Group payments to hospitals represent 50-75% of hospital billed payments. Proper costing studies of transplant procedures must consider the pre-transplant, transplant and post-transplant phases. The US Agency for Health Care Policy and Research has stated, “To assess the costs and benefits of liver transplantation, it is important to compare the actual costs of transplantation...cost data reported in the literature often do not include the same factors and some do not include all the relevant costs, which range from purchase of the donor organ and use of blood products to hospital costs, follow-up outpatient care, and drug costs” <12>.

The cost of a health intervention cannot be considered in isolation. The costs of alternative interventions must be taken into account, and the effectiveness of the alternatives evaluated. In the existing literature on the subject of liver transplantation, a true cost-effectiveness analysis has not been identified. For a health intervention for which the alternatives are either perfect health or immediate death, cost-effectiveness can be assessed using simple cost per year of life gained. However, this is rarely the case in health care, in which the alternatives are usually more complex. Frequently, there are many possible health states that individuals can occupy for varying lengths of time following an intervention. For example, it may be straightforward to conclude that an individual would prefer a year of perfect health to immediate death, it is less clear if the alternative to death is a year in constant pain. In order to properly establish the effectiveness of an intervention, the gain in life expectancy should be adjusted for the quality of the gained time. This adjustment can be done using a preference-based utility instrument, in which individuals rate the desirability of health states on a scale from 0
(death) to 1 (perfect health). A number of techniques have been developed to permit the calculation of utilities, including “standard gamble” and “time-trade-off” [75]. Combining health state utilities and the probabilities of the various health states, final expected utilities for interventions can be generated. Quality-adjusted life years (QALYs) gained are then calculated, and the cost per QALY established.
CHAPTER 3

METHODOLOGY

The present analysis is an attempt to determine the overall direct cost of liver transplantation in adults, from the perspective of third party payers, primarily the government of Ontario. The extent to which preoperative and postoperative factors could be used to predict costs is relevant to the appropriate allocation of healthcare resources. The cause and severity of liver disease, as well as postoperative complications, may be predictive of overall costs.

The study was a retrospective analysis using data from hospital charts and existing databases. A consecutive series of patients undergoing liver transplantation was followed longitudinally from the date of listing to the second anniversary of the transplant. Data were obtained on all adult patients who underwent primary liver transplantation at The Toronto Hospital in 1991 and 1992. Since some of these patients were listed for transplantation in 1990, and the two-year follow-up period was not complete until 1994, it was necessary to accumulate costing data from 1990, 1991, 1992, 1993 and 1994.

All data regarding clinical services provided to 121 adult primary liver transplant recipients at The Toronto Hospital in 1991 and 1992 were assembled. A number of data sources were used. Dr. Paul Greig, Director of GI Transplantation, maintains a clinical database of all liver transplants. This database contains patient demographic information, as well as diagnosis, severity of liver disease, specifics of the transplant operation, complications and survival. Data on some lab services, blood products and medication unit costs were available as parts of databases maintained by the relevant departments. Professional medical fees paid by OHIP were obtained from the departments of medicine, surgery, and Anesthesia Associates. It was necessary to manually extract from the hospital inpatient charts information on length of stay, hours in the operating room, perfusionist use, recovery room use, many lab tests, radiological investigations, medication use, and consultations. For two patients, inadequate data were available for thorough costing, so these patients were excluded from analysis.
The general formula for the calculation of the cost of specific services for individual patients has been described in the Ontario Guide to Case Costing <82>:

\[
\text{Patient Cost} = \text{Pt Specific Functional Centre} = \text{units of Service} \times \text{Centre Unit Cost} + \text{Pt. Specific Supplies Cost}
\]

The patient specific units of service were determined from the charts and other sources as specified. Functional Centre unit costs have been determined from the Functional Centre Detailed Reports by dividing the number of services provided (ie number of tests performed, total number of inpatient days on the ward) into the total actual expenditure of the functional centre. Tracking the cost of supplies to each patient was not practical, but if the costs of medications had not been separately calculated, individual cost differences may have been lost. As recommended <82>, medication costs have been tracked and assigned directly to the patient, and have therefore been excluded when calculating functional centre unit costs.

Drummond et al have defined the essential requirements for cost analyses of health care programs <13>. From the outset, it is essential to determine which costs are to be included. If all costs are to be considered, the organizing and operating costs of the program and the costs borne by patients and their families must be included. The range of costs included is decided upon by determining the viewpoint of the analysis. Possible viewpoints include society as a whole, the Ministry of Health, the provincial government, the patient, the employer, or other third party payers. In an in-depth review of the issues involved in cost-effectiveness studies, Gold et al <62> argued that the societal perspective should ideally be used. The analysis should consider everyone affected by the intervention and count all significant health outcomes and costs that result, regardless of who experiences the outcomes or costs. The measure of health needs to include longer life, better function, and unwanted side effects. Costs should include not only medical and other resources, but also the time of patients and unpaid caregivers. While this level
of rigour is desired, it is rarely achieved, and in the present analysis, the viewpoint of the third party payer has been used.

The viewpoint of the analysis determines whether direct costs, indirect costs, or costs external to the health sector will be considered. Direct costs include the organizing and operating costs within the health sector, such as health professionals' time, supplies, equipment, power, and capital costs, as well as costs borne by the patients. Indirect costs include time lost from work, and psychic costs to the patients and families. Costs borne external to the system include changes in the quality of life of patients and their families <13>. Recently it has been recommended that the term “indirect costs” no longer be used in this context, due to confusion with the traditional actuarial use of the term to mean overhead costs <61>.

For the present analysis the viewpoint was third party payers, primarily the government of Ontario. This viewpoint was chosen because the main area of interest was differential costs of patient-specific factors, such as diagnosis, severity of liver disease, age, sex, and postoperative complications. The health care costs provided in hospital were relatively easily obtained retrospectively. It would have been exceedingly difficult to collect data retrospectively on costs borne by the patient and family. However, it is unlikely that including all of these costs would have changed the significant patient-specific factors. Those factors that increased the cost to third party payers would probably have also increased the costs to the patients.

The costs that were considered were the costs of services provided in hospital, including medications, tests, operating room, recovery room, ward and intensive care unit costs, and professional fees. The hospital costs not included were some allied health professionals, such as physiotherapy, occupational therapy and social work. Ambulatory care visits were not directly costed, although professional fees and laboratory tests resulting from these visits were captured. Also, some medical consultant fees, especially radiologist fees, may have been missed. The costs of interns, residents and fellows have not been captured, but have been estimated. Many of the costs to the healthcare system not provided at The Toronto Hospital have also been missed. However, patients waiting for or recovering from transplantation usually were transferred to The Toronto Hospital when they developed serious illnesses.
The allocation of hospital overhead costs has been detailed by the Canadian Institute for Health Information (CIHI) in chapter 3 of the MIS Guidelines <59>. Hospital functional centres are considered in two groups. The first group provide supportive services not directly related to patient care, and are known as Transient Cost Centres (TCCs). The second group, Absorbing Cost Centres (ACCs) provide services directly to patients or programs, or research and education services. Costs from TCCs are allocated to ACCs to determine the relative value of administrative and support services utilized by the functional centres. CIHI lists four cost allocation methods; Direct Allocation, Step-down Allocation, Double Distribution-Double Apportionment Allocation, and Simultaneous Equation Allocation (SEAM). SEAM is felt to be the most appropriate for Canadian health care facilities. By creating linear equations for each functional centre, comprised of the known direct costs plus the number of functional centres, multiplied by the appropriate allocation coefficient, the full costs of all centres are determined by solving the equations simultaneously. This method was used by Bolley to allocate overhead costs at The Toronto Hospital, and the resulting overhead adjustment factors were used in the present analysis.

**Medication Costs**

The exact amount of each drug that each patient received was extracted manually from the medication records on the inpatient hospital charts at The Toronto Hospital. The value was recorded in an Excel spreadsheet. Each phase of the study period, pretransplant, transplant and post-transplant, was recorded separately. For the pre and post-transplant periods, these records were incomplete, since only those medications received while the patient was in the hospital would have been captured. The Pharmacy of the Toronto Hospital provided a list of every drug in the formulary, with the costs charged to the patient wards for each drug. These charges did not vary through the study period. The relevant drugs were extracted from the formulary list. Formulary prices were converted to unit costs, which in most cases was in dollars per mg. It was assumed that the price charged other functional centres for medications would have included at
least some pharmacy overhead costs. Therefore, overhead costs were not added to calculated medication costs.

Due to problems with the initial organization of the data, it was necessary to print out and reenter the data in a more analyzable format. After all patient data had been reentered, a complete list of the names of all drugs administered was compiled. It was necessary to individually examine and recalculate each medication administered to ensure that appropriate units were used. Considerable effort was necessary to adjust the names of administered drugs, since in many cases drugs were recorded under proprietary rather than generic names. Costs for all drugs for each patient during each of the three phases were calculated. Outliers were carefully examined, and in many cases it was necessary to return to initial data sheets to sort out errors. Specific drugs, such as gancyclovir and OKT3, were used as markers to identify patients with CMV infection and severe rejection, respectively.

**Operating Room Costs**

The number of hours of operating room time that each transplant consumed was extracted from the operating room record on the inpatient hospital chart and initially entered on an Excel spreadsheet. As noted previously, it was necessary to print out and reenter the data in a more analyzable format. It was anticipated that OR costs and hospital length of stay would be important factors in the overall costing, so all values were rechecked from the original data extraction sheets. One error was found, in which the hospital stay was short by ten days. The hospital charts were not reexamined, except for a small sample of four charts during the period when two individuals were being trained in data extraction. In 11 cases, the data extraction sheets did not contain operating room hours. The mean of all of the remaining 108 cases of operating room hours was calculated, and found to be 9.65 hours. This was used to replace the missing data. In cases where patients returned to the operating room for further surgery, these hours were counted in the relevant treatment phase.

The 1991, 1992, and 1993 Functional Centre Detailed Reports (FCDRs) for the
relevant costing centres were used to calculate OR hourly costs. The names of the relevant costing centres were, “OR Pool”, “OR Gen Surg”, and “OR NU” (4375, 4363, 4350, 3700). The total OR cost for these centres was divided by the total work hours output to yield an hourly cost. The cost of anesthesia supplies and drugs was determined by dividing the total cost by the total work hours from the relevant FCDR (4371), and this hourly cost was added to the OR cost noted above. This value was then multiplied by 1.3 in order to allow for overhead, as recommended by Bolley (unpublished data, 1992). The final hourly value for OR time was $479.71 in 1991, $580.97 in 1992 and $428.60 in 1993. Since the main outcomes under consideration were related to cost differences between individual patients and not cost differences over time, the median cost of the three values, $479.71 was used for all patients. This value was multiplied by the number of operating hours for each patient treatment phase to yield total operating room costs.

**Perfusion Costs**

At the discretion of the operating surgeon, veno-venous bypass was often used during the transplant operation. This involved the use of a perfusionist, a bypass apparatus, and disposable tubing. Whether or not perfusion services were used was recorded on the original data sheets from the OR record. From the relevant FCDR (4378) the total cost of all perfusion services was obtained, and divided by the total number of perfusion cases performed, yielding a cost of $1402.87/case in 1991 and $1283.69/case in 1992. This may have been an overestimation, since the costs associated with other perfusion cases, such as heart surgery, may have been more expensive. It was not possible to separate cardiac cases from transplants, so an overall mean value was used.

**Recovery Room Costs**

In most cases, following the transplant operation patients were taken directly to
the surgical intensive care unit. The only patients who were treated in the Recovery Room were those patients who had returned to the OR for further surgery. The relevant FCDR (4352) was used to calculate costs by dividing the total costs by the overall number of patients treated in the recovery room. This resulted in costs of $159.72/pt in 1991, $185.63/pt in 1992, and $184.71/pt in 1993. Once again, the median cost of $184.71/pt was used for the calculations.

**Intensive Care Unit Costs**

The number of days spent in the SICU and MICU was extracted from the hospital discharge record on the inpatient chart. For 6 patients, the number of SICU days was missing. In these cases, the mean of the remaining 113 patients was used, which was calculated to be 9 days. The total SICU costs were obtained from FCDR 4261. The cost of medications was subtracted from the total cost, since medications were costed separately as described above. The resulting value was divided by the total number of patient days for the SICU. The result was multiplied by 1.46, to account for overhead costs as recommended by Bolley. SICU daily cost for 1991 was $1437.09, compared to $1624.66 for 1992 and $1773.68 for 1993. MICU costs were calculated in an identical fashion from FCDR 4263. In both cases, the median of the three year values was used for all calculations.

**Ward Costs**

The number of days spent on each ward was extracted from the discharge record on the inpatient chart. For 6 patients, the data on hospital stay was missing. In these cases, the mean ward stay of the other patients was used, which was found to be 34 days. The FCDR for ward 10ES (4200) was used to calculate ward daily costs for all wards except 3GW, which was the transplant ward. Patients were treated on this ward after leaving the SICU. On this ward, staff levels were higher, and care was more intensive than on regular wards. Drug costs were subtracted from total costs, and the result was
divided by the total number of inpatient days. This value was multiplied by 1.82 to account for overhead costs. The cost of ward stay on 3GW was calculated from FCDR 4133 in an identical fashion. In both cases, the median of the three yearly values was used for all calculations.

Table 1 Ward and ICU Daily Costs

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Ward</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IOES</td>
<td>332.20</td>
<td>378.65</td>
<td>405.82</td>
</tr>
<tr>
<td>3GW</td>
<td>365.84</td>
<td>435.63</td>
<td>452.43</td>
</tr>
<tr>
<td>SICU</td>
<td>1437.09</td>
<td>1624.66</td>
<td>1773.68</td>
</tr>
<tr>
<td>MICU</td>
<td>2011.28</td>
<td>2651.83</td>
<td>2553.25</td>
</tr>
</tbody>
</table>

**Donor Costs**

For donors outside of southern Ontario, staff from The Toronto Hospital were flown by chartered plane to the location of the donor, which could have been anywhere in Canada, and in a small number of cases in the US. The cost of air transport for each donor run was obtained directly from Skycharter, who provided the actual amount charged to the Ontario government for each trip. To this was added the cost of two OR hours, plus a 12 hour ICU stay. These numbers were rough estimates of the time it takes the retrieval team to do the donor operation, and the time between the declaration of brain death and the actual donor operation. While these costs would have been different for each individual hospital, obtaining the data for each of the over one hundred hospitals involved would have been very difficult. Therefore, the costs calculated as above for The Toronto Hospital were used as an estimate.
MORE Program Costs

The Multiple Organ Retrieval and Exchange (MORE) program paid for all administrative costs related to transplantation. This included staff costs related to coordination, planning and retrieval. For donors in southern Ontario, in most cases ground transportation was used for retrieval, which came out of the budget for the MORE program. Donor surgical supplies, tubing, and organ preserving equipment and solutions were also included. The MORE program had its own functional centre (4119), and the total number of organ donors managed in the relevant years was obtained from the program records. This included all cadaver donors regardless of the organs retrieved. While some donors would not have yielded a liver used for transplantation, the mean cost for each donor was used in the present analysis.

Physician Costs

The actual amount paid by OHIP to surgeons for each patient was obtained from the transplant surgery office. The surgical payments were missing from 10 patients, so the mean value was used. Anesthesia Associates provided actual OHIP payments to anesthetists. Once again, the data were missing for 8 patients, and the mean value was used. Payments to hepatologists and intensivists were also directly obtained from relevant offices. For other physicians, such as hematologists, radiologists, thoracic surgeons, and many other consultants, the consults were noted from the individual chart reviews. For ease of calculation, consults were recorded in the “tests” category in the database. The payments made to the consultants were determined from the Schedule of Benefits of the Ontario Health Insurance Plan that was in effect at the time <58>. It proved difficult to obtain thorough billing data from the radiology department, so some payments made to radiologists may have been missed.

Blood Product Costs

The hospital blood bank maintained a database in which it recorded all blood products used by transplant recipients. This list was provided on diskette, and was imported into the database. The Canadian Red Cross provided an estimate of the cost of the various blood products
in 1991/92. These costs may not have been accurate, since detailed costing of blood acquisition and processing were not available.

Test Costs

The number of many tests performed on each patient was obtained from the charts. The hospital maintains a database of tests carried out on all patients (Ulticare). However, for the period under consideration, only hematology, microbiology and radiology services were included. The costs of provided services were calculated from workload unit costs. Workload unit costs were determined from the FCDRs for each relevant laboratory. The MIS guideline manuals, from which the number of workload units required for each test were extracted, have recently become available on cd-rom <59>. The relevant sections were used to determine the number of workload units for each test. In many cases, it was difficult to determine which method was used by the relevant laboratory to conduct a specific test. However, the range between the lowest and highest number of units per test was usually small. In the majority of cases, the highest value was used in the case of conflict.

Overall Cost Calculation

The number of units of service provided to each patient was multiplied by the cost of each unit of service. The total cost of each phase of the transplantation process was calculated by adding the costs of each of the services. The total cost of each of the three phases were then added to provide the overall measured cost for each patient.

Statistical Analysis

For the statistical analysis, the primary dependent variable was considered to be total cost, with secondary dependent variables being donor cost, hospital cost, drug cost, test cost and medical fees cost. Independent variables were patient age, sex, diagnosis, severity of disease as indicated by status, and complications. Age in decades was used as a
The analysis was carried out using SPSS statistical software (Version 5, SPSS Inc., Chicago).

Most of the costing data were not normally distributed. Because of the extremely skewed nature of the data, a log transformation of the data was attempted. However, the data were still unacceptably skewed, a condition which persisted even after a log-log transformation. The inability to achieve a normal distribution ruled out the use of applied regression models <85>. In applied regression, for any fixed value of \( X \), \( Y \) must have a normal distribution. When the normality assumption is not badly violated, the conclusions reached by a regression analysis will generally be reliable and accurate, but in the current analysis the normality assumption was so badly violated as to require alternative inference-making procedures. The data were separated into those above and below the median value for each variable. Patients were considered either high cost or low cost for each variable in each phase and for overall costs. Bivariate analysis was carried out for each variable in succession. The statistical significance of cost differences was assessed with the chi-square test and when appropriate, the Yates continuity correction for 2X2 tables was applied. Likelihood ratios were calculated, and the Mantel-Haenszel test for linear association carried out. For each phase, the variables that predicted high cost were identified. Multivariate logistic regression models were tested to estimate the independent effect of the above variables on cost. Prediction models for the transplant and post-transplant phases and for overall costs were created and evaluated. Odds Ratios, 95% confidence intervals, and \( p \) values were calculated based on the following regression model:

\[
\ln(P/1-P) = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \ldots + \beta_k X_k
\]

Where \( P \) = probability of high cost

\( \beta_0 \) = constant/intercept

\( \beta_k X_k \) = predictors of high cost
CHAPTER 4

RESULTS

Descriptive Statistics

During 1991 and 1992, 121 primary liver transplants were performed on adults at The Toronto Hospital. In two cases, hospital charts were missing and it was not possible to obtain essential data. Therefore the following analysis is based on the remaining 119 patients. Seventy-four of these patients were male, and 45 patients were female. The mean age of the patients at the time of transplantation was 45.2 years, with a range of 15 to 66. Candidates for liver transplantation in Canada are listed according to the severity of their liver disease. Status 1 patients are living at home awaiting their transplants. Fifty-four, or 45.4% of our patients were in this category. Forty-seven patients were status 2, in hospital on a regular ward. Fourteen patients were status 3, in an intensive care unit, and four were status 4, in fulminant hepatic failure.

The most common single diagnosis was primary sclerosing cholangitis, present in 21 patients. Eighteen patients had cirrhosis caused by hepatitis C, while 17 had primary biliary cirrhosis, and another 17 had cryptogenic cirrhosis. Thirteen patients had alcoholic cirrhosis, and nine had hepatitis B. The remaining 24 patients had a variety of conditions as shown in Table 2. There may have been some overlap between the hepatitis C and alcoholic cirrhosis groups. Patients who are infected with hepatitis C may be very sensitive to the hepatotoxic effects of alcohol, so distinguishing the cause of cirrhosis in an individual patient may be difficult. The two year survival of liver transplantation for these 119 patients was 75.6%.
Table 2  Primary Diagnosis

<table>
<thead>
<tr>
<th>DIAGNOSIS</th>
<th>NO. OF PATIENTS</th>
<th>% OF TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Sclerosing Cholangitis</td>
<td>21</td>
<td>17.6</td>
</tr>
<tr>
<td>Hepatitis C Cirrhosis</td>
<td>18</td>
<td>15.1</td>
</tr>
<tr>
<td>Primary Biliary Cirrhosis</td>
<td>17</td>
<td>14.3</td>
</tr>
<tr>
<td>Cryptogenic Cirrhosis</td>
<td>17</td>
<td>14.3</td>
</tr>
<tr>
<td>Alcoholic Cirrhosis</td>
<td>13</td>
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</tr>
<tr>
<td>Hepatitis B Cirrhosis</td>
<td>9</td>
<td>7.6</td>
</tr>
<tr>
<td>Autoimmune Cirrhosis</td>
<td>4</td>
<td>3.4</td>
</tr>
<tr>
<td>Alpha-1-AT Deficiency</td>
<td>4</td>
<td>3.4</td>
</tr>
<tr>
<td>Fulminant Hepatitis</td>
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</tr>
<tr>
<td>Hepatocellular Carcinoma</td>
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<td>2.5</td>
</tr>
<tr>
<td>Wilson’s Disease</td>
<td>2</td>
<td>1.7</td>
</tr>
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<td>1.7</td>
</tr>
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<tr>
<td>Hemochromatosis</td>
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<td>.8</td>
</tr>
<tr>
<td>Hepatic Artery Aneurysm</td>
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<td>.8</td>
</tr>
</tbody>
</table>

Initially, the costs were expressed for each phase of the transplant for the various cost categories. Throughout this analysis only services provided at The Toronto Hospital have been captured. It is probable that services for some patients were provided at other institutions. However, common practice when patients were awaiting or recovering from transplantation was to transfer them to The Toronto Hospital for significant illnesses (personal communication, Dr. P. Greig). Therefore, it is unlikely that services provided elsewhere would have significantly increased the overall cost.
Pre-Transplant Phase Costs

A small number of patients underwent operative procedures while waiting for transplantation. The mean operating room cost, calculated by multiplying number of OR hours for each patient by the cost of each hour, was C$26.20, with a range of C$0.00 to C$1439.13. These patients generated mean recovery room costs of C$10.09 (0.00-646.49). Intensive care unit mean costs were C$526.62 (0.00-21120.58). Ward hospitalization mean costs were C$3762.98 (0.00-37899.81). Medication mean costs were C$314.23 (0.00-11099.38). Mean costs for tests, investigations and consults not on the Ulticare database were C$817.29 (0.00-18861.74). Mean costs for tests and investigations included in the Ulticare database were C$298.39 (0.00-2224.47). The overall mean cost of the pretransplant phase was C$5755.80 (0.00-64107.91). Costs of outpatient services, such as ambulatory care clinics, were not captured.

Table 3  Pre-Transplant Phase Costs

<table>
<thead>
<tr>
<th>Category</th>
<th>Mean</th>
<th>Median</th>
<th>Minimum</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>OR</td>
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<td>0.00</td>
<td>0.00</td>
<td>1439.13</td>
</tr>
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<td>RR</td>
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<td>0.00</td>
<td>0.00</td>
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<td>0.00</td>
<td>0.00</td>
<td>21120.58</td>
</tr>
<tr>
<td>Ward</td>
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<td>0.00</td>
<td>0.00</td>
<td>37899.81</td>
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<tr>
<td>Drugs</td>
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<td>0.00</td>
<td>0.00</td>
<td>11099.38</td>
</tr>
<tr>
<td>Tests</td>
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<td>0.00</td>
<td>18861.74</td>
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<tr>
<td>Ulticare</td>
<td>298.39</td>
<td>193.48</td>
<td>0.00</td>
<td>2224.47</td>
</tr>
<tr>
<td>OVERALL</td>
<td>5755.80</td>
<td>545.73</td>
<td>0.00</td>
<td>64107.91</td>
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</tbody>
</table>
Transplant Phase Costs

The transplant phase was the most expensive of the three phases. The mean cost of retrieving the donor liver was C$7519.22 (1677.97-24517.27). Mean MORE program costs were C$5732.20 (5110.49-6386.08). The mean operating room cost was C$5194.60 (2158.70-23217.964), mean perfusion cost was C$690.39 (0.00-1283.69), and mean recovery room cost was C$20.10 (0.00-738.84). Intensive care unit costs showed a mean of C$14916.47 (0.00-178712.6), and regular ward costs a mean of C$15429.24 (0.00-162054.36). Total medication costs showed a mean of C$5071.50 (7.86-59970.59). Non-Ulticare tests, investigations and consults had a mean cost of C$5906.25 (237.61-74748.39), and Ulticare tests had a mean cost of C$1471.04 (0.00-10524.89). The mean cost for blood product transfusion was C$2123.66 (0.00-19903.00). For ease of database manipulation, all professional fees for surgeons, anesthetists, and internal medicine specialists were charged to the transplant phase. The mean surgical fee was C$3194.04 (1013.85-7143.28), and the mean anesthetist fee was C$1955.18 (1030.76-4744.11). Internists were paid a mean of C$667.97 (0.00-2385.10). The overall mean cost for the transplant phase was C$69891.87 (14353.08-514049.10)
### Table 4  Transplant Phase Costs

<table>
<thead>
<tr>
<th>Category</th>
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<th>Median</th>
<th>Minimum</th>
<th>Maximum</th>
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</thead>
<tbody>
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<td>5110.49</td>
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<td>1283.69</td>
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<tr>
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<td>0.00</td>
<td>0.00</td>
<td>738.84</td>
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<td>178713.00</td>
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<td>74748.40</td>
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<td>0.00</td>
<td>2224.47</td>
</tr>
<tr>
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<td>1386.00</td>
<td>0.00</td>
<td>6386.08</td>
</tr>
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<td>3131.31</td>
<td>1013.85</td>
<td>7143.28</td>
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<tr>
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<td>14353.08</td>
<td>514049.00</td>
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</table>
Post-Transplant Phase Costs

The costs of this phase included only those costs provided at The Toronto Hospital. Those patients who were readmitted and required retransplantation were costed in this interval. The mean operating room costs were C$251.14 (0.00-5660.58), mean recovery room costs were C$12.11 (0.00-461.78), and mean perfusion costs were C$10.79 (0.00-1283.69). Mean ICU costs were C$811.40 (0.00-68937.75), and mean ward costs were C$7829.63 (0.00-77542.14). The mean cost of non-Ulticare tests and consults was C$1698.12 (0.00-43151.31), and the mean cost of Ulticare tests was C$1490.82 (0.00-18440.55). The overall post-transplant cost was a mean of C$13418.77 (13.44-171362.00).

Table 5 Post-Transplant Phase Costs

<table>
<thead>
<tr>
<th>Category</th>
<th>Mean</th>
<th>Median</th>
<th>Minimum</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
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</tr>
<tr>
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<tr>
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<tr>
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</tbody>
</table>

Contribution of Cost Categories to Total Costs

For all phases, and for overall costs, the largest single measured cost component was inpatient care. The combination of ICU and ward care accounted for 74.53% of costs in the pre-transplant phase, 43.38% of costs in the transplant phase, 64.40% of costs in the post-transplant phase, and 48.54% of the overall measured cost. Tests accounted for 13.12% of overall measured costs, and medications for 7.52%. These data are shown in Table 6.
Table 6  Contribution of Each Category to Total Cost (percentage)

<table>
<thead>
<tr>
<th>Category</th>
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<th>PostTransplant</th>
<th>Overall</th>
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</thead>
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<td>6.44</td>
</tr>
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<td>7.43</td>
<td>1.87</td>
<td>6.14</td>
</tr>
<tr>
<td>Perfusion</td>
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<td>0.08</td>
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<td>0.78</td>
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<td>RR</td>
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<td>0.02</td>
<td>0.09</td>
<td>0.04</td>
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<td>6.05</td>
<td>18.20</td>
</tr>
<tr>
<td>Ward</td>
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<td>22.08</td>
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<td>30.34</td>
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<td>7.26</td>
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<td>7.52</td>
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<td>Tests</td>
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<td>8.45</td>
<td>12.65</td>
<td>9.46</td>
</tr>
<tr>
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<td>2.10</td>
<td>11.11</td>
<td>3.66</td>
</tr>
<tr>
<td>Blood</td>
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<td>2.38</td>
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<td>3.59</td>
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<td>Internist</td>
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<tr>
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<td>6.46</td>
<td>78.47</td>
<td>15.07</td>
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</table>
Bivariate Analysis

Bivariate analysis was used to examine the relationship between each variable and overall cost. The total cost of all three phases was a mean of C$89,066.44. The minimum cost was C$30,505.19, and the maximum cost was C$690,431.10. These costs were analyzed by the variables; sex, survival, diagnosis, age in decades, pretransplant status, severe rejection, CMV infection, additional operative procedure and biliary complication. Severe rejection was defined as treatment with OKT3, and CMV infection was defined as having received gancyclovir. Higher costs were observed with the preoperative variables; female sex, a diagnosis of alcoholic cirrhosis or to a lesser extent hepatitis C, age in the sixth decade, pretransplant status 3 (Table 7). Higher costs were also observed with the postoperative variables; presence of severe rejection, presence of CMV infection, additional operative procedures and biliary complications (Table 8). For severe rejection, CMV infection, and additional operative procedure, the pretransplant costs were dramatically lower for those who had the complication compared to those who did not. There was no difference in cost between those who lived and those who died. Higher pretransplant and transplant phase costs in those who died were countered by higher post-transplant costs in those who lived.

Bivariate analysis for low vs. high cost for all phases and overall costs was carried out. For the pretransplant phase, none of the examined variables were associated with a statistically significant increased probability of high cost at the p<.05 level. However, for the transplant phase, age in decades, sex, diagnosis, survival, postoperative CMV infection, and severe rejection were not associated with high cost, while status 3 or 4, additional surgical procedures, and biliary complications were associated with high cost. The only variable associated with high cost in the post-transplant phase was CMV infection. The variables that were found to not be associated with high overall cost were; age in decades, gender, diagnosis, survival, and biliary complications. The variables that were associated with high overall cost were preoperative status 3 or 4, CMV infection, severe rejection, and additional surgical procedures. Table 9 outlines the association between each of the variables and high cost in each of the phases. Those variables identified using bivariate analysis as being associated with a significantly increased
The probability of high cost (p<.05) have been highlighted.

Table 7 Costs by Pre-Transplant Variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>Number</th>
<th>Pre-Trans</th>
<th>Transplant</th>
<th>Post-Trans</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex- M</td>
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Table 8  Costs by Post-Transplant Variables

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<th>Post-Trans</th>
<th>Total</th>
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</table>

Table 9  Bivariate Relationship Between Predictor Variables and High Cost (p value)

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<th>OVERALL</th>
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<td>.31616</td>
<td>.00712</td>
</tr>
<tr>
<td>Biliary Comp</td>
<td>.97015</td>
<td>.00788</td>
<td>.27777</td>
<td>.12492</td>
</tr>
</tbody>
</table>
Multivariate Analysis

All of the variables were tested in stepwise regression models using both forward and backward methods. Only those variables that remained in the final model are reported here. Table 10 illustrates the logistic regression models for the three phases. For all variables in the model, the 95% confidence intervals do not include unity, and all p values are less than .05, verifying statistical significance between the indicated variables and high cost. In the pretransplant phase, none of the examined variables were independently associated with high cost. For the transplant phase, Status 3 or 4 patients were more likely to be independently associated with a high cost than status 1 or 2 patients (Odds Ratio=4.4), as were patients requiring additional surgery (OR=3.36), and patients with biliary complications (OR=7.71). In the post-transplant phase, only CMV infection (OR=6.62) was found to be independently associated with high cost. For overall measured cost, status 2 vs 1 (OR=2.23), status 3 or 4 vs 1 (OR=11.97), CMV infection (OR=6.12), additional surgery (OR=4.22), and biliary complications (OR=5.0), were all independently associated with high cost.
Table 10  Logistic Regression Models Predicting High Cost

Transplant Phase

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Status 3-4 vs 1-2</td>
<td>4.40</td>
<td>1.28, 15.10</td>
<td>.0184</td>
</tr>
<tr>
<td>Additional OR</td>
<td>3.36</td>
<td>1.31, 8.62</td>
<td>.0116</td>
</tr>
<tr>
<td>Biliary Comp</td>
<td>7.71</td>
<td>2.00, 29.66</td>
<td>.0030</td>
</tr>
</tbody>
</table>

Post-Transplant Phase

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMV Infection</td>
<td>6.62</td>
<td>2.46, 17.79</td>
<td>.0002</td>
</tr>
</tbody>
</table>

Overall Cost

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Status 2 vs 1</td>
<td>4.33</td>
<td>1.61, 11.64</td>
<td>.0037</td>
</tr>
<tr>
<td>3-4 vs 1</td>
<td>11.97</td>
<td>2.67, 53.67</td>
<td>.0012</td>
</tr>
<tr>
<td>CMV Infection</td>
<td>6.12</td>
<td>2.04, 18.39</td>
<td>.0012</td>
</tr>
<tr>
<td>Additional OR</td>
<td>4.22</td>
<td>1.48, 12.04</td>
<td>.0070</td>
</tr>
<tr>
<td>Biliary Comp</td>
<td>5.00</td>
<td>1.23, 20.27</td>
<td>.0242</td>
</tr>
</tbody>
</table>

The nature of the data precluded formal sensitivity analysis, since costs were considered in two categories, above and below the median for each patient. Altering one cost category would have changed the costing order, and generated a new median value. In sensitivity analysis, it is expected that the dependent variable (in this case cost) will be changed because of the sensitivity of the result to changes in one or more of the independent variables. However, in the current analysis, the observed changes in cost would probably be due to changes in the median values, which determine the cutoff point of cost categories. A meaningful comparison to numbers generated through previous analyses would not have been possible. It was possible to examine the contribution made by the various elements to the significant high cost variables. Figures1
and 2 show the differences in the costs of the various elements for the low and high cost groups for each variable in the overall measured cost that were associated with a significantly increased cost. For the cost increase noted for patients with more severe liver disease, the costs of blood products, medications, and ICU stay were the largest contributors. The patients with CMV infection had higher costs in the medications, tests, ICU stay and ward stay elements, while patients with additional surgery and biliary complications had higher costs in all five of the examined elements.

The impact of changes in individual cost categories can be estimated. If total inpatient costs were to be reduced by decreased length of stay, the total overall measured cost would be reduced by a predictable amount. The extent to which length of stay could be reduced was evaluated by exploring the minimum and maximum mean lengths of stay reported in the literature. The shortest length of stay following liver transplantation appears to be that in the JPPC analysis, which estimates a length of stay of 16 days. The longest mean length of stay appears to be that reported by Massachusetts Blue Cross and Blue Shield at 61 days. Using these estimates as the limits of length of stay, and a mean cost of one hospital day of $1006.43 (the weighted mean cost of one day of ward and ICU stay in the current analysis), the effect that changes in length of stay would have on overall cost can be estimated (Table 1). While decreasing length of stay would reduce inpatient costs, it would not necessarily reduce overall costs, since required outpatient services would increase. It is possible that this could lead to an increase in overall costs.
In a similar fashion, the impact of changes in other variables could be explored. If the cost of testing was reduced by fifty percent, the total cost could be reduced by 6.7%. A fifty percent reduction in medication costs would reduce overall costs by 3.8%.

Table 11  Effect of Length of Stay on Mean Measured Cost

<table>
<thead>
<tr>
<th>Length of Stay (days)</th>
<th>Hospital Stay Cost</th>
<th>Total Mean Measured Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>16</td>
<td>16102.8</td>
<td>61892.9</td>
</tr>
<tr>
<td>21</td>
<td>21135.0</td>
<td>66925.1</td>
</tr>
<tr>
<td>30</td>
<td>30192.9</td>
<td>75983.0</td>
</tr>
<tr>
<td>43</td>
<td>43276.3</td>
<td>89066.4</td>
</tr>
<tr>
<td>50</td>
<td>50321.5</td>
<td>96111.6</td>
</tr>
<tr>
<td>61</td>
<td>61392.2</td>
<td>107182.3</td>
</tr>
</tbody>
</table>
Figure 1 Contribution of Elements to Total Cost by Complication
(Canadian Dollars)
Figure 2 Contribution of Elements to Total Cost by Complication
(Percentage of Total Cost)
Estimation of Additional Costs

It has been noted previously that costing was not attempted for the period prior to the placement of the patient on the waiting list. However, in determining the overall cost of a liver transplant, these costs are relevant. In preparation for the transplant costing project of the Ontario Joint Policy and Planning Committee <60>, the Toronto Hospital estimated the costs of a workup and pretransplant care based on actual program data. The costs of nursing, diagnostic tests, administration and professional services was estimated to be C$8059 in 1998. (unpublished data, S. McIntaggart, TTH).

The cost of the residents and interns involved in the care of these patients was not captured. However, it is possible to estimate these costs using the Professional Association of Interns and Residents of Ontario pay rates for postgraduate trainees. At any one time the transplant service was staffed by two fellows, one junior resident and one intern. For 1991 and 1992, a total of C$400733 would have been spent on housestaff salaries <78>. If we allocate this equally to all 121 patients, this adds C$3312 to the cost of each transplant. This allocation will not have been strictly correct, since patients who died would probably have received less care, long stay patients would have received more care, and some of the patients cared for would not have been part of this study. In addition, there would undoubtedly have been services provided to the study patients by housestaff not directly on the transplant service, particularly in the intensive care units.

The cost of outpatient follow-up care, including co-ordination, medical day unit costs, support staff and bloodwork, was not captured. However, this has been estimated to be C$9800 for the first 12 months in 1998 (unpublished data, S. McIntaggart, TTH). Assuming that follow-up for the second year would cost two-thirds of the amount for the first year, total follow-up costs C$16333.

Because the main purpose of the current study was to compare costs between patients treated in a relatively short period of time, issues of discounting and inflation adjustment have not been emphasized. However, in the estimation of the overall cost of liver transplantation, these issues cannot be ignored. Discounting is necessary because money spent today is
considered to be more valuable than money to be spent in the future. Costs to be incurred in the future are worth less in today’s dollars than costs incurred today. Discount rates used in the literature vary between 3 and 7 percent <61>. In the present analysis, the pretransplant and transplant phases almost invariably occurred within the same year, so discounting is not needed for these costs. However, the post-transplant costs extended for two years after the transplant. For the purposes of these calculations, year 0 is considered to be 1991, so costs incurred in that year are not discounted. All follow-up costs are assumed to have been incurred at the end of 1991. The formula for the adjustment of costs for the appropriate discount rate is:

\[ P = \sum F_n (1+r)^n \]

Where \( P \) = present value, \( F_n \) = future cost at year \( n \), \( r \) = discount rate

Value of post-transplant costs in 1991 is (assuming \( r = .05 \));

Discounted Post-Transplant Cost in 1991 dollars = \( \frac{F_{\text{Year 1}}}{1.05} + \frac{F_{\text{Year 2}}}{(1.05)^2} \)

Total measured costs of two years post-transplant was C$13418.77. If it is assumed that two-thirds of these costs were incurred in year 1 and one-third in year two;

\[
\text{Discounted Post-Transplant Cost in 1991 dollars} = \frac{8945.85}{1.05} + \frac{4472.92}{1.1025} = 12576.93
\]

For the purposes of calculating an overall mean cost for liver transplantation, this discounted value can be substituted for the measured value. This changes the overall transplant cost from C$89066.44 to C$88224.59.

For the estimated outpatient follow-up costs, which occur in the two years following transplantation

Discounted Estimated Follow-up Costs 1998 dollars = \( \frac{9800}{1.05} + \frac{6533}{1.1025} = 15259 \)

The costs which were incurred in 1991 needed to be adjusted for inflation to 1998 values to permit estimation of the mean overall costs of a liver transplant in 1998. The Health and
personal care item from the Canadian Consumer Price Index was used to adjust 1992 costs for inflation <84>. With 1992 as the index year, a cost incurred in 1992 is assigned a value of 100, and a cost incurred at the end of 1997 was worth 105.9. Therefore, 1992 costs must be multiplied by \( \frac{105.9}{100} = 1.059 \). Table 12 shows a summary of all costs involved in a liver transplant, including the mean of those captured in the present analysis, plus those estimated from other sources. All of these values have been discounted and adjusted for inflation.

Table 12  Estimated Total Transplant Cost in 1998 Canadian Dollars

<table>
<thead>
<tr>
<th>Description</th>
<th>1998 C$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Measured Total Transplant Cost 1998</td>
<td>94853</td>
</tr>
<tr>
<td>(Post-Transplant discounted .05 pa)</td>
<td></td>
</tr>
<tr>
<td>Estimated Transplant Work-up Cost 1998</td>
<td>8059</td>
</tr>
<tr>
<td>Estimated Housestaff Cost 1998</td>
<td>3561</td>
</tr>
<tr>
<td>Estimated Follow-up Cost 1998</td>
<td>15259</td>
</tr>
<tr>
<td>(Follow-up discounted .05 pa)</td>
<td></td>
</tr>
<tr>
<td>Total Liver Transplant Costs Including Estimates of Work-up, Housestaff and</td>
<td>121732</td>
</tr>
<tr>
<td>Follow-up Costs 1998</td>
<td></td>
</tr>
</tbody>
</table>
CHAPTER 5

DISCUSSION

Costing Methodology

This analysis has been carried out in accordance with established principles for costing analysis <61, 62, 75, 79>. The Canadian Coordinating Office for Health Technology Assessment (CCOHTA) outlines three steps for the costing of health care interventions <79>. These steps involve the identification of resources, the measurement of resource use, and cost valuation. For resource identification, the event pathways for the intervention and a comparator intervention should be identified. Relevant resource categories should be determined, and included or excluded based on the perspective of the analysis. The level of detail required for the analysis will depend upon the effect that the cost estimate will have on the analysis. It has been common in the literature for the term “direct costs” to refer to resources consumed in the health care system, and the term “indirect costs” to refer to the time of patients and their families consumed by the program <13>. However, Drummond et al have recently recommended that these terms be abandoned <61>. Direct costs sometimes have included patients’ out-of-pocket expenses, and resources from other agencies. Indirect costs is a term used by the accountancy profession to denote overhead costs. Both these terms may be confusing, and should be replaced by careful description of the viewpoint of the analysis.

The CCOHTA lists five possible methods for hospital inpatient costing with increasing levels of precision. These are: generic per diem rate, specialty per diem rate, cost per weighted case, patient specific costing, and micro costing. For the measurement of resource use, synthetic methods, such as administrative databases, expert panels or chart reviews can be used. Alternatively, primary data gathering or the prospective collection of data specifically for the study may be employed. Resource consumption should be recorded in “natural units”, such as number of services provided, and presented by category.

The process of assigning prices to the resources used should be reported in sufficient detail to allow the reader to assess the validity of the method. The price of each resource should
approximate its opportunity cost, which is the value foregone by not putting the resource into the next best alternative use. These costs are not easily calculated, and for the purpose of the current analysis, the price of the resources were considered to reflect their opportunity costs. Allowances for fixed capital and overhead costs should be made when relevant.

Cost estimates can be distorted by a number of possible biases. Three sources of bias have been identified by Jacobs et al <80>. **Methods bias** results from the use of a costing method that yields costs unrepresentative of the true opportunity cost. The use of prevailing prices and the use of average costs instead of incremental costs may lead to oversimplification. **Case or service mix bias** may occur if the costing method used does not take into account the severity of the patient’s condition and the resource consumption pattern specific to this category of patient. **Site selection bias** results from the use of data from institutions in which the prices are not reflective of those that prevail in the locations where the intervention will take place. Of these three potential biases, only methods bias is likely to be of concern in this analysis. However, since the main outcome of interest is a cost comparison between patients in the same setting having the same intervention, this is unlikely to have affected the outcome.

In the present analysis, patient specific costing has been used. Costs derived from the tracking of individual patients allowed the analysis to uncover cost differences between patients within a single Case Mix Group (CMG 310 - liver transplant). The greatest variable cost was inpatient ward and ICU costs, accounting for 48.54% of the overall measured cost. These costs were determined from Functional Centre Detailed Reports for the appropriate wards. After extracting drug costs, which were analyzed separately, the costs for nursing wages, materials and supplies were left. This total ward cost was divided by the number of inpatient days provided for the year. It was assumed that nursing care and supplies were divided equally between all patients on the ward on a given day. This is unlikely to be the case, since sicker patients would have required more care and consumed more resources. In the present analysis, it was not possible to measure actual nursing care provided and supplies consumed.

Methods of costing nursing services have been developed in the United States <63>. It is difficult to compare costs between institutions due to differences in cost allocation and patient acuity measurement. A Relative Value Matrix was developed in Massachusetts to identify
nursing care requirements and unit costs and to permit comparisons between institutions. Using a split-cost accounting system, routine inpatient services were disaggregated into hospital, patient day and nursing care components. The nursing care component represents the average nursing care requirements provided to patients according to their illness and day of stay. Data from 30,000 patients in five hospitals were collected. Patient acuity data were collected daily and translated into minutes using institution specific minute per point time factors. These were converted to standardized points to allow interinstitutional comparisons, and merged with diagnostic and demographic data. Costs were obtained from the Medicare Cost Report for 1983. The hourly cost of nursing care was calculated by dividing the cost allocated to nursing care by the total hours of nursing care. This hourly cost was applied to each case by diagnosis, procedure or DRG. Nursing costs varied greatly between institutions for equivalent DRGs. Direct salary costs were the largest contributors to total costs in all five hospitals. Total unit cost of nursing services varied from 1983US$21 to US$25 per hour.

A study that is more relevant to the Canadian situation was carried out in Toronto in 1993 <64>. The traditional Canadian system of funding hospitals based on a global budget reduced the need to determine costs based on case mix, as has been done in the US through DRGs. However, as funding has moved to be partially dependent on case mix, Case Mix Groups (CMG) and Resource Intensity Weights (RIW) have become essential. RIWs were initially based on New York State Service Intensity Weights. Nursing costs were initially based on per diem charges developed through expert consensus. Canadian patient cost data have since been developed using a methodology described in the MIS Guidelines<59>. CMGs do not incorporate a measure of nursing intensity. Nursing costs are treated as a per diem rate within the medical case mix. However, nursing costs should not be treated as fixed per diem amounts within medical diagnostic groups, since they vary both between and within diagnostic categories. Several attempts have been made to measure nursing workload to provide estimates of direct and indirect nursing care. These techniques are useful in determining total hours of nursing staff required to care for patients. The differences between nursing workload systems may make comparisons between institutions difficult, and the process of estimating hours of care may not be consistent. Cockerill et al <64> compared the four most commonly used nursing
classification systems. Records of 256 patients in four different nursing units in a hospital, representing 37 different cardiovascular CMGs were assessed in 1990. Within CMG groupings there were wide variations in the hours of care estimates. These variations in the estimates of individual patient care requirement by alternative systems indicate serious reliability and validity concerns. Use of any of these systems introduces a source of error into workload estimation that raises important questions about case costing. In case costing terms the total cost of a hospital is the sum of the products of the price and the quantity of all CMG cases. The price of an individual case is the sum of the products of the price and quantity of labor, capital and supplies. The allocation of quantities of labor to CMG cases is critical to the case costing process, especially since nursing labor cost is usually the largest single component of a case cost. In a review of the methodology involved in Case Mix Groups and Resource Intensity Weights, Pink and Bolley have noted that there are serious questions about the homogeneity of resource use within particular CMGs <65>. Differences in severity of illness, complications, therapies, drugs, hospital characteristics, physician training and specialization, and other factors not accounted for by CMGs, may lead to variations in specific case costs. A US study of medical intensive care unit costs concluded that there were dramatic differences in cost of care within DRGs <66>. These differences were largely on the basis of variations in length of stay.

In the present analysis there was no attempt to allocate nursing costs by CMG. The majority of cases would have been in CMG 310 (liver transplant), so using CMGs would not have allowed any further cost breakdown or differentiation. The majority of nursing care costs were from the SICU and 3GW cost centres. On 3GW, all of the patients were transplant recipients, so the CMGs would have all been similar. In any case, the unreliability of nursing workload measurement systems suggests that a case costing system of nursing cost allocation would not have been more accurate than simply dividing total ward costs (minus medication costs) by inpatient days.

In the SICU, there are may not have been dramatic differences in nursing workload costs between CMG cases, since the majority of the nursing care was provided on a 1 to 1 basis. A British study on ICU costs looked at patient and non-patient related costs for 68 patients <77>. An activity-based costing methodology was used which
collected comprehensive service provision data on bedside computer terminals. Hospital overhead was apportioned to the ICU by the percentage of floor area that the ICU occupied. The average daily cost was found to be $1152, with a standard deviation of 243.

The Management Information System (MIS) Guidelines were developed through a joint effort between federal and provincial governments and hospital associations in the 1980s to provide standard accounting systems for Canadian hospitals. In the MIS Guidelines, functional centres are identified by the basic services they provide. Allowance is built into the system for program interdependency, recognizing that patients follow program lines which cross the boundaries of functional centres. The main interest is determining the relationship between functional centre inputs (ie labor, supplies and capital) and functional centre outputs (ie activity and workload). Costing is done on a period basis to identify major sources of changes in resource use. Within functional centres, costs may change with workload. Fixed costs, such as compensation for management and operational support personnel and depreciation on major equipment, do not vary appreciably in the short run with workload. However, variable costs, such as compensation for unit-producing personnel and patient-specific supplies, tend to vary directly with workload. The output of a functional centre is assessed by the number of workload units produced. In calculating the unit costs for functional centres that deliver diagnostic services, the number of workload units is the denominator. In calculating productivity indicators for the functional centre, the workload measure becomes the numerator.

The implementation of the MIS Guidelines has allowed for costing of services provided to individual patients. Major components, such as direct and indirect costs and workload measurement data are recorded. Financial, statistical and patient care data are incorporated into a common database. After the collection of appropriate financial and statistical information, administrative and support service costs are allocated. The costs of functional centres that provide administrative and support services are assigned to the centres that provide nursing, diagnostic and therapeutic
services. Financial and statistical data from the charts are brought into an allocation matrix. The interdependence of hospital departments is described by the matrices of administrative and support services and indirect cost results. Since patient care areas do not exist in isolation, support services are required and must be accounted for. Cost information and workload measures are then brought together. The combination of full costs with statistical data allows the calculation of full unit costs, which must then be tied to the care and treatment of patients. Multiplying the number of units of service per procedure from workload measurement systems by the full unit cost yields the total cost of the procedure.

In order to determine the costs of diagnostic tests in the current analysis, MIS guidelines were used to estimate workload units for each test, and this was multiplied by the cost per unit of work estimated from the appropriate FCDR for each relevant laboratory. The total cost of each test for each patient was easily determined once the number of tests performed was known. An American study sought to estimate the cost savings achievable from reductions in laboratory test volume. A management system was developed for the chemistry laboratory that estimated the fixed costs, variable costs and total costs. These authors found that substantial savings could be realized by reducing low-volume, high-variable cost tests, as opposed to high-volume, low-variable cost tests. In the present analysis, a fifty percent reduction in test costs would lead to a 6.7% reduction in overall costs.

The cost of blood products was problematic, since the Red Cross was unable to provide an estimate of cost based on reliable data. There is very little information in the literature on this topic. However, a process-flow analysis was carried out at MD Anderson Cancer Center in Houston, which concluded that the cost of a two unit transfusion of RBCs in a patient with a solid tumor was US$548. Total transfusion costs were insensitive to reasonable variations in the direct costs of blood tests and the blood itself, or the probability or extent of transfusion reaction.

The costs of medications were determined from the hospital pharmacy master list. The values on this list reflect the amount the pharmacy charges the hospital wards for drugs. In setting the prices for the medications, it was assumed that pharmacy fixed and variable costs
were taken into consideration. Gouveia et al have designed a cost-accounting system in a hospital pharmacy department <72>. Pharmacy resource use was defined using dosage forms and drug products. Costs were defined as variable or fixed based on whether they related to a specific medication order. Time standards were developed using time and motion studies. A standard cost for each drug was based on the weighted average of volume and cost of the individual line items.

In the area of costing organ procurement, several costing problems were identified by the Ontario JPPC group <60>. Donor services were provided in many hospitals, not just transplant centres. Some of the costs were not truly incremental costs, and some costs were already included in global budgets. The care of donors and potential donors are partially covered under the Adjustment Factors formula for determining global budgets. The usual practice when abstracting the hospital chart of an organ donor is to set the time of death as the time of pronouncement of brain death. Therefore, any services provided after this time, including organ extraction, are not included in the case weight for that case, and are not funded. However, these services were provided, and the provincial health care system ultimately paid the bill. For the purposes of the current analysis, it was assumed the donor spent 12 hours in the ICU prior to surgery, and used two hours of operating room time. Costs at The Toronto Hospital were used as approximations for these costs for all donors. All other donor related costs were assumed to have been paid by the MORE program.
Statistical Issues

The largest single contributor to costs was inpatient hospital care. The combined cost of ICU and ward costs accounted for 48.54% of the overall measured cost. Tests accounted for 13.12% of the overall measured costs, but no other element exceeded 10%. Bivariate analysis yielded four significant contributors to overall cost; severe liver disease, CMV infection, severe rejection, and additional operative procedures. The highly skewed nature of the data, which persisted even after log-log transformation of the data, made multivariate analysis difficult. For each variable of interest, individual patients were classified as either low or high cost when compared to the median. Multiple logistic regression models analyzing the contribution of variables to overall cost demonstrated that patients admitted to the ICU were 11.97 times more likely to be in the high cost group than those waiting at home for their transplant. The other significant variables were all postoperative, and included CMV infection, additional surgery and biliary complications. In all cases, the combination of ICU and ward costs was dramatically higher in the high cost group. Formal sensitivity analysis was not possible, since altering one category of costs would change the order of the patients, and alter the separation of cases into low or high cost.

Cost-effectiveness analysis for liver transplantation requires several additional components. First of all, the cost of providing all non-transplant care to patients with end-stage liver disease right up to the time of death must be established. Liver transplant costing must be extended for a longer period, preferably to death but for at least ten years. In order to establish effectiveness for both transplant and non-transplant treatment, quality-adjusted life years gained must be measured using an appropriate utility instrument. It is possible with the existing literature and the data from this study to do a rough approximation of cost per life year gained. Drummond et al <61> have stated the general formula for cost-effectiveness analysis as; \((C - S) / E\), where C is the measured cost of the program, S is the savings of the program (ie the cost of the alternative program), and E represents the changes in effectiveness or health status, compared to an alternative. One study previously quoted found that the non-transplant costs of end-stage liver disease amounted to 49% of the costs of transplantation <4>. If a transplant cost $121732, the costs of non-transplant treatment can be estimated to be $59830.
The two-year survival following transplantation has been found to be .74, compared to .31 for non-transplant treatment <27>.

\[
\text{Cost per year of life gained} = \frac{121732 - 59830}{.74 - .31} \times 1 \text{ year}^* = \$143958
\]

* assuming approximately one year expectancy gain for each death averted

This cost per life year gained is very high due to the short timeframe under consideration. If the time interval was ten years, the non–transplant survival would be virtually nil, but the transplant survival would be fairly stable. Transplant costs would increase slowly during follow-up, while non-transplant costs may increase as the patient nears death.

**Comparison to Existing Transplant Costing Studies**

Evans et al have published extensively on costing issues in transplantation <1, 42, 45, 52, 76>. This group solicited charge data from transplant centres throughout the US. Centres were asked to voluntarily submit all information concerning charges made to third party payers for various transplant procedures. From all received data, a representative sample was selected for detailed analysis. The most significant problem with the analysis is that charge data has been used instead of true cost data. While allowances can be attempted by using global cost to charge ratios, the resulting data are not reliable. Also problematic is that many transplant centres, simply refused to provide data. The Evans data may be useful for comparing charges between sites, and charge changes over time, but it cannot be used for comparing costs between groups of patients.

The Quebec study on heart transplantation <50> undertook a thorough approach to costing similar to the present analysis, except that no attempt was made to include capital costs. Actual costs for 303 patients were measured, and found to be more uniform than liver transplant costs. The authors did not examine group-specific costs, but did provide estimates of the total transplant program costs.
The 1987 study from the Netherlands presented detailed patient-specific costing on 81 liver transplant patients, but did not identify cost differences between groups of patients <5>. The total cost to the end of the second follow-up year was US$105,104. The only study in the published literature which attempted group-specific costing analysis of liver transplantation <40> found that bacteremia, CMV infection, abdominal re-exploration, age <16, and high number of units of blood transfused were all independently associated with increased cost. These authors collected data on actual services provided to 66 patients enrolled in a randomized trial of CMV immune globulin prophylaxis. As with the present study, there was a strong correlation between length of stay and total cost. This correlation has also been noted by the Pittsburgh group <44>. The Canadian study from Halifax claimed to have analyzed actual costs for 48 consecutive transplants <37>. The mean total recipient cost was C$25,253 in 1994/95. This is much lower than any value in the published literature. Unfortunately, details were not received from the authors, so assessment of the methodology was not possible.

The analysis of transplant costing in Ontario by the JPPC group had been intended to include a statistical analysis of liver transplant costing data. However, this proved to be unworkable due to a number of concerns about their data, including limited population numbers, wide variation in patient costs, and lack of audited data. The extreme variation in the patient-specific data made meaningful analysis impossible <60>. This was a serious problem with the data from the current analysis as well. Separation of the costing data into values above and below the median was necessary to permit meaningful data assessment.

The Ontario JPPC group produced a series of recommendations for a costing methodology for solid organ transplants. It was recommended that the direct costs of transplants be estimated with a patient-focused standardized methodology. It was recommended that the costs of ambulatory care be collected and tracked, and the utilization of the health care system by transplant recipients audited on an ongoing basis. An activity-based, prospective analysis of the costs of the organ donation process was also recommended. These authors recognized the shortcomings of retrospective analyses. Care delivered in the past may not be representative of care to be delivered in the future. This is particularly true of transplantation, in which dramatic changes may occur over a short period of time. Also, changes in overall patterns of health care
delivery have reduced hospital lengths of stay for many surgical procedures <81>. The current analysis was based on patients treated in 1991 and 1992, in which the mean ICU stay was 9 days, and the mean ward stay was 34 days. For the data submitted to JPPC, The Toronto Hospital assumed an ICU stay of 4 days, and a ward stay of 12 days. This appears to have been based on a small number of analyzed cases, and may not be representative of current mean values.

Delivering appropriate medical care in the future may involve dramatic changes in the location of health care services. Rather than delineating costs based on service provision at a specific site, in the future funds may follow the patient. To this end, JPPC recommended a provincial call centre for transplant patients, an expanded Community Care System, internet-based information services, increased telemedicine services, and information services which expedite the collection of follow-up data <60>. The total direct cost for an adult liver transplant in 1998 in Ontario was found by this group to be C$85749, compared to the estimate of C$121732 derived in the current analysis. There are several reasons for the discrepancy in estimated total cost. The JPPC group did not include professional fees, organ transportation costs, or hospital overhead costs. In addition, the JPPC assumed a total hospital stay of 16 days, compared to the measured mean value of 43 days in the present analysis. For these reasons, the present analysis is likely to be a closer reflection of the true cost of liver transplantation. Also, the JPPC project did not specifically track individual patients, making comparisons of costs between groups of patients impossible.

Public Policy Implications

Univariate analysis of the data from this study showed that higher cost was associated with female sex, a diagnosis of alcoholic cirrhosis, age in the sixth decade, pretransplant status 3, the presence of severe rejection, CMV infection, additional operative procedure and biliary complication. Multivariate logistic regression based on classification to low or high cost about the median concluded that, status 2 vs 1, status 3 or 4 vs 1, CMV infection, additional operative procedure and biliary complication were associated with a statistically significant increased likelihood of high cost.

The methodology employed in this study could be used in any healthcare system where
appropriate functional centre costing is used. The findings of this analysis should be
generalizable to other transplant centres. In Canada, liver transplantation is performed in only
six teaching centres, and similar practices exist in all settings. Other Canadian programs appear
to have a similar mix of indications for transplantation <73>, although the severity of the liver
disease at the time of transplantation has not been published. Costs of organ retrieval should be
comparable throughout Canada, and medical fees are similar. It is difficult to predict whether or
not these findings are generalizable to US centres. The indications for transplantation are very
similar to the Canadian experience <32,39,74,83>, but the severity of disease is difficult to assess
from the published data. Differences in practices may result in significant variations in overall
costs. However, in all patient groups studied, the combination of ward and ICU costs accounted
for roughly fifty percent of overall costs. In all likelihood, variations in length of stay between
centres would more than compensate for differences in any other category. An overall reduction
in hospital length of stay may be more effective in reducing costs than any other single action.
However, outpatient costs would probably increase, so the overall effect on cost is difficult to
predict.

Other authors have found that higher status (more severe liver disease) <4, 42>, and
alcoholic cirrhosis <8> were associated with higher cost of liver transplantation. The failure of
the current study to show a significantly higher cost in alcoholic cirrhosis may have been due to
low patient numbers. If transplanting alcoholic patients does cost more than non-alcoholic
patients, possibly the selection of candidates for transplantation within this group needs to be
more carefully analyzed. Since some research has shown that alcoholic patients may not benefit
as much as other patients from liver transplantation <19>, there may be subgroups of alcoholic
cirrhotics for whom transplantation is not the best option. Alternatively, payments to institutions
performing transplantation may need to be adjusted for the case mix treated by diagnostic group.
The fact that costs are higher for patients with more severe liver disease suggests that patients
should be transplanted earlier in the course of their disease. The limiting factor is donor organ
availability.

Postoperative CMV infection has now been clearly identified as an independent indicator
of increased cost in liver transplantation. Strategies should be developed to reduce this
complication, which may include rejecting infected donors, immunization of recipients, or earlier treatment with gancyclovir or other medications. Biliary complications were found in the present analysis to significantly increase costs. This may be an issue of surgical technique which deserves further consideration. There are two main methods of biliary anastomosis, duct-to-duct and choledochojejunostomy. It is possible that one of these techniques is associated with higher cost, but this was not examined in the current analysis. It is also possible that the use of T-tubes to stent the biliary anastomosis may influence costs. More careful evaluation of these patients may give more specific information about precisely which complications were more expensive (leaks vs strictures) but the numbers of these complications were too small to permit independent analysis.
Limitations of This Study

A number of costs have not been included in this analysis for a variety of reasons. In order to properly cost a transplant program, it would be necessary to include all costs from the moment of referral to the transplant program. This would include those patients who are ultimately not transplanted. It would also include the entire workup of the patient for consideration for transplantation. Unfortunately, formal records were not kept of patients who were referred to the program but ultimately did not receive a transplant.

Medications that patients received as outpatients have not been captured, but in many cases these would have been paid for out of pocket and would not have been part of this analysis in any case. Professional services provided by Toronto Hospital attending physicians have been captured for this group since OHIP payment data were used. The costs of housestaff services have been estimated. It is critical to point out that throughout this analysis no costs paid by the patients or their families have been captured. The cost incurred by patients and their families for this procedure including the opportunity costs to them, time away from work, and transportation costs to and from the hospital is unknown. These are undoubtedly significant considerations from the standpoint of the patient. However, it was noted from the outset that the viewpoint for this analysis was third party payers.

In the present analysis the transplant phase has been costed in detail, and the vast majority of the appropriate costs have been captured. However, there were a number of areas in which there may be missing costs. Initially it had been intended to collect data on social work, home care, physiotherapy, and occupational therapy. However, from the charts it became very difficult to accurately determine how frequently these patients had been seen. An attempt was made to obtain data from the occupational and physiotherapy departments about services provided, but reliable data was not available. Services provided by housestaff including interns, residents, and fellows were not captured, but were estimated as noted previously. While most transplant costing studies have not included these costs, they clearly were costs borne by the Ontario government.

In the postoperative period, data is not included on any services provided outside The Toronto Hospital. Professional services provided by physicians and tests done at The Toronto
Hospital have been captured through physician billing records and the Ulticare System. Medical services provided at any other health institution in the postoperative period have not been captured. This is unlikely to be significant since the majority of patients with serious medical problems would have returned to the Toronto Hospital for their care.
CONCLUSIONS

The factors which impact on the cost of liver transplantation on Canadian adults were explored. From the perspective of the government of Ontario, the cost of liver transplantation from the date of placement on the waiting list to the end of the second year of follow-up was studied. The overall mean measured cost of liver transplantation was found to be C$89066.44 (range 30505.19-690431.10). When estimates of non-measured costs were included, appropriate discounting for follow-up costs carried out, and adjustments made for inflation, the cost in 1998 Canadian dollars was $121732.

High overall cost was observed with the preoperative factors; female sex, a diagnosis of alcoholic cirrhosis, age in the sixth decade, and in-hospital status prior to transplant. The postoperative factors that demonstrated high overall cost were severe rejection, CMV infection, additional operative procedure, and biliary complications. Bivariate analysis showed that the factors associated with high overall cost were; in-hospital status prior to transplant (p=.00167), CMV infection (p=.00411), severe rejection (p=.02040), and additional operative procedure (p=.00712). Multivariate logistic regression models were developed for costs of each phase and overall costs. There were no examined variables that predicted increased cost in the preoperative phase. In the transplant phase, in-hospital status prior to transplant (OR=4.40), additional operative procedure (OR=3.36) and biliary complications (OR=7.71) were associated with high cost. In the postoperative phase, the only variable associated with high cost was CMV infection (OR=6.62). For the overall measured cost of liver transplantation, the variables associated with high cost were, in-hospital status prior to transplant (OR= 11.97), CMV infection (OR=6.12), additional operative procedure (OR=4.22), and biliary complications (OR= 5.00). For all variables, the element that contributed the most to the high cost was in-hospital stay.

In order to reduce the cost of liver transplantation, a strategy of transplanting patients earlier in the course of their disease should be considered. The elimination of CMV infection, and the reduction of biliary complications may also be desirable.
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