An Exploration of the Cost of Liver Transplantation Using the OrganOx Normothermic Machine Perfusion in Comparison to Static Cold Storage in the Canadian Setting

by

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Abstract

Liver transplantation is life-saving but costly for the health care system, the patient and their caregivers. Over the last decade there has been a decrease in the available liver grafts leading to an increased use of extended criteria donors and an increase in the waitlist mortality rate. The development and use of machine perfusion have been an ongoing focus in liver transplantation research. The OrganOx machine allows for normothermic machine perfusion (NMP) of liver grafts at physiologic temperature, oxygenation, and blood pressure and flow. It allows for assessment of synthetic and metabolic function prior to transplantation. Clinical research has proven safety and feasibility of the OrganOx machine for use immediately post-procurement, after a period of static cold storage (SCS), and for rescuing liver grafts that have been deemed unsuitable for transplantation. The OrganOx machine increases liver quality, lowers transaminase injury, and increases the number of grafts available by decreasing the discard rate and rescuing grafts. The cost of the OrganOx machine must be considered in relation to the cost of transplantation. The liver transplantation process is made up of three phases: pre-transplantation, transplantation admission, and post-transplantation. The cost of each of these range widely with driving factors. Patient frailty, severity of liver disease, and overall severity of illness are key driving factors for cost.

The cost of the liver transplantation operation and cost per run of the OrganOx machine were calculated from 106 in-province procurements, 237 out-of-province procurements, and 343 liver transplantations. The total cost for in-province procurement and transplantation ranged from $30,770 to $35,659 ($CAD 2019), when considering

physician billing modifiers. The total cost for out-of-province procurement and in-province transplantation ranged from $44,636 to $48,076. The cost per run of the OrganOx machine ranged from $18,593 to $20,241, when considering the variability of the exchange rate from Great British pounds sterling to Canadian dollars.

The cost of the transplantation admission was calculated from a retrospective cohort study of 59 OrganOx patients propensity score-matched to 176 SCS patients from date and time of transplant to date and time of hospital discharge. A multiple linear regression adjusting for matching, model for end-stage liver disease sodium (MELDNa) at transplant, age at transplant, and acute or chronic liver failure was completed. The mean total cost of the transplantation admission for OrganOx patients was $155,318 ($CAD 2020) compared to $119,424 for SCS patients. The mean adjusted difference was significantly higher at $32,221 ($p=0.023$), with the majority from the cost of the OrganOx machine during the transplantation operation ($21,673, $p<0.001$). The subgroup analyses support the current literature that higher costs are driven by increased severity of liver disease, severity of overall illness, and by those who died in hospital post-transplantation.

A cost-utility analysis calculated the cumulative costs, mean costs, and incremental effectiveness of a liver transplant program using SCS and the OrganOx machine (NMP) compared to a liver transplant program using SCS alone (control). A Markov model compared these two approaches with a 1-year cycle over a 5-year time horizon from the public health care payer perspective. Primary cost data and transition probabilities from

a single center and health utility values from the literature were applied. Scenario analysis and probabilistic sensitivity analysis (PSA) were completed. The NMP approach is both cost-saving and cost-effective, dominating the control approach. The results remained robust in the scenario analysis. The PSA showed NMP was cost-effective 63% of the time at the conventional willingness-to-pay threshold of $50,000. The addition of NMP to a liver transplant program is both cost-savings and cost-effective with an increase in quality adjusted life years gained from the public health care payer perspective.

Overall, this thesis has shown that the addition of the OrganOx machine to a Canadian liver transplant program is cost-saving and cost-effective when compared to SCS alone. Additionally, it reduces burnout in the clinical operating room team, which will impact the societal cost of the OrganOx machine. The increased costs for implementation of this technology are substantial but an increase in the number of transplantations leads to a decrease in the number of people awaiting transplant and waitlist mortality rate. The addition of the OrganOx machine will help address the issues of supply and demand mismatch that Canadian transplantation programs are currently facing.

Preface

This thesis is an original work by Alexandria Webb. The research project, of which this thesis is a part, received research ethics approval from the University of Alberta Research Ethics Board – Health Panel, Project Name “Cost Effectiveness of the OrganOx Perfusion Machine for Liver Transplantation”, No. Pro00097695, February 12, 2020.

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AW was responsible for the literature review, analysis, and manuscript composition. AS, DE, and DB contributed to concept formation and manuscript composition.

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AW was responsible for data collection, analysis, and manuscript composition. EL contributed to concept formation, analysis, and manuscript composition. AS, DE, and DB contributed to concept formation and manuscript composition.

Chapter 7 of this thesis:

Webb, A.N., Wozniak, L.A., Shapiro, A.M.J., Eurich, D.T., Bigam, D.L. Impact of the OrganOx Normothermic Machine Perfusion on the Clinical Liver Transplantation Operating Room Team

AW was responsible for data collection, analysis, and manuscript composition. LA contributed to concept formation, analysis, and manuscript composition. AS, DE, and DB contributed to concept formation and manuscript composition.

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List of Abbreviations

AST – aspartate aminotransferase
ASTS – American Society of Transplant Surgeons'
BMI – body mass index
CADTH – Canadian Agency for Drugs and Technologies in Health
CEA – cost-effectiveness analysis
CIHI – Canadian Institute for Health Information
CRRT – continuous renal replacement therapy
CUA – cost-utility analysis
DBD – donation after brain death
DCD – donation after cardiac death
EAD – early allograft dysfunction
ECD – extended criteria donors
EQ-5D – European Quality of Life 5 Dimension
HOPE – Human Organ Procurement and Exchange
HTK – Histidine-tryptophan-ketoglutarate
ICER – incremental cost-effectiveness ratio
ICU – intensive care unit
IHD – intermittent hemodialysis
INR – international normalized ratio
LOS – length of stay
MARS – Molecular Absorbent Recirculating System
MELD – Model for end-stage liver disease
MELDNa – Model for end-stage liver disease sodium
NMP – normothermic machine perfusion
OECD – Organization for Economic Cooperation and Development
OPO – Organ Procurement Organization
PNF – primary non-function
PSA – probabilistic sensitivity analysis
QALY – quality adjusted life year

RBC – red blood cells

RCT – randomized control trail

SCD – standard criteria donors

SCS – static cold storage

SD – standard deviation

TPN – total parenteral nutrition

UofA – University of Alberta

UK – United Kingdom

WTP – willingness to pay

1 Introduction

1.1 Statement of the Problem

In 2019 chronic liver disease and cirrhosis was the fifth leading cause of death in Canada for people 25 through 64 years of age[1]. The only curative treatment for end-stage liver disease is liver transplantation. An overarching criterion for transplantation is that patients must be of sufficient physical and mental health to withstand the stress of transplantation. However, some patients become too sick due to long waitlists, leading to death while awaiting a transplant. Indeed, current estimates have waitlist mortality as high as 27%[2, 3]. As per the Canadian Institute for Health Information (CIHI), in 2019, there were approximately 500 adults on the waiting list for liver transplantation in Canada [3].

Organ donation in Canada has been on the rise over the last ten years, with donation after brain death (DBD) increasing by 21% and donation after cardiac death (DCD) increasing by 429% as of December 2018 [4]. However, the proportion of liver grafts used for successful transplantation is declining with the highest proportion in 2010 at 83% to the lowest proportion in 2018 at 60% [4]. The increasing prevalence of metabolic syndrome, diabetes, and obesity in an ageing population has led to lower quality liver grafts and higher discard rates. Not surprisingly, this has led to an increasing gap between the supply and demand for liver transplantation in Canada [5]. In an attempt to increase supply, there has been an acceptance of extended criteria donors (ECD). ECD has occurred in two waves. The first expansion is the conventional factors of liver steatosis, higher donor age, alcohol abuse, donor infection, DBD requiring vasopressor use, the elevation of liver function tests, and hypernatremia [6]. The second expansion is

considered the non-conventional factors of DCD and Hepatitis B and C infections [6]. The acceptance of ECD comes with the risk of post-transplant complications including biliary complications, early allograft dysfunction (EAD), hepatitis C re-infection, and graft failure due to the stress from static cold storage (SCS), reperfusion injury, and extended warm ischemia time in DCD [7-9].

Over the last decade there has been substantial research in the area of ex-vivo machine perfusion for liver grafts with four main protocols for this: hypothermic perfusion, hypothermic oxygenated perfusion, subnormothermic perfusion, and northothermic perfusion [10]. Multiple strategies exist for using machine perfusion in conjunction with static cold storage (SCS) [10]. The American Society of Transplant Surgeons (ASTS) in 2018 published a report on the standards of ex-vivo machine perfusion to discuss the role and required knowledge of this technology [11]. ASTS set six criteria for the ideal machine perfusion technology [11].

1. A preservation environment able to maintain cell viability for a prolonged time and halt preservation injury even in the most severely damaged grafts
2. An organ assessment platform capable of predicting posttransplant function
3. An opportunity to evaluate and recondition initially untranslatable grafts
4. Economic efficiency sufficient to encourage widespread use
5. The potential to be transportable to allow broader sharing of recovered and perfused grafts within our current policy (or reasonable policy revisions)
6. A reliable perfusion platform with a safe and dependable backup plan in case of device failure. [11]

Current research suggests that machine perfusion benefits include better graft function, targeted treatments specific to each graft while attached to the machine, and longer preservation periods allowing for more daytime transplantations [10]. The most significant proposed benefit of machine perfusion is the ability to assess the viability of the graft with the potential to increase available grafts for transplantation and lower the discard rate [10]. To date, the clinical research has been focused mostly on criteria 1 through 3. Criteria 4 is an important aspect of health care technology decisions and should be considered once safety is established and comparable clinical outcomes are proven. Currently, the economic evaluations of this technology are limited.

One ex-vivo machine is the OrganOx metra, developed by OrganOx Ltd. in the United Kingdom, used for normothermic machine perfusion (NMP) [12]. The OrganOx machine perfuses the liver graft at physiologic temperatures, blood pressure and flow, and oxygenation [12]. Throughout the perfusion both metabolic and synthetic function of the graft can be assessed by the transplant surgeon leading to a better informed decision on graft viability [12]. There have been seven clinical studies that have proven the safety and feasibility of the OrganOx machine with promising clinical results [13-19]. There have been four studies, including a randomized control trial, that have compared the OrganOx to SCS, which have shown comparable clinical outcomes for length of stay, biliary complications, primary non-function, early allograft dysfunction, graft survival, and patient survival [14, 17-19]. Safety and feasibility have also been proven in two studies comparing perfusion of OrganOx after a period of SCS to immediate perfusion on OrganOx after procurement [13, 15]. A study using the OrganOx to rescue liver grafts that

have been deemed unsuitable for transplantation has also been proven safe and feasible [16]. The use of OrganOx clinically looks promising but the cost to the health care system still requires further exploration. A cost-utility analysis based out of the United Kingdom has been completed and has shown the OrganOx machine to be cost-effective with an incremental cost effectiveness ratio of £7,876 per quality adjusted life year gained in 2018 Great British pounds sterling at a willingness to pay threshold of £20,000 [20]. The cost of the OrganOx machine and cost-effectiveness has not been explored in a Canadian setting. There are likely differences in the patient population and health care systems between countries that may impact cost. Therefore, further research about the cost of this technology and economic effectiveness is required in a Canadian setting before Canadian transplant programs can decide about implementing this technology.

1.2 Summary

The supply and demand of grafts for liver transplantation is mismatched as a smaller proportion of liver grafts are used, leading to waitlist mortality. The lack of ideal liver grafts is secondary to an ageing population with an increasing prevalence of obesity, diabetes, and metabolic syndrome. In efforts to address this mismatch, the transplantation of ECD has increased but at the risk of more post-transplantation complications and death. The use of ex-vivo machine perfusion may improve liver grafts and allow for assessment of viability to increase the number of available transplantable liver grafts. The OrganOx machine used for NMP has shown promising clinical outcomes, with cost-effectiveness proven in the United Kingdom. The economic impacts of this technology are yet to be assessed in a Canadian setting.

1.3 Objectives of this Thesis

1. To synthesize the current research, including clinical outcomes and the potential role the OrganOx machine, in liver transplantations.
2. To understand the cost and driving factors of the liver transplantation process from the perspective of pre-transplantation, transplantation admission, and post-transplantation.
3. To determine the average actual cost of a liver transplantation operation, considering the location of procurement, and the cost of the OrganOx machine per run.
4. To determine the cost of the index transplantation admission and the difference between the NMP and SCS groups.
5. To determine the cumulative cost and incremental cost-effectiveness of a liver transplant program using both the OrganOx machine and SCS to a program using SCS alone.
6. To determine the impacts on well-being from the implementation of the OrganOx machine on the clinical operating room team.

The first objective was addressed through a literature review of the clinical studies using the OrganOx machine. This review also identified two areas of limited research that is required for further decisions about OrganOx machine implementation in liver transplantation programs (Chapter 2). The second objective was addressed through a literature review of studies looking at the cost of the various components of the

transplantation process and factors that have been associated with increased costs (Chapter 3). The third objective was addressed by micro-costing in-province liver procurement, out-of-province liver procurement, liver transplantation, and one run of OrganOx (Chapter 4). The fourth objective was addressed by a retrospective propensity score matched cohort study analyzed with multiple linear regression (Chapter 5). The fifth objective was addressed by a cost-utility analysis using a Markov model comparing two transplant programs in 1 year cycle lengths over a 5-year time horizon from the public health care payer perspective (Chapter 6). The sixth objective was addressed with the completion of a survey about well-being by the clinical operating room team with calculation of frequency of responses and summative content analysis (Chapter 7).

1.4 References

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2 Clinical Normothermic Liver Preservation with the OrganOx Metra – Outcomes and Areas for Further Research

Webb, A.N., Shapiro, A.M.J., Eurich, D.T., Bigam, D.L.

2.1 Abstract

Liver transplantation graft supply does not equal the required demand. There has been an increased use of extended criteria donors (ECD) to help address this. They are more susceptible to damage from static cold storage (SCS) with increasing complications post-transplantation. Over the last decade there has been substantial research into the use of ex-vivo perfusion in liver transplantation, especially for ECD. The OrganOx machine is a normothermic machine perfusion (NMP) device used to preserve and assess grafts' viability before transplantation. Clinical studies have proven feasibility and safety in three distinct clinical settings. The first is the use of NMP immediately after procurement in comparison to SCS. The second is the use of NMP post-SCS in comparison to NMP immediately after procurement. The third is the use of NMP to rescue grafts that initially were deemed unsuitable for transplantation. Studies have shown that the use of OrganOx has led to a lower discard rate and rescue of grafts leading to an increase in the number of successful transplantations. In addition to larger clinical studies further research is required to build standardized viability perfusion characteristics and cost analyses to assess whether the upfront costs of the technology justify the projected benefits.

2.2 Introduction

There is an ever-widening gap between increasing waitlist for liver transplantation and limited liver supply. The Canadian Institute for Health Information (CIHI) documented that while organ donation has risen over the last 10 years the proportion of liver grafts used has been declining, with the highest proportion of 82.7 in 2010 to 59.5 in 2018 [4].

This has led to an increasing waitlist mortality rate. CIHI documented waitlist mortality of 26.6% in 2019, an increase from 22.4% in 2018 [3, 21]. This has been documented despite an increase in the use of extended criteria donors (ECD) [7, 8]. The use of ECD is an important aspect to help address the mismatched supply and demand. This has come with its own concerns due to ECD having less ability to withstand the effects of static cold storage (SCS) and having an increased risk of complications post-transplant [7, 8].

To help address both the mismatched supply and demand of liver grafts and the complications from ECD use the development of ex-vivo machine perfusion has grown substantially over the last decade. There are many different protocols for machine perfusion [10, 22]. One of the common protocols is normothermic machine perfusion (NMP), where the graft is kept between 35-38 degrees Celsius [10, 22]. There are three machines available for NMP: OrganOx, Liver Assist, and Organ Care System [10].

The OrganOx metra machine was built by OrganOx Ltd, a United Kingdom based company [12]. The machine is used for NMP of liver grafts, where physiologic blood flow and pressure, temperature, and oxygenation are maintained [12]. Transplant surgeons are able to assess the synthetic and metabolic function of the liver graft throughout NMP allowing for a more informed decision about graft suitability for transplantation [12]. Throughout this review the use of NMP will be synonymous with OrganOx unless otherwise noted. This review will look at the clinical outcomes of the OrganOx and areas requiring further research to better inform transplant programs about the implications of implementing this technology.

2.3 Overview of OrganOx Studies

The first study published on the use of the OrganOx machine was by Ravikumar et al. from the United Kingdom [18]. This was a Phase 1 trial of the OrganOx machine with the primary endpoint of 30-day graft survival [18]. This study compared 20 NMP grafts with 40 matched SCS grafts [18]. This was quickly followed by the first North American study on the OrganOx machine by Selzner et al. from Toronto, Ontario [19]. It was a pilot study using Steen™ solution as opposed to Gelofusine® [19]. This study compared 10 NMP grafts with 30 matched SCS grafts and proved safety with the use of Steen solution [19]. A second North American study by Bral et al. from Edmonton, Alberta followed with the preliminary results from their clinical trial [14]. This study compared 10 NMP grafts with 30 matched SCS grafts with the primary endpoint of 30-day graft survival [14]. In 2018 a ground-breaking randomized control trial (RCT) was published in Nature by Nasralla et al. comparing NMP and SCS [23]. To date this is the largest study on NMP and the only RCT of NMP published at this time. This RCT had 121 NMP patients and 101 SCS patients [23]. This study showed promising results in all areas from the use of the OrganOx machine [23]. These four studies all proved the safety and feasibility of using the OrganOx machine in liver transplantation [14, 18, 19, 23].

In these four studies all grafts were placed onto the OrganOx machine immediately after procurement at the donor hospital [14, 18, 19, 23]. If the donor and recipient hospitals are different there are additional costs and logistical considerations for the additional personnel and space required to safely monitor and transport the OrganOx machine,

especially in countries where the distances are large and planes are required for transport [13, 19]. This consideration was explored in two studies. Bral et al. 'base-to-base' study compared grafts that underwent procurement and SCS until return to the recipient hospital where it was then run on NMP (SCS-NMP, n=26) to grafts that were locally procured and run on NMP immediately (NMP, n=17) [13]. The primary endpoint was 30-day graft and patient survival [13]. Ceresa et al. compared grafts that underwent SCS prior to NMP (n=30) to grafts that were immediately were run on NMP (n=104) with the primary endpoint of 30-day graft survival [15]. These two studies proved safety and feasibility of a period of SCS prior to NMP [13, 15].

A United Kingdom based case series by Mergental et al. was published in 2016 on the safety of transplantation of grafts that were going to be discarded but were then rescued with the use of NMP [24]. Out of the 5 successful transplantations 1 of them was perfused using the OrganOx machine while the other 4 used the Organ Assist machine [24]. Due to this study only having 1 OrganOx liver graft the detailed results of this case series will not be further discussed. This group then went on to complete the Phase 2 viability testing and transplantation of marginal livers (VITTAL) clinical trial [16]. This study looked at the feasibility of using NMP for viability testing of grafts that were initially discarded followed by successful transplantation [16]. This study looked at 31 initially declined liver grafts initially procured to SCS and then run on NMP, where 22 (71.0%) grafts were successfully transplanted [16]. This study assessed the viability criteria used for discarded grafts on NMP and patient outcomes of the 22 grafts compared to 44 matched controls [16].

These eight studies have provided substantial initial knowledge about the use of the OrganOx machine in liver transplantation. This review will look at the outcomes from these studies in regards graft survival, patient survival, laboratory findings, length of stay (LOS), primary non-function (PNF), early allograft dysfunction (EAD), biliary complications, major complications as per the Clavein-Dindo classification, re-transplantation rates, discard rates and the number of additional livers transplanted.

2.3.1 Graft Survival

NMP compared to SCS

Ravikumar et al. had a 30-day and 6-month graft survival of 100% for NMP versus 97.5% for SCS, due to a postoperative day 0 cardiovascular event for one control patient (**Table 2-1**) [18]. Selzner et al. had a 3-month graft survival of 100% for both the NMP and SCS groups [19]. Bral et al. initially had 10 livers in the NMP group but 1 (10%) liver was unable to undergo perfusion secondary to an occult portal venous twist and the graft was discarded [14]. The intention to treat 30-day graft survival was 90% in the NMP group, due to the discarded graft, and 100% in the SCS group; this difference was not significant [14]. At 6 months, the graft survival was 80.0% for the NMP group and 100% for the SCS group, which was also not significant [14]. Nasralla et al. had a 1-year graft survival of 95% for NMP and 96% for SCS, which did not reach statistical significance [23]. There were 6 (5%) graft failures in the NMP group, which led to 3 (2.5%) deaths [23]. There were 4 (4%) graft failures in the SCS group, which led to 2 (2%) deaths [23]. Overall, graft survival was comparable between groups in all four studies.

SCS followed by NMP compared to immediate NMP

Bral et al. had a 30-day and 3-month graft survival of 100% for both groups [13]. At 6-months, graft survival was not significantly different between groups, the SCS-NMP group had 1 (3.8%) re-transplant and the NMP group had 1 (3.8%) graft loss secondary to hepatitis C infection [13]. Ceresa et al. had a 30-day graft survival of 94% due to 2 (6.5%) graft losses secondary to hepatic artery thrombosis [15]. At 1 year, the graft survival was 84% for SCS-NMP and 94% for NMP, not reaching a significant difference [15]. Overall, the graft survival was not different between groups for these two studies.

NMP rescued grafts compared to matched controls

Mergental et al. had a 90-day graft survival of 100% for the NMP group and 93.2% for the control group [16]. At 1-year graft survival was 86.4% for the NMP group and 86.4% for the control group [16].

2.3.2 Patient Survival

NMP compared to SCS

Ravikumar et al. had a 30-day and 6-month patient survival of 100% for NMP versus 97.5% for SCS, with 1 control patient death on postoperative day 0 from a cardiovascular event (**Table 2-1**) [18]. At one year, the NMP patient survival was 95% after 1 death secondary to alcohol [18]. Selzner et al. had a 3-month patient survival of 100% for both the NMP and SCS groups [19]. Bral et al. had a 30-day patient survival of 100% for both groups [14]. At 6 months the patient survival was 89.0% in the NMP group

after 1 patient died at 3 months post-transplant secondary to recurrent hepatitis C [14]. The SCS group had a patient survival of 100% at 6 months [14]. Nasralla et al. documented 10 deaths during their study period, 6 (5%) in the NMP group and 4 (4%) in the SCS group [23]. At 1 year, patient survival was 95.8% in the NMP group and 97% in the SCS group; the difference did not reach statistical significance [23]. Overall, patient survival was comparable between both groups in all four studies.

SCS followed by NMP compared to immediate NMP

Bral et al. had a 30-day patient survival of 100% in both groups [13]. At 3 and 6 months the SCS-NMP group had 100% patient survival and the NMP group had 88% patient survival [13]. Ceresa et al. had a 1-year patient survival of 90% in the SCS-NMP group and survival for the NMP group is not presented [15].

NMP rescued grafts compared to matched controls

Mergental et al. had a 90-day patient survival of 100% in both groups and a 1-year patient survival of 100% in the NMP group and 95.5% in the control group [16].

2.3.3 Laboratory Findings

NMP compared to SCS

Ravikumar et al. found that the peak aspartate aminotransferase (AST) level in the first seven days was significantly lower in the NMP group than in the SCS control group (**Table 2-2**) [18]. The bilirubin and international normalized ratio (INR) levels were not statistically different on day seven [18]. Selzner et al. found that peak AST levels in the

first 48 hours and ALP levels at 1 week were both non-significantly lower in the NMP group compared to the SCS group [19]. At 1 week the INR and bilirubin were comparable between the NMP and SCS group [19]. Bral et al. found that the peak AST level in the first 7 days was non-significantly higher in the NMP group compared to the SCS group [14]. At 1 week the INR was comparable and bilirubin was non-significantly higher in the NMP group [14]. Nasralla et al. found that the peak AST level in the first 7 days was significantly lower by 49.4% in the NMP group [23]. In subgroup analysis, the NMP group had significantly lower peak AST levels for both DBD and DCD grafts [23]. In the first week the INR was not significantly different with both groups having an average of 1.1 and bilirubin was significantly lower in the NMP group [23]. Overall, 2 of these studies showed a significantly lower peak AST in the NMP group, the bilirubin was usually lower in the NMP group with 1 study showing statistical significance and comparable INR between groups in all studies.

SCS followed by NMP compared to immediate NMP

Bral et al. found that peak AST levels in the first 7 days was non- significantly higher in the SCS-NMP group (**Table 2-2**) [13]. In the first week the peak value of INR was comparable, and bilirubin was non-significantly higher in the NMP group [13]. Ceresa et al. found that the peak AST levels in the first 7 days was comparable between groups [15]. Overall, the peak AST was not statistically different between groups in these two studies.

NMP rescued grafts compared to matched controls

Mergental et al. did not comment on the laboratory values post-transplantation [16].

2.3.4 Length of Stay

NMP compared to SCS

Ravikumar et al. had a comparable LOS between groups, with intensive care unit (ICU) median being 3 days for both groups and ward stay median being 12 for NMP and 14 for SCS (**Table 2-3**) [18]. Selzner et al. had comparable LOS between groups, with the median ICU LOS of 1 for NMP and 2 for SCS and a median total LOS of 11 for NMP and 13 for SCS [19]. Additionally, 3 NMP patients and 5 SCS patients did not require a post-transplantation admission to ICU [19]. Bral et al. found that both the ICU LOS and total LOS for the NMP group were significantly longer [14]. The NMP group had a median ICU LOS of 16 days and a total LOS of 45 days in comparison to 4 days and 25 days for the SCS group [14]. Nasralla et al. found that the ICU LOS and total LOS were not significantly different between groups [23]. Overall, the ICU LOS and total length of stay were comparable between groups in 3 studies with LOS being significantly higher in 1 study.

SCS followed by NMP compared to immediate NMP

Bral et al. had a significantly shorter ICU LOS (2 days vs. 6 days) and total hospital LOS (16 days vs. 43 days) for the SCS-NMP group in comparison to the NMP group respectively (**Table 2-3**) [13]. Ceresa et al. had comparable ICU LOS and total LOS between groups, with a median ICU LOS of 3 days for SCS-NMP and 4 days for NMP and median total LOS of 13 days for SCS-NMP and 14 days for NMP [15]. Overall, 1

study showed both the ICU and total LOS to be significantly shorter for the SCS-NMP group while the other study had comparable LOS.

NMP rescued grafts compared to matched controls

Mergental et al. had comparable ICU LOS and total hospital LOS, with a median ICU LOS of 3.5 days for the NMP group and 2 days for the control group and median total LOS of 10 days for the NMP group and 9 days for the control group (**Table 2-3**) [16].

2.3.5 Primary Non-Function

PNF was defined as liver graft dysfunction that was permanent and led to death or re-transplantation within the first 10 days post-operatively [23]. The PNF results for the four studies comparing NMP with SCS are as follows. Ravikumar et al., Selzner et al., and Bral et al. had no PNF in either group [14, 18, 19]. Nasralla et al. had 1 (0.8%) NMP patient experience PNF and no SCS patients [23]. Neither of the studies comparing SCS followed by NMP and immediate NMP had PNF in either group [13, 15]. The study by Mergental et al. looking at rescued grafts had no PNF in the NMP group and 1 (2.3%) patient in the control group [16]. Overall, there was only 1 NMP graft that had PNF in all of these studies.

2.3.6 Early Allograft Dysfunction

EAD was defined as an INR of greater than 1.6 on postoperative day 7, a peak AST of >2000 international units/L during the first 7 days post-operatively, or a bilirubin of greater than 170 μmol/L on postoperative day 7 [23].

NMP compared to SCS

Ravikumar et al. had 3 (15%) NMP patients and 9 (22.5%) SCS patients with EAD [18]. EAD rates were higher when specifically analyzing DCD grafts, 1 NMP (25%) and 4 SCS (50%) [18]. Selzner et al. did not comment on EAD in their study [19]. Bral et al. had 5 (55.5%) NMP patients and 8 (29.6%) SCS patients demonstrate EAD, however, this did not reach statistical significance [14]. Nasralla et al. had a significantly lower rate of EAD in the NMP group with 12 (10.1%) NMP patients and 29 (29.9%) SCS patients demonstrating EAD [23]. Overall, 2 studies showed lower rates of EAD in the NMP group with 1 study showing higher rates of EAD in the NMP group.

SCS followed by NMP compared to immediate NMP

Bral et al. found that the SCS-NMP group had a non-significantly lower incidence of EAD in comparison to the NMP group (19% versus 35%) [13]. Ceresa et al. had comparable rates with 13% in the SCS-NMP group and 11% in the NMP group experience EAD [15]. Neither of these studies reached statistical significance.

NMP rescued grafts compared to matched controls

Mergental et al. found a significantly higher rate of EAD in the NMP group, with 7 (31.8%) patients in the NMP group and 4 (9.1%) patients in the control group [16].

2.3.7 Biliary Complications

NMP compared to SCS

Ravikumar et al. had 4 (20%) anastomotic biliary strictures in the NMP group, all in DBD grafts [18]. Selzner et al. had no biliary complications in the NMP group while the SCS group had biliary strictures, but no specific numbers were presented [19]. Bral et al. had no biliary complications in the NMP group but the SCS group had 4 (14.8%), while the location of stricture was not presented [14]. Nasralla et al. documented anastomotic strictures, non-anastomotic strictures, and ischemic cholangiopathy all of which were not significantly different between the NMP and SCS groups [23]. For anastomotic strictures the subgroup analyses for the DCD grafts showed there were 13 (48.1%) NMP patients and 11 (57.9%) SCS patients and for the DBD grafts there were 22 (40.7%) NMP patients and 23 (41.8%) SCS patients [23]. For non-anastomotic strictures the subgroup analyses for the DCD grafts showed there were 3 (11.1%) NMP patients and 5 (26.3%) SCS patients and for DBD grafts there were 4 (7.4%) NMP patients and 3 (5.4%) SCS patients [23]. For ischemic cholangiopathy there was 1 (0.8%) NMP patient and 1 (1%) SCS patient who underwent re-transplantation in the first year [23]. Overall, no study showed significantly different rates of biliary complications between groups.

SCS followed by NMP compared to immediate NMP

Bral et al. documented both non-anastomotic and anastomotic strictures, with no significant differences between groups. The SCS-NMP group had 4 (15%) biliary complications, where 2 (7.7%) were non-anastomotic and 2 (7.7%) were anastomotic [13]. The NMP group had 4 (24%) biliary complications, where all 4 were anastomotic [13]. There was no ischemic cholangiopathy in the study population [13]. Ceresa et al. documented 1 (3.2%) anastomotic stricture and 1 (3.2%) anastomotic leak in the SCS-

NMP group with no ischemic cholangiopathy [15]. Overall, there were no significantly different rates of biliary complications between groups in these two studies.

NMP rescued grafts compared to matched controls

Mergental et al. documented both non-anastomotic and anastomotic strictures in both groups, with non-significantly higher rates in the NMP group [16]. The NMP group had 4 (18.2%) patients with non-anastomotic strictures and 2 (9.1%) patients with anastomotic strictures, with higher frequency in DCD grafts compared to DBD grafts [16]. The control group had 1 (2.3%) non-anastomotic stricture and 3 (6.8%) anastomotic strictures [16].

2.3.8 Major Complications

NMP compared to SCS

Ravikumar et al. does not comment specifically on rates of grade 3 or higher Clavien-Dindo complications but 4 (20%) patients had documented sepsis who may have required intervention [18]. Selzner et al. classified major complications as grade 3b or higher, which was documented in 1 (10%) NMP patient and 7 (23%) SCS patients [19]. Bral et al. classified major complications as grade 3 or higher, which was documented in 2 (22%) NMP patients and 10 (37%) SCS patients [14]. Nasralla et al. classified major complications as grade 3b or higher, where 21 (16.4%) NMP patients and 36 (22%) SCS patients had documented major complications [23]. Overall, the rates of major complications were comparable between groups.

SCS followed by NMP compared to immediate NMP

Bral et al. did not comment on the overall complication rate [13]. Ceresa et al. classified major complications as grade 3b or higher, with 23% in the SCS-NMP group and 24% in the NMP group [15].

NMP rescued grafts compared to matched controls

Mergental et al. classified complications as grade 3b or higher, where the complication rate between groups was not significantly different [16]. The NMP group had 7 (31.8%) patients and the control group had 17 (38.6%) patients experience major complications [16].

2.3.9 Re-transplantation rates

NMP compared to SCS

Ravikumar et al., Selzner et al., and Bral et al. did not have any patients that required re-transplantation during their study period [14, 18, 19]. Nasralla et al. documented 3 (2.5%) NMP patients and 2 (2%) SCS patients undergoing re-transplantation during their study period [23]. In each group 1 re-transplant was for ischemic cholangiopathy and the other causes of re-transplantation are not directly mentioned [23].

SCS followed by NMP compared to immediate NMP

Bral et al. had 1 (3.8%) re-transplantation in the SCS-NMP group, which was due ongoing biliary sepsis secondary to stenosis of venous and arterial flow [13]. Ceresa et al. had 2 (6.5%) re-transplantations in the SCS-NMP group due to hepatic artery thrombosis [15].

NMP rescued grafts compared to matched controls

Mergental et al. had 4 (18.2%) re-transplantations in the NMP group during their study period; indication was not documented [16].

2.3.10 Discard Rate

In the RCT by Nasralla et al. the discard rate was significantly lower in the NMP group, where there were 16 (11.7%) livers in the NMP group and 32 (24.1%) livers in the SCS group [23]. Bral et al. discarded 3 (6.5%) grafts from the SCS-NMP group due to poor clearance of lactate during NMP [13]. Ceresa et al. discarded 3 (8.8%) grafts from the SCS-NMP group due poor functioning while on NMP [15]. Mergental et al. discarded 9 (29%) grafts after attempted rescue using NMP; however, these grafts had already been deemed unsuitable for transplantation [16]. The commonality in all of these studies is that the discarded grafts did not show good viability, as per their research teams, during NMP, and the decision was made to discard the graft.

A recent study from the US looked at the discard rate between NMP and SCS in all liver grafts; of note, this was for all NMP machines and not specifically for OrganOx [25]. MacConmara et al. found the NMP group had a discard rate of 3.5%, which was significantly lower than the discard rate of 13.3% in the SCS group [25]. This low discard rate was despite the fact that significantly more ECD underwent NMP than SCS [25]. The use of NMP led to a 73.5% reduction in the discard rate [25]. Therefore, the use of NMP

allows for a reduced discard rate thereby making more grafts available for transplantation.

2.3.11 Additional Livers Transplanted

One of the many proposed benefits of the NMP is the ability to rescue marginal and potentially discarded liver grafts allowing for more transplantations to help close the gap between supply and demand [10]. Mergental et al. looked to prove the ability to rescue liver grafts that had been declined by multiple transplant surgeons [16]. In their study 31 grafts deemed unsuitable for transplantation underwent NMP and 22 (71%) met the pre-determined viability criteria leading to successful transplantation [16]. This led to a rescue rate of 71%, which was statistically significant [16]. This study not only proved the feasibility of rescuing grafts with the use of NMP but also suggests that the use of this technology would lead to a significant increase in the number of available grafts for transplantation [16].

2.3.12 Summary

These studies have proved the feasibility and safety of using the OrganOx in three different settings. Firstly, the use of NMP immediately after procurement in comparison to SCS. Secondly, the use of NMP after a period of SCS, usually due to travel from a remote donor hospital site, compared to NMP immediately after procurement. Thirdly, the use of NMP in grafts that have been deemed unsuitable for transplantation and had a period of SCS prior to NMP.

These studies have proven that further research of clinical normothermic liver preservation technology is warranted. The majority of these studies have been small sized trials and larger trials are required to further build knowledge about the use of the OrganOx. Currently, there are two Canadian clinical trials and a multi-center RCT in the United States ongoing [26-28]. In addition to larger trials for clinical outcomes, there are a couple of specific areas that require further research. This includes, but is not exclusive to, the pre-defined viability perfusion characteristics and cost analyses.

2.4 Viability Perfusion Characteristics

Currently, there are no agreed upon viability criteria to be met for grafts while on the OrganOx machine. There has been documentation of perfusion characteristics from various studies (**Table 2-4**), but further research is required to create standardized viability criteria. There are three main criteria: synthetic, hemodynamic, and metabolic parameters [23].

The RCT by Nasralla et al. presented the average perfusion characteristics of the grafts that went on to successful transplantation after NMP [23]. The synthetic parameter was bile production at 9.17 mL/h; however, not all successfully transplanted grafts produced bile and this did not impair outcomes [23]. The hemodynamic parameters were portal vein flow at 1.11 L/min and hepatic artery flow at 280 mL/min [23]. The metabolic parameters were lactate clearance of 9.99 mmol/L at 15 min to 0.93 mmol/L at 4 hours and pH of 7.31 [23].

Mergental et al. set validity criteria that were required to be met within the first 4 hours of NMP for the graft to be transplanted [16]. All grafts had to have lactate clearance of less than or equal to 2.5 mmol/L [16]. In addition, the grafts had to meet two or more of these criteria: pH greater or equal to 7.30, homogenous perfusion, evidence of bile production, metabolism of glucose, and portal venous flow greater or equal to 500 mL/min and hepatic artery flow of greater or equal to 150 mL/min [16].

The perfusion characteristics documented in the 4 four studies are similar to the pre-determined viability criteria used in Mergenetal et al. (**Table 2-4**) [13, 15, 16, 19, 23]. However, further work is required to have consensus on standardizing these viability criteria. These criteria are important to ensure liver grafts are suitable for transplantation after NMP to allow for an increase in the number of grafts available for transplantation, thereby helping fill the gap between supply and demand.

2.5 Cost Analysis

The focus of OrganOx research thus far has been primarily on safety, feasibility, and clinical outcomes. The study outcomes, as discussed in this review, have shown that the use of OrganOx has a favourable future in liver transplantation protocols and warrants considering the cost associated with the use of this health technology. Currently, there is a lack of published data on the cost of the OrganOx machine and supplies.

The American Society of Transplant Surgeons' Standards Committee commented that the cost of machine perfusion, not specific to OrganOx, per transplant center could make it difficult for widespread use of this technology [11]. However, machine perfusion completed through an Organ Procurement Organization (OPO) could allow for the cost to be spread evenly amongst transplant centres [11]. This may be beneficial in the United States where multiple transplant centers are in close proximity and associated with one OPO. This approach is less feasible in Canada, where transplant centers are geographically further apart, each with their own OPO [29].

The cost of machine perfusion is expected to increase the pure cost of liver transplantation, estimated to be $25,000-$50,000 US per transplant [11]. However, the upfront technology costs need to be considered within the context of changes in patient utility, decrease in waitlist mortality, and increase in successful transplantations. The increase in available functioning liver grafts, by way of the rescue of discarded grafts or decreasing the discard rate, will change the landscape of the liver transplant waiting list and mortality rate. Therefore, cost-utility and cost-effectiveness studies to assess the economic impact this technology has on the health care system and society are required. These cost analyses should be completed in parallel to the ongoing clinical research to allow for a broader understanding of the implications of using OrganOx. This will allow for a well-informed decision about the implementation of this technology into liver transplantation programs. One cost-utility analysis has been completed with data from the United Kingdom and shown cost-effectiveness [20]. Given two clinical trials

are ongoing in Canada it is important to assess the cost of OrganOx in a Canadian setting.

2.6 Conclusions

In conclusion, the use of the OrganOx machine has been shown to have comparable outcomes to SCS in multiple clinical scenarios. Its use has been associated with a decreased discard rate of liver grafts and the ability to rescue grafts that initially were deemed unsuitable for transplantation, both leading to an increased number of successful transplantations. This will open up possibilities of increasing the number of liver transplants and decreasing the waitlist mortality rate. Further research is required for standardized viability perfusion characteristics and cost analyses in a Canadian setting prior to transplant programs deciding about the implementation of this technology.

Table 2-1: Comparison of graft and patient survival

Reference	**Graft Survival**			**Patient Survival**		
	NMP	**SCS**	**p-value**	**NMP**	**SCS**	**p-value**
Ravikumar et al. (2016)	n=20	n=40		n=20	n=40	
30 day	100%	97.5%	1.0	100%	97.5%	1.0
6-month	100%	97.5%	1.0	100%	97.5%	1.0
Selzner et al. (2016)	n=10	n=30		n=10	n=30	
3-month	100%	100%	-	100%	100%	-
Bral et al. (2017)	n=10	n=30		n=10	n=30	
30 day	90%[a]	100%[a]	0.25	100%[b]	100% [b]	-
6-month	80%[a]	100%[a]	0.06	89% [b]	100% [b]	0.25
Nasralla et al. (2018)	n=121	n=101		n=121	n=101	
1-year	95%	96%	0.71	95.8%	97%	0.67
	SCS-NMP	**NMP**	**p-value**	**SCS-NMP**	**NMP**	**p-value**
Bral et al. (2019)	n=26	n=17		n=26	n=17	
30-day	100%	100%	>0.99	100%	100%	>0.99
3-month	100%	100%	>0.99	100%	88%	0.1
6-month	94%	93%	>0.99	100%	88%	0.1
Ceresa et al. (2019)	n=31	n=104		n=31	n=104	
1-year	84%	94%	0.08	90%	-	-
	NMP	**Control**	**p-value**	**NMP**	**Control**	**p-value**
Mergental et al. (2020)	n=22	n=44		n=22	n=44	
1-year	86.4%	86.4%	1.0	100%	95.5%	0.55

[a] intention to treat analysis
[b] per protocol analysis

NMP – normothermic machine perfusion
SCS – static cold storage

Table 2-2: Comparison of laboratory values

Reference	AST peak in first 7 days			Bilirubin at 7 days			INR at 7 days		
	NMP	**SCS**	**p-value**	**NMP**	**SCS**	**p-value**	**NMP**	**SCS**	**p-value**
Ravikumar et al. (2016)	n=20	n=40		n=20	n=40		n=20	n=40	
	417 (84-4681)	902 (218-8786)	**0.03**	25 (8-211)	30 (9-221)	0.20	1.05 (0.88-1.40)	1.03 (0.90-2.22)	0.92
Selzner et al. (2016)	n=10	n=30		n=10	n=30		n=10	n=30	
	-	-	-	1.5 (1.0-7.7)	2.78 (0.4-15)	0.49	1.1 (1-1.56)	1.1 (1-1.3)	0.47
Bral et al. (2017)	n=10	n=30		n=10	n=30		n=10	n=30	
	1252 (383->2600)	839 (153->2600)	0.52	79 (17-344)	53 (8-340)	0.35	1.1 (1.1.-1.6)	1.1 (0.9-1.5)	0.44
Nasralla et al. (2018)[a]	n=120	n=100		n=120	n=100		n=120	n=100	
	488.1 (408.9 - 582.8)	964.9 (794.5 -1172)	**<0.0001**	38.5 (21-73.2)	49.1 (26-85.5)	**0.03**	1.2 (1.2-1.4)	1.2 (1.2-1.4)	0.64
	SCS-NMP	**NMP**	**p-value**	**SCS-NMP**	**NMP**	**p-value**	**SCS-NMP**	**NMP**	**p-value**
Bral et al. (2019)	n=26	n=17		n=26	n=17		n=26	n=17	
	863 (460-1640)	709 (283-1921)	0.63	74 (39-157)	124 (45-170)	0.43	1.4 (1.2-1.7)	1.4 (1.3-1.7)	0.95
Ceresa et al. (2019)	n=31	n=104		n=31	n=104		n=31	n=104	
	457 (92-8669)	465 (68-8822)	0.92	-	-	-	-	-	-

Presented as median (lowest value – highest value)
[a]Adjusted by transplant centre and donor type

NMP – normothermic machine perfusion
SCS – static cold storage
AST – aspartate aminotransferase
INR – international normalized ratio

Table 2-3: Comparison of length of stay for the intensive care unit and the total hospital stay

Reference	**ICU LOS**			**Total LOS**		
	NMP	**SCS**	**p-value**	**NMP**	**SCS**	**p-value**
Ravikumar et al. (2016)	n=20	n=40		n=20	n=40	
	3 (1-8)	3 (1-41)	0.46	12 (6-34)	14 (8-88)	0.1
Selzner et al. (2016)	n=10	n=30		n=10	n=30	
	1 (0-8)	2 (0-23)	0.54	11 (8-17)	13 (7-89)	0.23
Bral et al. (2017)	n=10	n=30		n=10	n=30	
	16 (2-65)	4 (1-29)	**0.004**	45 (13-114)	25 (9-89)	**0.01**
Nasralla et al. (2018)[a]	n=121	n=101		n=121	n=101	
	4 (2-7)	4 (3-7)	0.34	15 (10-24)	15 (11-24)	0.93
	SCS-NMP	**NMP**	**p-value**	**SCS-NMP**	**NMP**	**p-value**
Bral et al. (2019)	n=26	n=17		n=26	n=17	
	2 (2-4)	6 (3-48)	**0.004**	16 (12-20)	43 (22-61)	**0.001**
Ceresa et al. (2019)	n=31	n=104		n=31	n=104	
	3 (1-20)	4 (10-24)	0.93	13 (7-31)	14 (10-24)	0.88
	NMP	**Control**	**p-value**	**NMP**	**Control**	**p-value**
Mergental et al. (2020)	n=22	n=44		n=22	n=44	
	3.5 (3-4)	2 (1-5)	0.57	10 (8-17)	9 (8-11)	0.82

Presented as median (lowest value – highest value)
[a]Median (IQR)

NMP – normothermic machine perfusion
SCS – static cold storage
LOS – length of stay
ICU – intensive care unit

Table 2-4: Comparison of viability perfusion characteristics

Reference	Perfusion Time (hours)	Final Lactate (mmol/L)	Final pH	Bile Production (ml/hour)	Hepatic artery flow (ml/min)	Portal venous flow (L/min)
Selzner et al. (2016)	8.0 (5.7-9.7)	1.6 (0.6-1.7)	7.26 (7.13-7.33)	61 (14-146)[a]	300 (200-400)	1.3 (1.2-1.3)
Nasralla et al. (2018)[b]	9.1 (6.2-11.8)	0.9 (0.6)	7.31 (0.17)	9.2 (11.2)	280 (120)	1.1 (0.2)
Bral et al. (2019) SCS-NMP NMP	 7.8 (4.0-16.8) 10.3 (3.3-22.4)	 1.5 (1-2.3) 0.7 (0.4-1.3)	 - -	 13.1 (2.4-24.3) 8.0 (4.5-14.3)	 600 (500-620) 470 (400-500)	 1.0 (0.9-1.0) 1.1 (1.1-1.1)
Ceresa et al. (2019)[b] SCS-NMP NMP	 14.1 (4.8) 12 (4.2)	 0.9 (0.5) 0.7 (0.6)	 7.33 (0.06) 7.35 (0.09)	 11 (0-50) 9 (0-42)	 440 (150) 290 (120)	 1.1 (0.1) 1.1 (0.1)
Mergental et al. (2020)[c]	Minimum of 4	<=2.5	>=7.30	Evidence of production	>=150	>=0.5

Presented as median (lowest value – highest value)

[a]ml
[b]mean (standard deviation)
[c]pre-determined criteria

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3 The Cost of Liver Transplantation and the Cost Driving Factors

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3.1 Abstract

Liver transplantation is the only definitive treatment for end stage liver disease. It is a cost and resource intensive treatment, but life-saving. There are three main time periods that make up the liver transplantation process: pre-transplantation, transplantation admission, and post-transplantation. A literature review was performed, and common driving factors of the liver transplantation process were identified. Each of these time periods have a wide range of cost and there are factors within in each that drive the cost. The pre-transplantation period driving factors are longer waitlist times, amount of time spent as an inpatient, poor overall functional status, and the chronicity of the liver failure. The transplantation admission period is typically the most expensive and the driving factors are increased length of stay, increasing severity of liver disease at the time of transplantation, severity of overall illness, poor overall functional status, post-operative complications, and extended criteria grafts. The post-transplantation period typically has a very expensive first year, but the entire period's costs are driven by overall functional status, amount of time as an inpatient, and medication costs. Identification of these factors allows for clinical intervention, such as formal frailty assessment and pre-transplantation physical therapy, where the upfront costs could lead to an overall cost savings for the liver transplantation process as a whole.

3.2 Introduction

Liver transplantation is the only definitive and life-saving treatment for end stage liver failure. It is well known that liver transplantation is both a resource and cost intensive process for both the patient and health care system, and that these costs vary widely

between centres and between countries. There are many ways to consider the costs of the liver transplantation process and this varies substantially between cost studies. However, there are three distinct periods of time in relation to liver transplantation. The first period of time is pre-transplantation. This usually considers the workup and waitlisting of patients for transplantation as well as their ongoing care for their liver disease and other medical comorbidities. During this period of time costs can arise from both inpatient and outpatient care. Outside of the direct costs to the health care system there are societal costs secondary to unemployment and psychosocial impacts on patients and their caregivers [30, 31].

The second period of time is the transplantation admission. This cost typically entails the cost of the liver transplantation operation itself, which may or may not include the cost of procurement depending on the health care system or study, and the cost of the hospital admission following transplantation.

The third period of time is post-transplantation. This cost starts after the index transplantation admission to death or the end of study follow up. This can be further broken down into the costs for the first-year post-transplantation and costs after the first year. These costs can arise from both inpatient and outpatient care. The goal of liver transplantation is to have the patient return to employment and actively participate in society after their recovery in this phase. This study will assess the cost of each period and the driving factors of cost within.

3.3 Methods

A literature review was performed using PubMed database using the following keywords: (cost) AND ((liver transplant) OR (liver transplantation)). Abstracts were reviewed for inclusion based on the manuscript being an original article assessing the cost of the waitlist list for liver transplantation, deceased donor adult liver transplantation admission, or post-transplantation period. Manuscripts fitting inclusion were reviewed in detail. Literature was appraised for the perspectives of pre-transplantation, transplantation admission, post-transplantation, and total cost. Manuscripts that presented total costs for the various periods and for the entire transplant process were converted to Canadian dollars and adjusted for inflation to year 2020 [32-34]. Common driving factors for each time period were identified.

3.4 Results

3.4.1 Pre-Transplantation

The pre-transplantation period is the first in the process of liver transplantation (**Table 3-1**). Taylor et al. found that pre-transplantation costs had a wide range with a median of $546 and mean of $5,756 in 1998 CAD$ [35]. This equates to a median of $819, and mean of $8,634 in 2020 CAD$ (**Figure 3-1**) [33]. Harries et al. found that the pre-transplantation median cost was 9,466€ in 2013 Euro [36]. This equates to $14,510 in 2020 CAD$ (**Figure 3-1**) [32, 33]. It was found that the majority of the pre-transplantation costs were from inpatient care (72%) as opposed to outpatient care (3%), while the other 26% was made up by medication costs [36]. Turri et al. found in a micro-costing analysis of 482 patients on the liver transplantation waiting list, followed over 2 years,

that the inpatient cost was double the outpatient cost [37]. In their analysis the cost for the intensive care unit (ICU) length of stay (LOS) and ward LOS were the same even though the number of days in ICU was a quarter of days on the ward [37].

Harries et al. found that costs significantly increased the longer a patient was on the waitlist and that increases the odds of accruing higher costs during the transition through their overall transplantation journey [36, 38]. In addition, Harries et al. found that patients with lower model for end-stage liver disease (MELD) scores had higher costs, which was likely due to the fact that they were on the transplant waiting list for longer, and tended to live longer [36]. In contrast to this Buchanan et al. found that a higher MELD score led to higher pre-transplantation charges [39].

When considering the overall functional status of patients, Serper et al. found that in comparison to independent patients those with low functional status accrued three times the cost in the 180 days leading up to their liver transplantation [40]. The chronicity of liver failure also impacts costs as the pre-transplant work-up for acute liver failure is much less in comparison to chronic liver failure patients [41]. However, Åberg et al. found that patients with acute liver failure accrued substantial inpatient costs prior to transplantation in comparison to chronic liver failure as they were more likely to be in the ICU and requiring invasive interventions, such as Molecular Absorbent Recirculating System (MARS) or alternative dialysis or plasma exchange approaches [42].

3.4.2 Transplantation Admission

The transplantation admission is the second period of time and usually the most costly (**Table 3-2**) [35]. A meta-analysis in 2009 by van der Hilst et al. stated that the estimated cost of the liver transplantation and the admission post-operatively was $163,438 in 2005 US$ for the US as opposed to $103,548 in 2005 US$ for other Organization for Economic Cooperation and Development (OECD) countries [43]. This equates to $257,238 for the US and $162,976 for OECD countries in 2020 CAD$ (**Figure 3-1**) [33, 34]. Taylor et al. found that the transplantation admission had a wide range with a median of $54,795 and a mean of $69,892 in 1998 CAD$ [35]. This equates to a median of $82,192 and mean of $104,838 in 2020 CAD$ (**Figure 3-1**) [33]. This study also showed that 48.54% of the transplantation admission cost was from the LOS costs in the ICU and surgical ward [35].

Bhutiani et al. found that patients who developed complications had double the LOS of those without complications and that the combination of complications and increased LOS led to a 64% increase in cost [44]. In their study the most common and costly complications were related to bleeding, infection, and pulmonary [44]. Ammori et al. found that higher costs were associated with complications, where the two most common types were infectious and biliary [45]. More specifically development of pneumonia led to a statistically significant increase cost of $83,718 in 2005 US$ [45]. In addition to infection and biliary complications, any re-operation, hepatic artery thrombosis, inferior vena cava stenosis, and acute renal failure was also found to significantly increase cost [45]. Ammori et al. found that post-operative complications increased the cost more than having a

high MELD score at the time of transplantation [45]. Van der Hilst et al. found that donation after cardiac death (DCD) grafts had higher grade complications using the Clavien-Dindo classification, where the most costly complications were in relation to infection, liver, and biliary [46].

Foxton et al. found that higher MELD scores at the time of transplantation led to an increased overall LOS and ICU LOS, with increased ICU interventions and a higher likelihood of requiring renal replacement therapy [47]. Similarly, Buchanan et al. found that higher MELD scores led to increased overall LOS and ICU LOS, and additionally if readmitted to ICU that LOS was double [39]. Dutkowski et al. compared costs from Switzerland changing from a center organ allocation process to allocation based on the MELD score and found that the change led to a statistically significant increase in transplantation admission costs [48]. This increase of $45,000 in 2010 US$ was suggested to be due to patients having more severe liver disease at the time of transplantation in the MELD based allocation system [48]. Salvalaggio et al. found that individually a higher MELD score and a higher donor risk index increased the cost of the index transplantation admission but when both are elevated they synergistically interact to increase the cost even more [49]. Serper et al. found that the combination of poor overall functional status and high MELD scores lead to higher cost with each increase in the MELD score [40]. Ammori et al. found that in addition to complications a higher MELD score drove higher costs and that hospital cost increased by $3,368 in 2005 US$ per additional MELD score [45]. Ruiz et al. found that with each 1 unit increase in the MELD score above 20 the total cost increased by 2% [50]. Additional studies found that higher

MELD scores were predictive of higher costs during the index transplantation admission [38, 51, 52]. While the MELD score includes serum creatinine Ruiz et al. found that increasing serum creatinine alone led to an increased costs [50]. If a patient's kidney function was poor enough to require pre-operative hemodialysis a higher admission cost was predicted [51].

With the addition of extended criteria grafts and the use of DCD grafts there have been increased costs associated with it. Jay et al. found that DCD in comparison to donation after brain death led to significantly higher costs [53]. Similarly, van der Hilst et al. found that the increased costs after DCD was due to increased complications, post-operative interventions, ICU LOS, and ward LOS [46].

Poor overall functional status at the time of transplantation has been found to lead to increased admission costs and LOS with a more likely discharge to a care facility or rehabilitation facility as opposed to home [40]. A discharge to a rehabilitation or care facility will carry a higher cost into the post-transplantation phase from both a health care perspective but also from a societal perspective as these patients will not be returning to work right away or ever [54]. In addition, patients with poor functional status were more likely to require hemodialysis or longer intubation, which are both costly interventions [40]. Dhar et al. also found that poor functional status was predictive of higher costs [51]. While the overall severity of illness of the patient prior to transplant, which was seen in patients who were hospitalized and in the ICU, also predicted higher costs [35, 51, 52].

Ruiz et al. found that the number of transfused units of packed red blood cells was a strong predictor of high admission costs with transfusion of 6 to 11 units having a 51% increase in costs and greater than 12 units having a 81% increase in costs when compared to less than 5 units transfused [50]. This was also seen in a study by Nedelcu et al. where the LOS and cost were reduced when patients had fewer transfusions during the transplantation operation [55].

3.4.3 Post-Transplantation

Post-transplantation is the third and final period of time in the process of liver transplantation (**Table 3-3**). Taylor et al. found that the post-transplantation cost ranged widely with a median of $4,882 and a mean of $13,418 in 1998 CAD$ [35]. This equates to a median of $7,323 and a mean of $20,127 in 2020 CAD$ (**Figure 3-1**) [35]. Åberg et al. looked at costs up to 5 years post-transplantation and found that 80% of the cost was from the first-year post-transplantation [42]. In their cost analysis the first year of costs was mainly from inpatient care (75%) while years 2 through 5 were mainly from the costs of immunosuppressive medication (59%) [42]. Harries et al. found that the first-year post-transplantation had a median cost of 105,566€ in 2013 Euro mainly from inpatient care (83%) and cost of medications (14%) [36]. While the post-transplantation time in years 2 through 3 had a median cost of 20,115€ in 2013 Euro mainly from the cost of immunosuppressive and adjunctive medications (75%) [36]. This equates to $161,826 for the first year and $30,835 for years 2 through 3 in 2020 CAD$ [32, 33]. The cost of medication was found to be higher in patients with viral etiologies of liver disease

and hepatocellular carcinoma due to more costly medications that are specific to these [38, 41].

The total cost post-transplantation relies on the length of survival of the patient [36]. Harries et al. found that when comparing patients who survived with patients who died the costs were different based on death being in the first-year post-transplant or years 2 through 3 post-transplantation [36]. Patients who died in the first year were more likely to have been cared for in the ICU leading to higher costs whereas patients who died in years 2 to 3 spent less time in this post-transplantation period with fewer interventions leading to lower costs [36]. In patients with acute liver failure the first year cost was lower than for chronic liver failure patients due to their lower survival rates [41]. Åberg et al. also found that the costs for years 2 through 5 post-transplantation were higher for chronic liver failure in comparison to acute liver failure [42]. This cost was also found to increase by more than 40% for patients with poor overall functional status at the time of transplantation as they had a higher likelihood of having at least one readmission during the first-year post-transplantation [40].

Although, the MELD score was predictive of high cost during the transplantation admission Buchanan et al. found that a higher MELD sore did not increase the costs post-transplantation [39]. DCD grafts had higher rates of biliary complications, which led to higher costs secondary to readmissions, re-transplantations, and increased number of interventions [53].

3.4.4 Total Cost

Cost studies have primarily focused on costs from the time of transplantation on, while fewer studies look at the cost of the liver transplantation process in its entirety (**Table 3-4**). A German study by Harries et al. found that the median total cost from waitlist to 3 years post-transplantation was 144,424€ in 2013 Euro, which equates to $221,393 in 2020 CAD$ [32, 33, 36]. However, the total cost range was 16,162€ to 887,418€ in 2013 Euro [36]. This cost was comprised of inpatient care (72%), medications (26%), and outpatient care (3%) [36]. If a patient required a re-transplantation it led to a median increase cost of 101,849€ in 2013 Euro [36]. A second study by Harries et al. found that 75% of patients had costs of 242,157€ in 2013 Euro or below while 25% of patients, classified as high-cost cases, had costs above that from the time of being waitlisted to 3 years post-transplantation [38]. It was found that the 25% of patients classified as high-cost cases were responsible for 50.7% of the total transplantation costs of the study population [38]. A Canadian study by Taylor et al. found that the mean cost from waitlist to 2 years post-transplantation was $89,066 in 1998 CAD$, which equates to $133,599 in 2020 CAD$ [33, 35]. However, the range of total cost was wide from $30,505 to $690,431 in 1998 CAD$ [35]. Similar to Harries et al. study this cost total was comprised mostly from inpatient care [35].

3.5 Discussion

The pre-transplantation period has not been as extensively studied as the other two time periods. The pre-transplantation cost has a wide range but is influenced by the

amount of time spent as an inpatient, longer waitlist time, lower overall functional status, and the chronicity of the liver failure. It is known that inpatient care is more expensive than outpatient care, with higher inpatient costs in the ICU rather than care on a regular ward. However, the high costs in the pre-transplantation phase presents bimodally with one portion of the population presenting with lower severity of liver disease and a longer waitlist time and a second portion of the population presenting with higher severity of liver disease and shorter waitlist time with costs accruing in a costly hospital setting.

It is expected that the cumulative costs for patients with higher severity disease in the ICU would be far more expensive than those who have longer waitlist time with lower severity of disease. The current cost data does not capture this, and this may be due to not fully capturing the entire cost for complex ICU admissions or differences in patient populations between studies. The majority of the cost data comes from European countries or the United States, where differences in the health care systems and patient population will play a role in the costs.

The transplantation period is the most expensive period. There are many driving factors of the transplantation admission cost with the most notable factors being increased LOS, high MELD score at time of transplantation, post-operative complications, severity of overall illness, poor overall functional status, and extended criteria grafts. Length of stay can add substantial cost and therefore, any factor that increases the LOS will likely increase the total cost for this period of time. Additionally, it has been well documented

that a higher MELD score at the time of transplantation predicts increased cost during the transplantation admission.

The post-transplantation cost varies depending on the length of survival post-transplantation, and while the first year usually is the most expensive the overall cost is influenced by the amount of inpatient care, medication costs, and functional status. The goal of transplantation is not only to treat the liver disease allowing for a longer life but also to help the patient return to being a productive member of society. This has been well documented in cost-utility studies of kidney transplantation in comparison to dialysis [56]. This has not been documented in liver transplantation as there are no comparable options for treatment of severe liver disease. There has been documentation of an increase in quality of life and return to employment after liver transplantation, however, it is hard to know whether this is cost-effective [54, 57].

Overall, the total cost of the liver transplantation process is expensive. Determining the factors that drive cost allows for identification of areas of improvement leading to cost reductions. One factor that drives cost in all three periods is the overall functional status of a patient. Functional status is likely subjectively considered during workup for liver transplantation but is not necessarily formally assessed and documented. It has been shown that physical therapy prior to liver transplantation has impacts on both physical health and quality of life, with impacts stretching into the transplantation admission and post-transplantation period [58, 59]. Implementing a formal functional status assessment would allow for identification of patients who would benefit from pre-transplantation

physical therapy, thereby leading to impacts on patient health and quality of life and cost. The American Society of Transplantation in 2019 published a pathway for formal assessment of frailty for every liver transplant candidate followed by suggestions for physical therapy pre-transplantation and post-transplantation [60]. Further work is required to assess whether the implementation of standardized frailty assessment and physical therapy leads to improved patient health and quality life and cost during the transplantation process.

The overall severity of illness is a driving factor for costly inpatient care during the pre-transplantation period and for the transplant admission. The switch to a MELD based allocation process was shown to increase the cost of the transplant admission due to patients being sicker at the time of transplantation [48]. Costs will continue to rise due to patients being sicker at the time of transplant from the MELD based system in combination with an aging population with multiple co-morbidities, the supply and demand of liver grafts being mismatched, and the use of extended criteria grafts. The use of machine perfusion in liver transplant has been a focus of ongoing research over the last decade. The OrganOx machine, used for normothermic machine perfusion, has shown to decrease the discard rate and to rescue liver grafts deemed unsuitable for transplantation leading to an increase in the number of available grafts for transplantation [16, 23]. Use of machine perfusion technology has the potential to help fill the gap between supply and demand leading to a decreased waitlist mortality and overtime having enough liver grafts that transplant patients have less severe liver disease and overall illness at the time of transplantation. Further research would be

required to assess these proposed benefits once machine perfusion is incorporated into more transplantation centers.

This study was not a systematic review of the literature on liver transplantation costs. There are many studies looking at cost effectiveness of liver transplantation in contrast to treatment for specific etiologies of liver disease and studies for living donor liver transplantation. These studies were not included as the focus of this study was to assess the cost and driving factors for the deceased donor liver transplantation process for all etiologies of liver disease.

3.6 Conclusion

The liver transplantation process is resource intensive and costly, but life-saving for patients with alternative refuge in the medical system. There are three distinct periods of time made up of pre-transplantation, transplantation admission, and post-transplantation. While all three of these periods can have a wide cost range, each have driving factors. The pre-transplantation period driving factors are longer waitlist times, amount of time spent as an inpatient, poor overall functional status, and the chronicity of the liver failure. The transplantation admission period is typically the most expensive and the driving factors are increased LOS, higher MELD score, severity of overall illness, poor overall functional status, post-operative complications, and extended criteria grafts. The post-transplantation period typically has a very expensive first year, but the entire period's costs are driven by overall functional status, amount of time as an inpatient, and medication costs. Each driving factor identified represents an area where

potential improvement could be made to impact cost. Implementation of formal frailty assessment with physical therapy pre-transplantation and implementation of machine perfusion are potential clinical improvements that would have upfront costs but could decrease costs in the overall transplantation process.

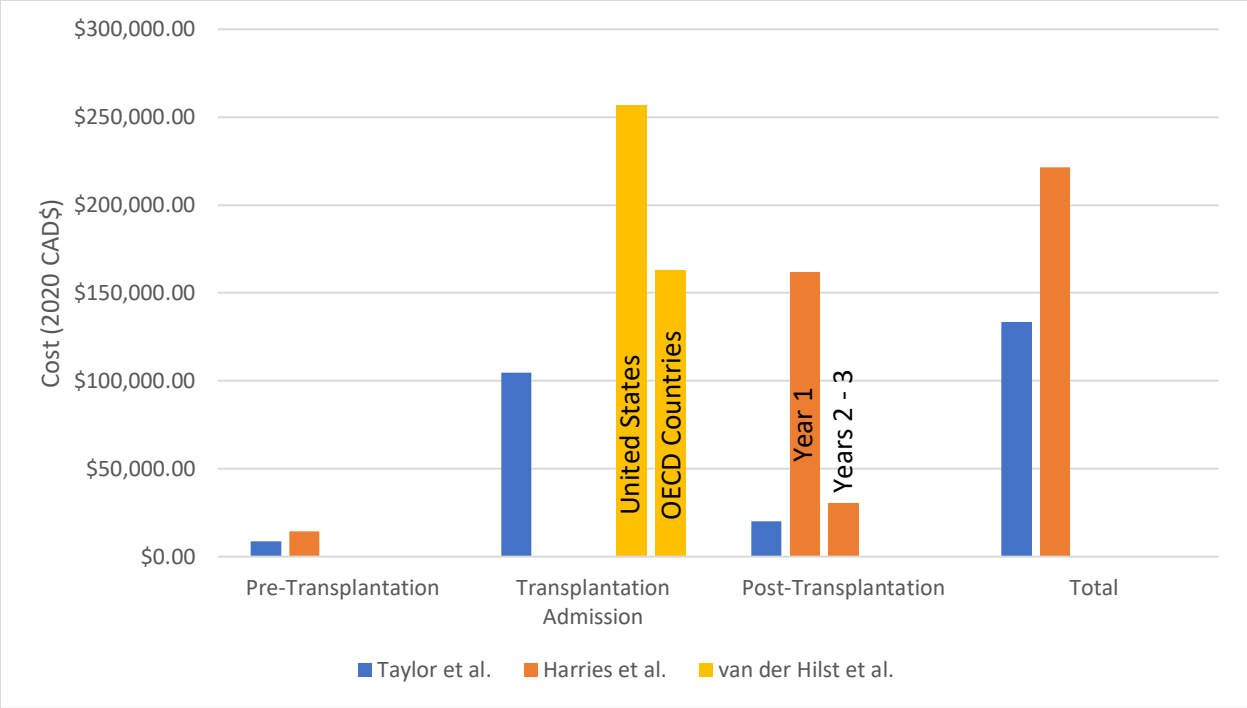

Figure 3-1: Costs in 2020 Canadian dollars of the three transplantation time periods and total cost for Taylor et al. (mean costs), Harries et al. (median costs), and van der Hilst et al. (mean costs) [35, 36, 43]

Table 3-1: Costs and driving factors of the pre-transplantation phase

Reference	Currency	Cost	Driving Factors
Taylor et al. (2002)	1998 CAD$	5,756 (mean) 546 (median)	
Harries et al. (2017)	2013 Euro	9,466 (median)	-inpatient care -medications -longer waitlist time -lower MELD score
Buchanan et al. (2009)			-higher MELD score
Serper et al. (2018)			-poor overall functional status
van Agthoven et al. (2001)			-chronic liver failure
Åberg et al. (2011)			-acute liver failure in ICU

Table 3-2: Costs and driving factors of the transplantation admission phase

Reference	Currency	Cost	Driving Factors
Taylor et al. (2002)	1998 CAD$	69,892 (mean) 54,795 (median)	-length of stay -overall severity of illness
Buchanan et al. (2009)			-higher MELD score -length of stay -longer ICU readmission
Serper et al. (2018)			-poor overall functional status -higher MELD score -these two factors work synergistically
van der Hilst et al. (2009)	2005 US$	163,438 (US) 103,548 (OECD Countries)	
Bhutiani et al. (2018)			-complications -length of stay
Ammori et al. (2008)	2005 US$	83,718 for pneumonia 3,368 per MELD score	-complications -higher MELD score
van der Hilst et al. (2013)			-donation after cardiac death grafts
Foxton et al, (2010)			-higher MELD score
Dutkowski et al. (2011)	2010 US$	$45,000 increase with MELD score allocation	-MELD allocation rather than center organ allocation
Salvalaggio et al. (2011)			-higher MELD score -higher donor risk index -these two factors work synergistically
Ruiz et al.			-2% increase with each increase in MELD score above 20 -16% increase with increasing serum creatinine -higher number of transfused packed red blood cells (51% with 6-11 units, 81% with 12 or more units)
Dhar et al. (2018)			-pre-operative hemodialysis -poor overall functional status -severity of overall illness
Earl et al. (2008)			-severity of overall illness
Nedelcu et al. (2019)			-higher number of transfused packed red blood cells

Table 3-3: Costs and driving factors of the post-transplantation phase

Reference	Currency	Cost	Driving Factors
Taylor et al. (2002)	1998 CAD$	13,418 (mean) 4,882 (median)	
Harries et al. (2017)	2013 Euro	105,566 (median) first year 20,115 (median) years 2-3	-first year: inpatient care and death -years 2-3: medications -viral liver disease or hepatocellular carcinoma
van Agthoven et al. (2001)			-chronic liver failure
Åberg et al. (2011)		80% in first year	-first year: inpatient care -years 2-5: immunosuppressive medication -poor overall functional status
Jay et al. (2010)			-donation after cardiac death grafts

Table 3-4: Costs and driving factors of the total transplantation process

Reference	Currency	Cost	Driving Factors
Taylor et al. (2002)	1998 CAD$	89,066	-inpatient care
Harries et al. (2017)	2013 Euro	144,424 (median) 101,849 (median) increase for re-transplantation	-inpatient care -medications
Harries et al. (2019)	2013 Euro		-25% of patients are considered high cost and are responsible for 50% of costs

3.7 References

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4 The Actual Operative Costs of Liver Transplantation and Normothermic Machine Perfusion in a Canadian Setting

Adapted from:

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4.1 Abstract

Background Liver transplantation is an effective treatment for end-stage liver disease. However, waiting lists continue to lengthen as demand exceeds supply. Use of extended criteria donors has helped but is associated with increased rates of complications. The application of normothermic machine perfusion (NMP) has been shown to be protective, especially in more marginal grafts. Despite this benefit, no cost-effectiveness studies have been published.

Objective This study serves as a prelude to a cost-effectiveness analysis of the costs of liver procurement, transplantation, and machine perfusion in a Canadian setting.

Methods The total costs were calculated for 106 in-province procurements, the set cost for 237 out-of-province procurements, and 343 liver transplantations. These costs include overheads, supplies, anaesthesia technologist and nursing salaries, and physician billings. Base and modified costs for all procedures were calculated, with consideration of physician billing modifiers. The total cost per run of NMP was calculated, with a range based on variations in the exchange rates for Great British pounds (£) to Canadian dollars ($Can), year 2019 values.

Results Costs were $Can30,770.22 for in-province and $Can44,636.73 for out-of-province liver procurement and transplantation. These increased to $Can35,659.22 and 48,076.18 when considering modifiers. The minimum cost per NMP run was $Can18,593.02.

Conclusions Although the cost per run is substantial, NMP could potentially lead to cost savings by decreasing night-time salary premiums, complications, and patient length of stay. A formal cost-effectiveness study of NMP in liver transplantation is underway to help clarify the financial benefit or burden of this new technology.

4.2 Key Points for Decision Makers

This paper defined actual costs per run for normothermic machine perfusion used in liver transplantation from a Canadian single-payer perspective as well as the potential cost savings accrued through a transition from night-time to daytime transplant surgery hours.

This paper provides insight into the actual costs for transplant surgery and the per run cost of normothermic machine perfusion. This is the prelude to a formal cost-effectiveness analysis to inform healthcare decisions based on the outcome of length of stay with the addition of machine perfusion to transplant programmes.

4.3 Introduction

Liver transplantation remains the only life-saving treatment for many forms of liver disease; however, a mismatch between the supply and demand for liver transplants results in up to one-quarter of listed patients dying while on the waiting list [2]. The 2018 statistics from the Canadian Institute for Health Information stated that 507 adults were awaiting liver transplantation, where 358 were actively awaiting and 149 were on hold

[21]. A total of 190 adults were removed from the waiting list: 80 had died and 110 withdrew due to improvement or deterioration of their condition, giving a waiting list death rate of 22% [21].

To address the gap between the supply and demand for liver transplants, the acceptance and transplantation of extended criteria donors (ECD) has increased. This has occurred in two waves [6]. The initial criteria expansion was for conventional factors such as age, abnormal liver function tests, liver steatosis, etc., and the second wave was for non-conventional factors such as hepatitis B- and C-infected grafts and donation after cardiac death [6]. The use of ECD grafts is associated with an increased risk of early allograft dysfunction, biliary complications, and graft failure, with further risk when combined with the use of standard static cold storage (SCS), compared with the use of standard criteria donors (SCD) [9]. In an effort to improve post-transplant complications from ECDs, the development and use of machine perfusion has become a focal point of current research.

OrganOx Ltd is a Europe-based company that has created a machine called metra for normothermic machine perfusion (NMP) [61]. The use of NMP allows for physiologic numbers to be maintained, including temperature, oxygenation, and blood flow and pressure [61]. Variables including bile output, lactate clearance, glucose metabolism, transaminase levels, and blood gas analysis allow transplant surgeons to assess the

liver's metabolic and synthetic functioning ex vivo before exposing a recipient to the graft [61]. In 2016, the first clinical trial of the OrganOx metra machine proved safety and feasibility [18]. In 2018, Nasralla et al. [23] published the first randomised controlled trial (RCT) of machine perfusion with the OrganOx metra device. Both of these studies showed a statistically significant improvement in peak aspartate aminotransferase (AST) level and lower rates of early allograft dysfunction [18, 23]. This led to a further large multicentre RCT in the USA that is awaiting completion, with the primary outcome of measuring early allograft dysfunction [27, 61]. In Canada, two clinical trials with the OrganOx machine are ongoing [26, 28], but no detailed cost analyses of the OrganOx machine have been published to date.

The American Society of Transplant Surgeons' standards committee is expecting that the addition of machine perfusion will add $US25,000–50,000 to the overall cost of one liver transplant [11]. Although there have been estimations of the added financial burden from machine perfusion, no data have been released to show an expected actual cost. The purpose of this study is to show the actual operating room costs associated with liver procurement, liver transplantation, and machine perfusion using the OrganOx machine in a Canadian setting.

4.4 Methods

The cost analysis was prompted by the liver transplant team at the University of Alberta (UofA) Hospital and conducted from the Canadian single-payer perspective. All costs are based out of the UofA Hospital in Edmonton, AB, Canada, and presented in Canadian dollars ($Can), year 2019 values. This cost analysis considers overheads, supplies, and staffing for the operative costs of liver procurement, transplant, and OrganOx metra. The costs presented in this study are actual costs as opposed to standard costs. The total calculated costs are based on the costs that the UofA Hospital and Alberta Health Services—the provincial health authority— pay for overheads, supplies, and salaries. This is compared with setting a standard total cost for the procedure and all components.

4.4.1 Liver Procurement and Transplant

4.4.1.1 Overhead and Supply Costs

The average case costs, including salaries and supplies, were collected from the LightHouse Surgical Financial System for the multivisceral organ procurement and liver transplantation operations. LightHouse is a financial monitoring system used by the UofA operating room to track the actual costs of operative cases [62]. The UofA Hospital is the only hospital in the province of Alberta that completes liver transplantations, so all liver transplant operative costs are captured in the LightHouse data. LightHouse collects the actual cost data directly from the UofA Hospital using their electronic tracking systems for each operation to account for the overhead costs of the operating room,

supply costs from the case, and nursing salaries [62]. Using the cost data, the average cost for a specific operation can be compared between individual surgeons and an average cost based on all surgeons who complete that operation [62]. In this cost analysis, the average case cost is the average based on all liver transplant surgeons at the UofA Hospital, which represents the actual case cost based on the actual operative costs used by the UofA Hospital. All costs were collected from April 2015 to July 2019 for 106 in-province multivisceral organ procurement and liver transplantations. The Hospital Reciprocal Claims Guide provided the set cost for 237 out-of-province organ procurements [63].

The Human Organ Procurement and Exchange (HOPE) programme provides additional operative supplies specific for liver procurement (**Table 4-S1**). The HOPE programme is a subdivision of Northern Alberta Transplant Services through Alberta Health Services [64]. The HOPE programme coordinates the process of deceased organ donation, overseeing the details of donation, allocation, recovery, and distribution [64]. These supply costs were added to the average case costs.

4.4.1.2 Staff

The surgeon and anaesthesiologist billing costs were collected from the regional Health Service Codes Fee Navigator for donor total hepatectomy, recipient total hepatectomy, and liver transplantation [65]. The billing costs were calculated for each operation and

range from the base pay without modifiers to the base pay with maximum modification. Modification is applied to both the surgeon and the anaesthesia billing for a body mass index (BMI) > 40 and for timing of the operation, based on evening (1700–2200 h), night evening (2200–2400 h), and night morning (2400–0700 h) (**Table 4-S2**) [65]. The nursing salaries are part of the average case costs collected from LightHouse.

4.4.1.3 Total Cost

The total cost of in-province procurement is made up of the average case cost, HOPE supplies, surgeon billing, and anaesthesia billing. The total cost of out-of-province procurement is made up of the Alberta Reciprocal Claim and HOPE supplies. The recipient total hepatectomy and liver transplant cost is made up of the average case cost, surgeon billing, and anaesthesia billing.

4.4.2 OrganOx Machine Perfusion

4.4.2.1 Overhead and Supplies

The average case costs for the OrganOx machine, run by anaesthesia technicians, were collected through LightHouse for April 2017 to July 2019. The average case cost is the cumulative cost of overheads for the operating room, operative supplies, and nursing salaries. The UofA Hospital provided the costs of the materials they supply (**Table 4-S3**). OrganOx Ltd provided the costs of the OrganOx machine annual lease and supplies, based on the contractual agreement between OrganOx and UofA of

completing a minimum of 15 OrganOx runs per year, in Great British pounds (£), year 2019 values (**Table 4-S4**). The minimum of 15 runs per year was an initial agreement to the volume to be utilised with potential for decreasing costs with increased utilisation. The costs were converted from £ to $Can, year 2019 values, based on the exchange rate range between 30 August 2018 and 30 August 2019. The conversion rate ranged from 1.5955 to 1.7743 [66].

4.4.2.2 Staff

The average case cost from LightHouse covers the salaries of the nurses who set up the operating room and are present until the liver is attached and running on the OrganOx machine. Once the machine is running, an anaesthesia technician monitors the liver until it is taken off the machine for transplantation. The average hours of liver perfusion were collected for all completed OrganOx perfusions. The salary of an anaesthesia technician is $Can40–50/h, depending on seniority; when called in overnight, pay is double time at $Can80–100/h [67]. The average salary for the anaesthesia technician was calculated from the average number of hours based on overtime for runs during night-time hours (1900–0700 h) and base pay for runs during daytime hours (0700–1900 h).

4.4.2.3 Total Cost

The cumulative OrganOx run cost was calculated with the average case cost, hospital supply costs, OrganOx supply costs, and anaesthesia technician salary. The cumulative costs of liver procurement, liver transplantation, and OrganOx perfusion were calculated for both in-province and out-of-province procurement and transplantation. The costs of standard transplant and transplant with OrganOx were compared using a t-test, with a p-value of 0.05 considered statistically significant.

4.5 Results

4.5.1 Liver Procurement and Transplant

The cost of a liver transplant from an operative perspective involves staffing salaries and supply costs for multivisceral organ procurement of the donor, recipient total hepatectomy, and recipient liver transplantation. Multivisceral organ procurement occurs outside of the regional hospital two-thirds of the time. Therefore, additional travel costs need to be included.

The multivisceral organ procurement case costs from LightHouse provided the average case cost, made up of supplies and salaries. The average case cost from the last 5 years was $Can9537.20 ± standard deviation (SD) 753.13 (**Table 4-1**). This was broken down to an average supply cost of $Can7485.60 ± 652.29 and an average salary cost of $Can2051.40 ± 502.99. The salary cost did not include the payments for which the

surgeon and the anaesthesiologist bill. The surgeon's base pay for a donor total hepatectomy is $Can2857.70. The base pay for the anaesthesiologist is $Can681.59. In addition to the base pay, modifiers apply for BMI and for the time of day at which the operation is completed, which apply to both the surgeon and the anaesthesiologist. Therefore, surgeon billings range from $Can2857.70 (base pay) to 3854.49, and anaesthesiologist billings range from $Can681.59 to 1134.35. The average supplies did not include the supplies that are provided by the HOPE programme, which total $Can1077.85. This yields a total cost of in-province procurement of $Can14,154.34–15,603.89 (**Table 4-2**).

The average costs for liver transplantation obtained from LightHouse incorporate the case costs of the recipient total hepatectomy and deceased donor liver transplant. The average case cost from the last 5 years was $Can6246.40 ± 497.52 (**Table 4-3**). This was broken down to an average supply cost of $Can2913.40 ± 355.34 and an average salary cost of $Can3362.40 ± 210.43. The surgeon billings were separated by recipient total hepatectomy and liver transplantation. The surgeon base pay for recipient total hepatectomy is $Can2377.01. Once modifiers were considered, the range was $Can2377.01–3253.62. The surgeon base pay for liver transplantation is $Can5018.14–6555.04 with modifiers. In total, the surgeon billing cost for both procedures ranged from $Can7395.15 to 9808.66. The anaesthesiologist billing for liver transplantation was $Can2974.33–4000.27 with modifiers. The total operative cost for the combination of recipient total hepatectomy and liver transplantation ranged from $Can16,615.88 to

20,055.33 (**Table 4-2**). In total, the operative cost of in-province procurement and transplantation was $Can30,770.22–35,659.33 (**Table 4-2**).

At times, procurement occurs at a distant site, so additional travel costs must be considered. Currently, the billing cost for out-of-province liver procurement is $Can26,943, as per the Hospital Reciprocal Claims [63]. This is an all- inclusive set cost for travel, supplies, salaries, and operating room costs and, with the addition of the HOPE supplies, the total cost for out-of-province procurement is $Can28,020.85 (**Table 4-4**). In total, the cost of a liver transplant with an out-of-province procurement is $Can44,636.73–48,076.18 (**Table 4-4**). Additional travel costs were considered for procurements occurring at a nearby regional hospital ($Can190) or in a different city within the same province ($Can5175).

4.5.2 OrganOx Machine Perfusion

For deceased donor liver grafts, OrganOx machine perfusion costs are in addition to the traditional liver transplantation costs. Current costs are made up of four distinct areas. The first is operating room costs (**Table 4-5**), which include the operating room nursing salaries and case supplies. This is an average of $Can1667 ± 192.57. The second is the costs of medications and solutions purchased through the UofA Hospital, a total of $Can1617.36.

The third is the cost of the annual lease of the OrganOx machine and the cassettes and solutions purchased from OrganOx Ltd. The costs of the lease and materials purchased from OrganOx Ltd were converted to $Can, year 2019 values. The total cost of supplies per run for the OrganOx machine is $Can14,708.66–16,356.99, based on the agreement between OrganOx and UofA for completion of a minimum of 15 OrganOx runs per year. The fourth is the salaries of the anaesthesia technicians. The OrganOx machine runs for an average of 9.08 h, usually between 0300 and 1200 h. Given this, the average additional costs for the anaesthesia technicians is $Can600.

The cumulative operative cost for one run of OrganOx perfusion machine was $Can18,593.02–20,241.35 (**Table 4-6**). Overall, the total cost of in-province procurement, liver transplant, and OrganOx was $Can49,363.24–55,900.68. The total cost of out-of-province procurement, in-province transplantation, and OrganOx was $Can63,229.75–68,317.53. The cost difference between liver transplant including OrganOx compared with standard liver transplant was statistically significant for both in-province (p=0.042) and out- of-province (p = 0.024) transplant.

4.6 Discussion

Machine perfusion has been a core element of liver transplantation research for the last decade. The use of NMP for livers has been shown to have benefits for both the liver and the recipient. Nasralla et al. [23] published an RCT in 2018 that showed that peak

AST, a marker of predicted graft and patient survival, was 49.4% lower in livers that underwent NMP. In addition, the odds of early allograft dysfunction was 74% lower in the NMP livers, including both ECD and SCD grafts, than for SCS [23]. Post-reperfusion syndrome in NMP versus SCS was significantly reduced for recipients of NMP livers, and recipients also had a decreased requirement for vasopressors during the post-reperfusion period [23, 68]. It has also been shown that hepatic ischaemic reperfusion injury, using AST as a surrogate marker, is an independent risk factor for acute kidney injury post transplantation, which may require renal replacement with prolonged intensive care unit and hospital stays [69]. NMP has the potential to decrease this.

In addition to the potential clinical benefits of NMP, the surgical teams may also benefit. Traditionally, many transplantations occur during night-time hours [70]. Although studies have shown that patient outcomes are not impacted by night-time transplants, over time, the combination of night-time operating and a busy transplantation service can lead to transplant team burnout and potentially a lack of personnel available for call coverage [70-74]. The introduction of NMP has enabled a shift of transplantation from night-time to daytime hours, as NMP can be run overnight [13, 23]. However, successful NMP does require the transplant fellows at UofA to complete night-time operating to ensure final dissection and attachment of the liver graft to the OrganOx machine, which does play a role in fatigue specific to the fellows. Overall, 58 OrganOx liver transplants have been completed at UofA between 2015 and 2019, and 49 (84.48%) of those switched from a potential night-time (1900–0700 h) to a daytime (0700–1900 h)

transplant because of the use of NMP. This is in comparison with 64% of SCS liver transplants being completed during daytime hours [13]. The shift to daytime transplantation will hopefully decrease the burnout that transplant services are being faced with.

In addition, shifting transplantation from night to day will impact costs via transplant team salaries. Daytime operations will remove the evening and night-time modifiers from the salaries of the surgeon and anaesthesiologist. In total, for the anaesthesiologist and the surgeon in recipient hepatectomy and liver transplantation, the total savings is $Can847.08. Currently, a transplantation that occurs overnight requires a transplant scrub nurse to be called in. That scrub nurse requires a minimum of 3 h of overtime pay at a rate of $Can84–106/h depending on seniority; this is double time of the base pay with a shift differential of $Can5/h [75]. However, the liver transplant cases range from 8 to 12 h, with an additional 2–3 h of setup and clean up. Therefore, this yields a cost of $Can252–1500 for the scrub nurse alone. If transplantation begins in the morning, this salary cost is eliminated. Therefore, the overall cost savings of salaries for transplantation may be up to $Can2347.08 (4.86% for in province, 3.71% for out of province). Although the salary cost savings are minimal, the potential exists for larger cost savings in the post-transplant time with fewer complications, investigations, and shorter length of stay, which will be considered in the future cost-effectiveness analysis (CEA) while considering the recipient's clinical status and Model for End-Stage Liver Disease score.

Use of the OrganOx machine also has the potential to increase the number of ECD accepted for perfusion and successful transplantation [13, 23]. This will lead to more liver transplants taking place and therefore decrease the waiting time for transplantation. This will ideally lead to fewer people dying on the wait list or becoming too sick to tolerate the stress of a transplant. If people receive their transplants earlier, this may also decrease the healthcare costs from the possible hospital stays and interventions that would have been required as their disease progressed. Overall, an increased number of usable livers will lead to more lives being saved and an increase in healthcare costs associated with liver transplantation. A further CEA will be completed to assess these concerns.

The area of cost has been considered, but no data have been published. The purpose of this study was to determine the actual operative costs of liver procurement, liver transplantation, and OrganOx machine perfusion. The cost of the OrganOx per run is substantial. Despite this, the clinical efficacy and considerations discussed with the use of the OrganOx may outweigh the costs given the possible decrease in investigations, complications, and length of stay post transplantation, which will be considered in the future CEA. In turn, this will lead to better quality of life and return to social functions for patients post transplantation. Overall, this may lead to a decreased cost to the medical system, and the future CEA will help clarify this by assessing length-of-stay outcomes.

This study has some limitations. First, these costs relate only to the operating room and not all the preoperative investigations and the hospital stay for the donor or the investigations, care management, hospital stays, clinic visits, and interventions completed for the recipient before their transplantation. The salaries for the managerial and nursing staff employed by the HOPE programme are also not included. Overall, these additional costs can be significant to the system but will likely be similar between the two groups. Costs related to post-operative care for the recipient are being collected for the CEA but are not currently considered; however, if the promising results from Nasralla et al. [23] are generalizable, we would expect the post-operative costs to be lower in the OrganOx group.

In addition, the costs are calculated within a Canadian setting, so the data may not be transferable to other countries with different protocols and billing setups for transplantation. In the Canadian setting, the costs of organ procurement and transplantation are covered in their entirety by the provincial organ donor programmes. Other countries have different payment models, including charge-based models, which may lead to different costs. In particular, it should be noted that all costs for organ procurement and transportation are covered separately through direct government funding across Canada, whereas in the USA, for example, these substantial costs with additional overheads are passed on to the recipient hospital and the recipient's insurance scheme. In the 2017–2018 fiscal year, the cost of one liver transplant

admission in the region was $Can102,597, excluding the physician costs. In comparison, in 2017, the estimate of charges for one liver transplant admission in the USA was $US463,200, excluding physician costs [76].

In addition to these limitations, potential exists for the overall cost of liver transplant to increase substantially if the use of NMP allows for more livers to be useable and therefore available for transplantation, thereby leading to an increased number of lives saved. This study only shows the operative costs associated with organ procurement, transplantation, and NMP but does not account for the many additional costs incurred by the healthcare system for each individual transplant patient. While, clearly, incremental costs associated with the application of NMP are excluded from the current analysis, these costs become relatively much smaller if the total costs of donor and recipient transplant care, including transportation, are also included in the equation. As further research is conducted and the current clinical trials and RCTs completed, knowledge of the benefits of machine perfusion will be more extensive. This may lead to an increased use of machine perfusion. However, for healthcare systems to consider making additions to their protocols, the costs must be considered. This study of the costs of liver procurement, transplantation, and NMP is the prelude to a CEA of NMP.

4.7 Conclusion

The purpose of this study was to present the operative costs of liver transplantation and expected costs of OrganOx machine perfusion as a prelude to a CEA. The cost of liver transplant ranges from $Can30,770.22 to 35,659.22 for in-province and from $Can44,636.73 for 48,076.18 for out-of-province procedures. The cost of OrganOx per run is $Can18,593.02–20,241.35. Although upfront costs are substantial, the possibility of NMP leading to a decreased length of stay and complications leads to a potential for cost savings in the Canadian system. In addition, the use of NMP usually shifts transplantation to daytime hours, thereby decreasing the premium night-time salaries. These potential cost savings may mean NMP is cost effective, and this question is currently undergoing formal CEA.

Table 4-1: Multivisceral Organ Procurement Case Costs

	2019/2020 (n=5)	2018/2019 (n=19)	2017/2018 (n=33)	2016/2017 (n=25)	2015/2016 (n=24)	Average (sd)
Average Salaries	$1,248	$2,154	$1,930	$2,422	$2,503	$2,051.40 ($502.99)
Average Supplies	$7,558	$8,338	$7,333	$6,530	$7,669	$7,485.60 ($652.29)
Average Case Cost	$8,806	$10,493	$9,263	$8,952	$10,172	**$9,537.20 ($753.13)**

Table 4-2: Total Operative Costs for In-Province Procurement and Transplantation

Donor Total Hepatectomy	Average Case Cost	$9,537.20 ($753.13)
	HOPE Supplies	$1,077.85
	Surgeon	$2,857.70 to $3,854.49
	Anesthesia	$681.59 to $1,134.35
	Total	**$14,154.34 to $15,603.89**
Recipient Total Hepatectomy and Liver Transplantation	Average Case Cost	$6,246.40 ($497.52)
	Surgeon	$7,395.15 to $9,808.66
	Anesthesia	$2,974.33 to $4,000.27
	Total	**$16,615.88 to $20,055.33**
Cumulative Total		**$30,770.22 to $35,659.22**

HOPE – Human Organ Procurement and Exchange Program

Table 4-3: Liver Transplantation Case Costs

	2019/2020 (n=23)	2018/2019 (n=73)	2017/2018 (n=97)	2016/2017 (n=80)	2015/2016 (n=70)	Average (sd)
Average Salaries	$3,412	$3,102	$3,195	$3,612	$3,491	$3,362.40 ($210.43)
Average Supplies	$3,478	$2,565	$2,660	$2,932	$2,932	$2,913.40 ($355.34)
Average Case Cost	$6,889	$5,668	$5,855	$6,544	$6,276	**$6,246.40 ($497.52)**

Table 4-4: Total Operative Costs for Out-of-Province Procurement and In-Province Transplantation

Out-of-Province Donor Total Hepatectomy	Alberta Reciprocal Claim	$26,943
	HOPE Supplies	$1,077.85
	Total	**$28,020.85**
Recipient Total Hepatectomy and Liver Transplantation	Average Case Cost	$6,246.40 ($497.52)
	Surgeon	$7,395.15 to $9,808.66
	Anesthesia	$2,974.33 to $4,000.27
	Total	**$16,615.88 to $20,055.33**
Cumulative Total		**$44,636.73 to $48,076.18**

HOPE – Human Organ Procurement and Exchange Program

Table 4-5: OrganOx Perfusion Operating Room Case Costs

	2019/2020 (n=1)	2018/2019 (n=14)	2017/2018 (n=12)	Average (sd)
Average Salaries	$1,057	$1,393	$1,405	$1,285 ($197.54)
Average Supplies	$391	$347	$408	$382 ($31.48)
Average Case Cost	$1,449	$1,740	$1,813	**$1,667 ($192.57)**

Table 4-6: Total OrganOx Case Cost Per Run

Operative Room Average Cost	$1,667 ($192.57)
Regional Hospital Supply Cost	$1,617.36
OrganOx LTD Supply Cost	$14,708.66 to $16,356.99
Anesthesia Technician Cost	$600
Cumulative Total	**$18,593.02 to $20,241.35**

Table 4-S1: HOPE Supply Costs

Item	Amount	Cost
HTK	8L	$1,000
Aortic cannula	1	$27.45
Perfusion Line	1	$27.70
Sterile Bags for Organ Storage	3	$18
Vessel Cup	1	$2
Sterile Bags for Vessel Storage	2	$2.70
Total		**$1,077.85**

HOPE – Human Organ Procurement and Exchange Program
HTK – Histidine-tryptophan-ketoglutarate

Table 4-S2: Physician Billing Modifiers

BMI of 40 or greater	Increase base pay by 25%
Weekday evening 1700-2200	Add $48.70 to base pay
Weekend and Statutory Holiday 0700-2200	Add $48.70 to base pay
Night Evening 2200-2400	Add $116.83 to base pay
Night Morning 2400-0700	Add $116.83 to base pay

BMI – body mass index

Table 4-S3: University of Alberta Hospital Supply Costs

Item	Amount	Cost
Cefuroxime	750 mg	$4.35
Calcium Gluconate	10 ml of 100 mg/ml	$14.63
Heparin	35 ml of 1000 U/ml	$9.80
Humulin Insulin	3 ml	$3.75
Epoprostenol Sodium (Flolan)	5 ml of 0.5 mg/5 ml	$20.42
pH12 sterile diluent for Flolan	10 ml	$11.39
Sodium Bicarbonate	100 ml of 8.4%	$35.74
Standard Cold Flush Solution (HTK)	2000 ml	$250
Packed RBCs	3 units	$1,266
Sodium Chloride	100 ml	$1.28
Total		**$1,617.36**

HTK – Histidine-tryptophan-ketoglutarate
RBCs – Red blood cells

Table 4-S4: OrganOx LTD Supply Costs

Item	Amount per Run	Cost in 2019 GBP	Cost in 2019 Canadian Dollars	Cost per Run
Sterile single use disposable set (cassettes)	1	£7,500	$11,966.25 to $13,307.25	$11,966.25 to $13,307.25
Terumo shunt sensor	1	Included with cassettes	Included with cassettes	Included with cassettes
Gelofusine	1500 ml	£120 for twenty 500 ml bags	$191.46 to $212.92 for twenty 500 ml bags	$28.72 to $31.94
Nutriflex	1500 ml	£160 for five 1500 ml bags	$255.28 to $283.89 for five 1500 ml bags	$51.06 to $56.78
Sodium Taurocholate	5.6 g	Included with cassettes	Included with cassettes	Included with cassettes
Gas A and Gas B	1	£180 for 83 calibrations	$285.94 to $319.40 for 83 calibrations	$3.46 to $3.85
OrganOx Machine	1	£25,000 Annually	$39,887.50 to $44,357.50 Annually	$2,659.17 to $2,957.17
Total				**$14,708.66 to $16,356.99**

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5 The Cost of Liver Transplantation Admission for OrganOx Normothermic Machine Perfusion Compared to Static Cold Storage in the Canadian Setting

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5.1 Abstract

Background: Liver transplantation has a mismatch between supply and demand. The use of normothermic machine perfusion (NMP) has clinically improved allograft supply and post-transplant complications, especially with the use of extended criteria grafts. We investigated the costs of liver transplantation admission with and without NMP.

Methods: A retrospective cohort study of 59 OrganOx patients propensity score matched to 176 static cold storage (SCS) patients was completed from the time of liver transplantation to hospital discharge, transfer, or death. Data from hospital activity was used to total hospital admission costs. Multiple linear regression calculated the difference in costs between the two groups adjusting for matching, age at transplantation, acute or chronic liver failure, and model for end-stage liver disease score at transplantation.

Results: The total mean adjusted cost was $32,221 2020 CAD$ (p=0.023) higher for OrganOx in comparison to SCS. Transplantation operative costs were significantly higher for OrganOx ($21,673; p<0.001). Costs for length of stay ($4,450; p=0.894), intensive care unit interventions ($7,121; p=0.182), procedures ($4.87; p=0.9), physician billing ($283.55; p=0.9), and radiology ($34.36; p=0.829) were all non-significantly higher for the OrganOx group. Costs for takeback operations (-$960.32; p=0.113) and blood products (-$746.29; p=0.607) were non-significantly lower for the OrganOx group.

Discussion: Although OrganOx use may theoretically lead to cost savings in terms of staff and patient outcomes, we did not see this in the current study. Total cost of the transplantation admission was significantly higher for the OrganOx group compared to

the SCS group. This was mainly from the increased costs of the OrganOx machine at the time of transplantation.

5.2 Introduction

Liver transplantation is the only curative treatment for end-stage liver disease. However, over the last decade there has been a decrease in the available liver grafts for transplantation [4]. This has led to an increase in the use of extended criteria donors (ECD), which increases the risk of post-transplantation complications due to ECD being more susceptible to static cold storage (SCS) [7, 8]. Normothermic machine perfusion (NMP) has been a focus of liver transplantation research to helps address both these concerns. The OrganOx metra machine, based out of the United Kingdom (UK), is one machine used for NMP [12]. Additionally, the OrganOx machine allows for assessment of the graft prior to transplantation [12].

A randomized control trial (RCT) by Nasralla et al. comparing the OrganOx machine and SCS, which showed no statistical difference between groups for total length of stay (LOS), intensive care unit (ICU) LOS, primary non-function, biliary complications, major complications, re-transplantation rates, graft survival, and patient survival [23]. The RCT did show significantly lower rates of graft discard, rates of early allograft dysfunction, and peak aspartate aminotransferase (AST) levels in the OrganOx group [23]. The promising clinical results of this RCT suggests that assessment of the cost of this technology is important prior to a transplantation program considering implementing the OrganOx machine. There have been very few studies assessing the cost of this

technology. It would be expected based on the Nasralla et al. RCT that the only additional cost during the liver transplant admission would be for use of the technology itself. This study will provide the transplantation admission costs and compare the cost differences between the OrganOx machine and SCS.

5.3 Methods

Ethics approval was obtained through the Health Research Ethics Board – Health Panel. All adult deceased donor liver transplantations at the University of Alberta (UofA) hospital were identified from the liver transplantation database between April 23, 2013 to Dec 31, 2019. A total of 59 patients were identified as receiving an OrganOx liver transplantation and 368 patients who received a SCS liver transplantation. The 59 OrganOx patients were propensity score matched with up to three nearest neighbours of SCS patients using the matching characteristics of age at transplantation, Model for End-Stage Liver Disease Sodium (MELDNa) score at transplantation, and acute or chronic liver failure. Of the 59 OrganOx patients 58 had 3 controls and 1 patient had 2 controls. The final study population included 59 OrganOx patients and 176 propensity score matched SCS patients, totaling 235 patients.

A retrospective chart review was completed for the cohort to obtain data on activity from the date and time of liver transplantation to the date and time of hospital discharge, hospital transfer, or in-hospital death. All costs are in 2020 Canadian dollars. The length of stay (LOS) was divided by time in the intensive care unit (ICU) and ward. The LOS cost was calculated from Evans et al. with each cost for readmission to the ICU or ward

starting again at the day 1 cost (**Table 5-S1**) [33, 77]. The number of physician consultations and number of daily rounds, for both the most responsible physician and consulted physicians, was documented and billing cost applied from the regional Health Service Codes Fee Navigator [65].

The transplantation operation date, time, and body mass index (BMI) of patients were collected and cost was calculated based on the previous study published by our group [78]. Costs for basaliximab and thymoglobulin post-transplantation was provided by the University of Alberta pharmacy (**Table 5-S2**). Takeback operations, classified as operations to manage post-transplantation complications, were identified and costs were calculated with the average case cost from the Lighthouse Surgical Financial System and surgeon and anesthesiologist billings from the regional Health Service Codes Fee Navigator [65]. Lighthouse is a financial monitoring system used by the operating room to track actual costs of operative cases, including overhead costs, supply costs, and nursing salaries [62]. Other operations, classified as operations not for post-transplantation complications, and other procedures/interventions were calculated from the regional Health Service Codes Fee Navigator (**Table 5-S1**) [65].

All radiological investigations and interventions were obtained through the Impax radiology software advanced search using the dates of transplantation and hospital discharge with a specific patient identifier. All radiological costs were provided by the University of Alberta Radiology Department (**Table 5-S3**).

The ICU database provided in minutes the use of intubation, continuous renal replacement therapy (CRRT), intermittent hemodialysis (IHD), vasopressors, total parenteral nutrition (TPN), and enteral nutrition. The vasopressors collected were dobutamine, epinephrine, isoproterenol, milrinone, norepinephrine, phenylephrine, and vasopressin. Costs were calculated from the literature and the University of Alberta pharmacy and distribution center (**Table 5-S2**) [79, 80]. The amount of blood product was totaled and costs were calculated from Alberta Precision Laboratories, literature, and verbal reference (**Table 5-S4**) (Susan Nahirniak, M.D., email communication, Nov 12, 2020) [81].

All statistical analysis was completed using STATA 16.1 (StataCorp LLC, College Station, Texas USA) with statistical significance set as a p value of less than 0.05. A multiple linear regression model adjusting for matching, age at transplantation, MELDNa at transplantation, and acute or chronic liver failure was completed. As a sensitivity analysis a number of additional analyses were completed including non-parametric, 5% trimming to remove outliers, multiple linear regression without adjustment for matched characteristics, and generalized linear modeling. The first subgroup analysis was completed after the removal of patients who died in hospital or were transferred to another hospital during the admission with matching maintained. Two further subgroup analyses were completed where matching was not maintained: second for status 1 and 2 patients and third for status 3 and 4 patients. In the Canadian transplantation system status 1 patients are coming in from home, status 2 patients are admitted to a non-ICU

hospital ward, status 3 patients are admitted to ICU but are not intubated, and status 4 patients are admitted to ICU and are intubated [82].

5.4 Results

A total of 235 patients underwent chart review, 59 having had an OrganOx liver transplantation and 176 having had SCS liver transplantation. The two groups were comparable in baseline characteristics (**Table 5-1**). For data that is not normally distributed the median can be more reflective of the central tendency than the mean, for this data set multiple costs had a median and an interquartile range of zero. Therefore, the means have been presented. In the sensitivity analyses, all results remained robust and were nearly identical to the main analysis (data not shown)**.** The mean total cost of the transplantation admission was $119,424.20 for the SCS group and $155,318.50 for the OrganOx group (**Table 5-2**). The mean adjusted difference was significantly higher at $32,220.61 (p=0.023) for the OrganOx group (**Table 5-2**). This cost difference is largely from the increase cost of the transplant operation, $21,673.43 (p <0.001). which is mainly from the cost of the OrganOx machine and its supplies. The average OrganOx cost per transplantation in the 59 patients was $20,746.62.

The addition of the cost per run of the OrganOx machine to the mean total cost for the SCS group is a 17% increase (**Figure 5-1**). The mean total cost for the OrganOx group was an extra 11% higher than that (**Figure 5-1**). The additional 11% is from LOS and ICU intervention costs (**Table 5-2, Figure 5-2**). Overall, the majority of the mean total

cost is from the transplant operation and LOS, where this accounts for 77% of the total cost in both groups (**Figure 5-3 and 5-4**).

The overall LOS was comparable between the groups, while the OrganOx group was in ICU for an additional 2.7 days with a shorter ward stay by 2.3 days, leading to an additional $4,450.70 for overall LOS cost for the OrganOx group (**Table 5-2**). Due to the increased ICU LOS the OrganOx group had an additional $7,121.12 for ICU interventions, mainly from intubation (**Table 5-3, Figure 5-5**). The total cost of the ICU admission and the breakdown of the individual ICU costs were not significantly different between groups (**Table 3**). However, the OrganOx group had higher costs for length of stay ($6,117.72; p=0.36), intubation ($7,017.68; p=0.175), dialysis ($90.04; p=0.748), and procedures in ICU ($15.43; p=0.705). The OrganOx group had lower cost for feeds ($-0.64; p=0.996).

The rest of the total cost is made up of the main regions of takeback operations, procedures, physician billings, radiology, and blood costs. There were no statistically significant differences in these costs between the two groups (**Table 5-2**). However, the OrganOx group had a higher cost for ICU interventions ($7,121.12; p=0.182), procedures ($4.87; p=0.9), physician billing ($283.55; p=0.677), and radiology ($34.36; p=0.829). The OrganOx group had a lower cost for takeback operations (-$960.32; p=0.113) and blood (-$746.29; p=0.607).

The total cost for radiology was not statistically different between groups (**Table 5-4**). The OrganOx group had a significantly lower cost for abdominal magnetic resonance imaging (MRI) ($17.07; p=0.028) and interventional radiology ($23.34; p=0.019). The OrganOx group had non-significantly higher costs for x-ray ($51.93; p=0.289), ultrasound ($13.90; p=0.871), and computed tomography (CT) ($23.49; p=0.273). The OrganOx group had non-significantly lower costs for magnetic resonance imaging (MRI) (-$9.17; p=0.498) and other radiologic interventions (-$22.32; p=0.492).

The total cost of blood product was not significantly different between groups (**Table 5-5**). The OrganOx group had a significantly lower cost for cryoprecipitate (-$201.75; p=0.022). The OrganOx group had non-significantly higher costs for albumin ($171.80; p=0.166) and other blood products ($584.41; p=0.435). The OrganOx group had non-significantly lower costs for packed red blood cells (-$955.46; p=0.303), platelets (-$6.68; p=0.944), plasma (-$234.25; p=0.253), and fibrinogen (-$104.40; p=0.544).
In the first subgroup analysis only patients who were successfully transplanted and discharged home were included. Matching was maintained and the baseline characteristics were comparable, except for re-transplantation (p=0.042) (**Table 5-S5**). The total cost between the two groups was no longer statistically significant, however, the OrganOx group still had a higher cost of $23,597.05 (p=0.074) (**Table 5-S6**). The higher total cost for the OrganOx group was primarily due to the higher transplant operation cost from use of the OrganOx machine, $21,629.02 (p<0.001) (**Table 5-S6**). The total LOS of the OrganOx group was shorter by 1 day with the ICU LOS being 1.5 days longer and the ward LOS being 2.7 days shorter compared to the SCS group. The

total LOS cost was $294.03 (p=0.97) lower for the OrganOx group. All other major cost regions were not statistically different. However, the OrganOx group only had higher costs for ICU interventions ($4,398.25; p=0.347) while the OrganOx group had lower costs for takeback operations (-$720.45; p=0.259), procedures (-$12.01; p=0.749), physician billing (-$101.14; p=0.884), radiology (-$5.99; p=0.97), and blood products (-$1,086.07; p=0.47).

The second subgroup analysis of status 1 and 2 patients showed that the total cost was non-significant higher for the OrganOx group at $28,230.52 (p=0.061) with a higher transplant operation cost of $21,536.83 (p<0.001) (**Table 5-S7**). The total LOS was 0.78 days shorter, with ICU LOS 2.36 days longer and ward LOS 3.14 days shorter for the OrganOx group in comparison to the SCS group.

The third subgroup analysis of status 3 and 4 patients showed that the total cost was significantly higher for the OrganOx group at $104,416.30 (p=0.015) with a higher transplant operation cost of $23,028.75 (p<0.001) (**Table 5-S7**). The total LOS was 17.65 days longer, with ICU LOS of 10.99 days longer and ward LOS 6.66 days longer for the OrganOx group in comparison to the SCS group. In addition to the higher transplant operation costs the higher costs for LOS and ICU intervention leads to the significantly higher total cost for the OrganOx group in status 3 and 4 patients.

5.5 Discussion

The mean cost of the OrganOx machine per run would be an additional 17% above the mean total cost of the SCS transplantation admission. The mean total cost of the OrganOx transplantation admission was 11% higher, an additional $10,000. This additional cost was attributable to longer ICU LOS and ICU interventions. This is from patients that were transferred to another hospital or died during their transplantation admission as the subgroup analysis excluding these patients showed a total cost that was primarily from cost of the OrganOx machine itself. This suggests that patients who died or were transferred had a longer ICU LOS and more ICU interventions leading to higher total costs. Similarly, Harries et al. found that patients who died in the first-year post-transplantation had significantly higher costs than those who survived, secondary to medical care in the ICU [36].

This study showed OrganOx patients had a slightly longer total and ICU LOS in comparison to the SCS group. This is different from the results of the Nasralla et al. randomized control trial (RCT) where total LOS and ICU LOS were not significantly different between treatment arms [23]. This difference is likely due to variation in characteristics of this study population compared to characteristics of those in the RCT. This study population had higher mean MELD scores with a wider range, more males, higher BMIs, and more DBD grafts [23]. Indication for transplantation also varied with this study population having about half the amount of cirrhosis secondary to alcohol and double the amount of hepatocellular carcinoma [23].

One of the driving factors of transplant admission costs is the overall severity of illness of the patient prior to transplantation [35, 51, 52]. The subgroup analysis of status 1 and 2 patients showed that the OrganOx group had a higher mean total cost of $28,000, with $21,500 attributable to use of the OrganOx machine and $7,000 attributable to longer ICU LOS and ICU interventions. Matching was not maintained in this subgroup analysis but the mean MELDNa score for both groups was 17. The mean total costs of the status 1 and 2 patients (OrganOx $141,126.60 SD $100,900.10 and SCS $110,062.40 SD $98,086.63) were similar to the mean total costs in the subgroup analysis excluding deaths and transfers. The subgroup analysis of status 3 and 4 patients showed a significantly higher cost for the OrganOx group, with both groups having substantially higher mean total costs compared to the main analysis. This further supports that severity of overall illness is a driving factor of the index transplant admission costs. Matching was not maintained in this subgroup analysis with the mean MELDNa score of 37.8 in the OrganOx group and 33.1 in the SCS group. It has been well documented that higher MELD scores at the time of transplant predict higher admission costs, longer ICU LOS, increased ICU interventions, and longer total LOS [38, 39, 45, 47, 49, 51, 52]. This increased cost in this analysis was attributable to longer ICU and ward LOS, ICU interventions, and takeback operations. The higher MELDNa score in the OrganOx group is the driving factor leading to the higher cost in this analysis. It should be noted that the status 2 through 4 patients will have costs associated with their pre-transplantation hospital admission that are not accounted for in the costing for this study.

It should be noted that the cost per run of the OrganOx machine in this study is the projected commercial cost based on the costs presented in Webb et al. [78]. Currently, the OrganOx machine is still pending full Health Canada approval and is currently undergoing clinical trial in the United States of America, Toronto Canada, and Edmonton Canada [26-28, 32]. During the clinical trial the actual cost of the OrganOx machine to the health system is lower, as there is no cost for the machine itself.

This study has multiple limitations. The costing in this study does not include any costs from the time of waitlist to the time of transplantation or costs accumulated after post-transplantation hospital discharge or transfer, which could include outpatient or inpatient care. These costs to the health system can be substantial but were not the focus in this study but should be considered in a formal economic evaluation. Secondly, the literature-based costs may not be reflective of the actual costs. Thirdly, the opportunity costs for the hospital were not assessed nor were the potential costs and societal losses for the patient and their caregivers.

This cost analysis adds to the evolving knowledge around the use and cost of the OrganOx machine, however, a formal economic evaluation should be completed to help further inform decisions about the use of the OrganOx machine in liver transplant programs. A cost-utility analysis of the OrganOx was recently published in 2020 and showed OrganOx to be cost-effective with an incremental cost-effectiveness ratio (ICER) of £7,876 per quality-adjusted life year (QALY) gain in 2018 United Kingdom

pound sterling [20]. At a £20,000 willingness to pay threshold the OrganOx has a 99% probability of being cost-effective [20]. The majority of the clinical outcomes for their model came from the Nasralla et al. RCT [20]. As discussed earlier, there are multiple differences in the baseline characteristics of this study population and RCT study population; therefore, an economic evaluation is warranted in the Canadian setting using this cost data.

In conclusion, this cost analysis showed the OrganOx group to have a significantly higher cost than the SCS group. The majority of the increased cost comes from the OrganOx machine and supplies with the additional costs coming from treatment in the ICU of patients who died or transferred to another hospital. This study supports the current literature of higher MELD scores and overall severity of illness being cost driving factors in liver transplantation. This data will be used to complete an economic evaluation of the OrganOx machine in the Canadian setting.

Table 5-1: Baseline characteristics of study population

	OrganOx Liver Transplant	**Static Cold Storage Liver Transplant**	**P Value**
Participants	59	176	
Age at Transplant (SD)	53.85 (11.20)	54.56 (9.63)	0.526
Sex **Male (%)** **Female (%)**	 46 (77.97) 13 (22.03)	 140 (79.55) 36 (20.45)	0.749
MELDNa at Transplant (SD)	19.07 (9.49)	18.63 (9.24)	0.663
Re-Transplants (%)	5 (8.47)	15 (8.52)	0.318
Liver Failure **Acute (%)** **Chronic (%)**	 5 (8.47) 54 (91.53)	 6 (3.41) 170 (96.59)	0.064
Procurement Location **Alberta (%)** **Outside Alberta (%)**	 36 (61.02) 23 (38.98)	 127 (72.16) 49 (27.84)	0.112

MELDNa – Model for End-stage Liver Disease Sodium

Table 5-2: Overview of Length of Stay and Major Cost Regions

	Mean (SD)		Mean Adjusted Difference (95% Confidence Interval)[1]	P Value
	OrganOx Liver Transplant (n=59)	Static Cold Storage Liver Transplant (n=176)		
Length of Stay				
Total	26.40 (23.34)	25.37 (24.22)	0.393 (-5.48 – 6.26)	0.894
ICU	10.42 (16.42)	7.25 (11.48)	2.728 (-1.09 – 6.54)	0.158
Ward	15.98 (12.81)	18.12 (17.59)	-2.34 (-6.37 – 1.70)	0.251
Total Cost ($CAD)	155,318.50 (110,165.30)	119,424.20 (99,101.23)	32,220.61 (4,540.56 – 59,900.66)	**0.023**
Length of Stay Cost ($CAD)				
Total	61,253.37 (60,417.22)	54,810.19 (55,169.26)	4,450.70 (-11,638.65 – 20,540.04)	0.582
ICU	36,501.66 (50,641.87)	28,607.06 (40,952.68)	6,117.72 (-7,166.56 – 19,402.01)	0.36
Ward	24,751. 71 (20,004.03)	26,203.13 (24,789.59)	-1,667.03 (-7,733.53 – 4,399.48)	0.584
Transplant Operation ($CAD)	57,968.48 (6,887.86)	36,070.96 (6,651.12)	21,673.43 (19,571,48 – 23,775.38)	**<0.001**
ICU Interventions ($CAD)	17,418.86 (42,019.31	9,285.53 (23,131.24)	7,121.12 (-3,431.42 – 17,673.65)	0.182
Takeback Operations ($CAD)	744.85 (1,975.10)	1,701.04 (8,794.76)	-960.32 (-2,154.51 – 233.87)	0.113
Procedures ($CAD)	122.09 (300.68)	120.37 (349.25)	4.87 (-71.98 – 81.72)	0.9
Physician Billing ($CAD)	4,688.12 (5,748.95)	4,252.62 (5,369.52)	283.55 (-1,073.04 – 1,640.14)	0.677
Radiology ($CAD)	1,301.74 (1,251.84)	1,249.74 (1,383.45)	34.36 (-282.18 – 350.91)	0.829
Blood Product ($CAD)	9,538.41 (10,120.51)	9,995.59 (12,583.00)	-746.29 (-3,637.60 – 2,145.02	0.607

1 adjusted for age at transplant, MELDNa at transplant, chronic liver failure, and matched participants
$ in 2020 Canadian Dollars
ICU – Intensive Care Unit

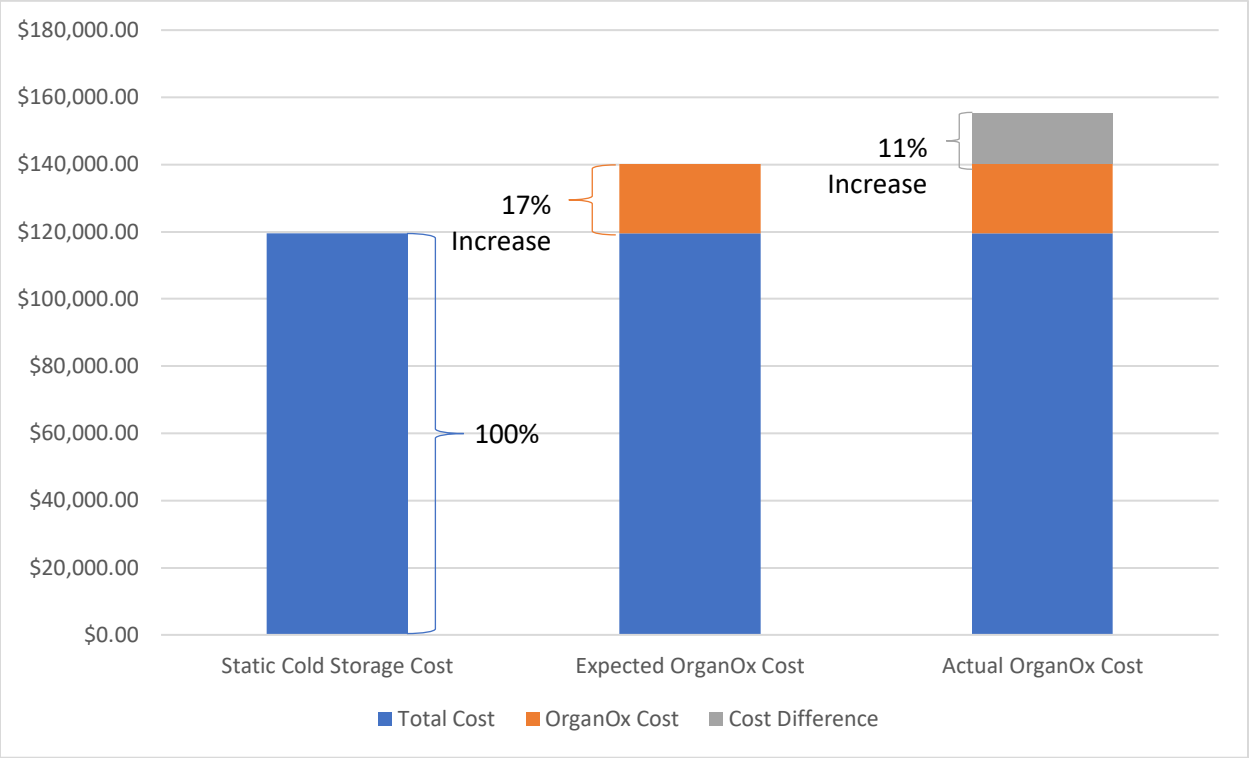

Figure 5-1: The percent increase above the static cold storage transplant admission cost for the expected OrganOx transplant admission cost and the percent increase above the expected OrganOx transplant admission cost for the actual OrganOx transplant admission cost

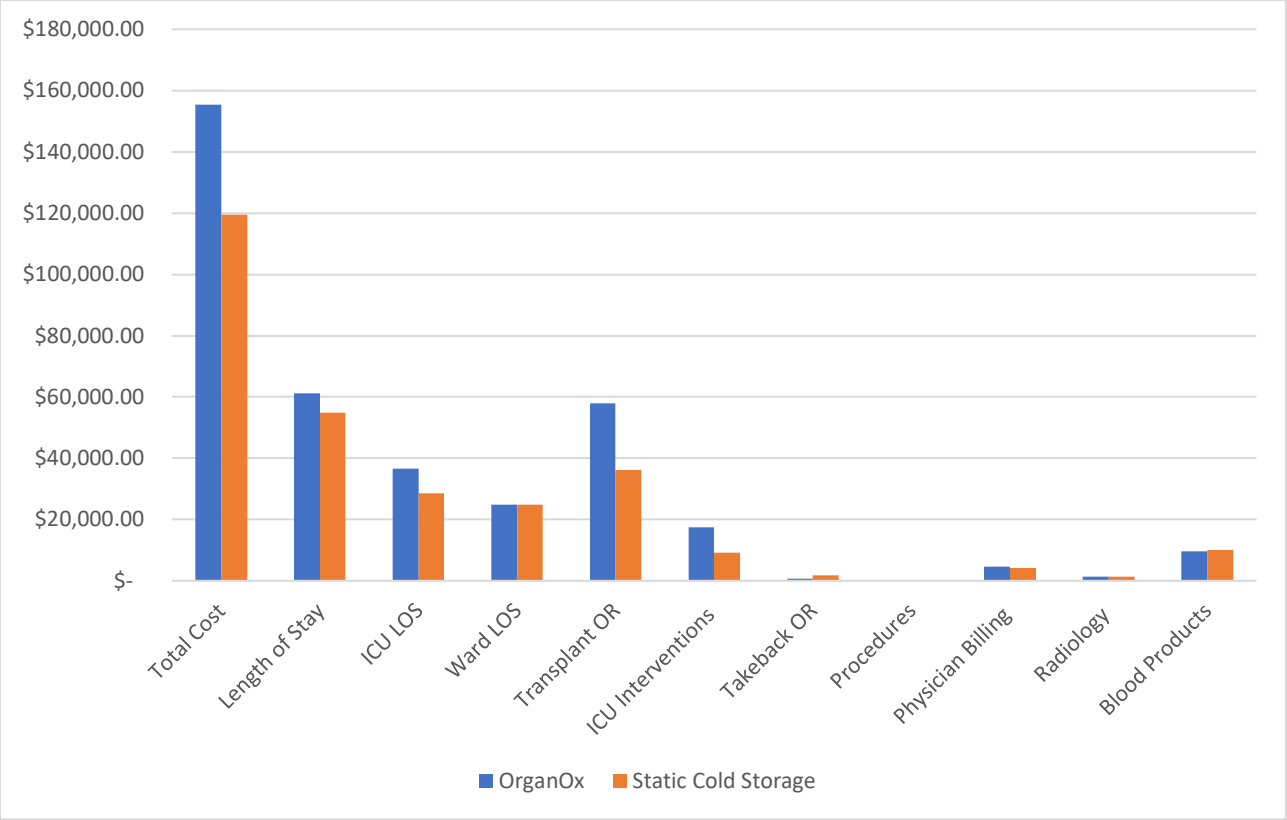

Figure 5-2: Major Cost Categories for OrganOx group and Static Cold Storage group

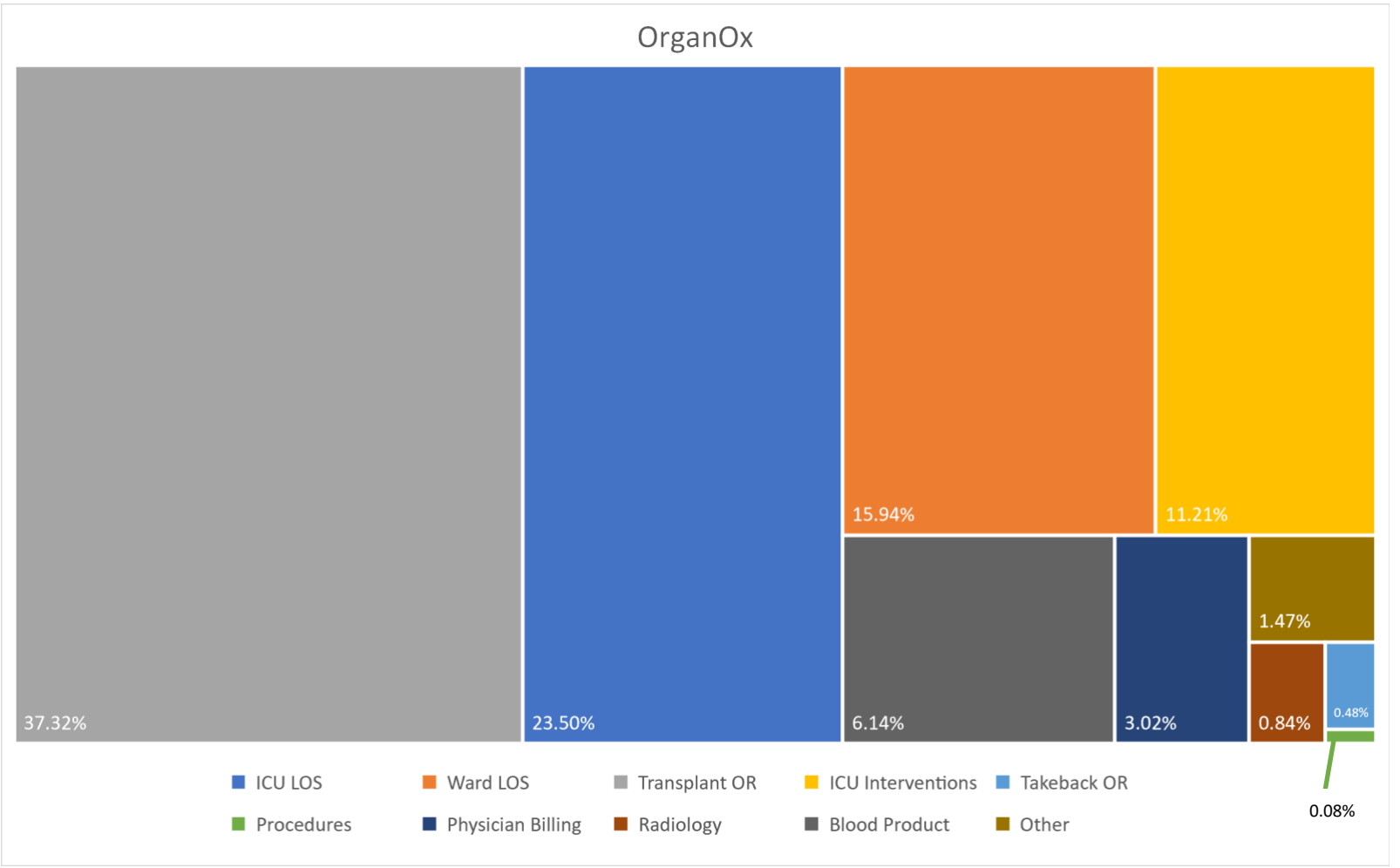

Figure 5-3: Breakdown of OrganOx group cost categories

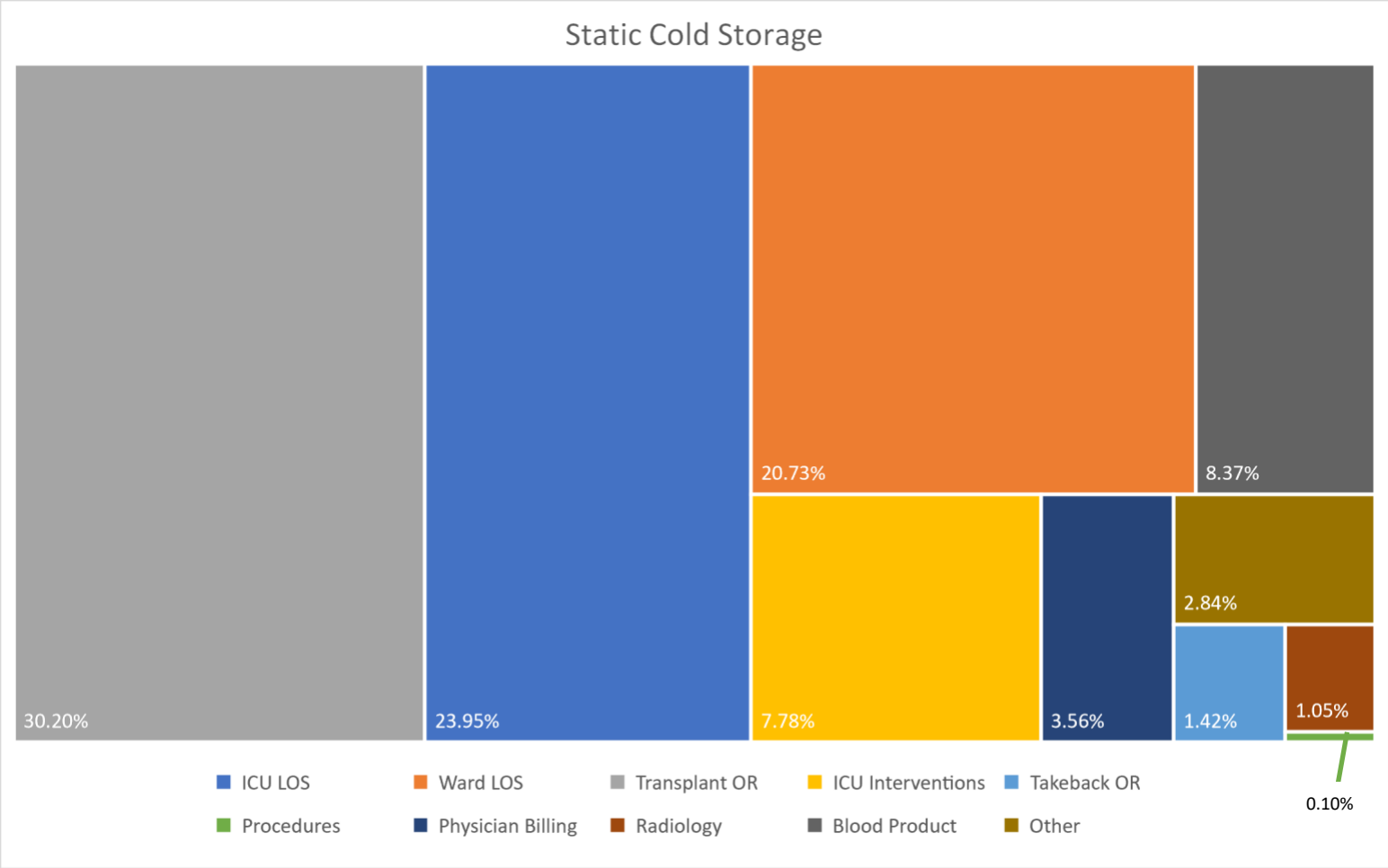

Figure 5-4: Breakdown of Static Cold Storage group cost categories

Table 5-3: Intensive Care Unit Cost Breakdown

	Mean (SD)		Mean Adjusted Difference (95% Confidence Interval)[1]	P Value
	OrganOx Liver Transplant (n=59)	Static Cold Storage Liver Transplant (n=176)		
Total ($CAD)	54,009.95 (87,355.29)	37,964.98 (62,836.70)	13,254.26 (-8,962.37 – 35,470.90)	0.237
Length of Stay Cost ($CAD)	36,501.66 (50,641.87)	28,607.06 (40,952.68)	6,117.72 (-7,166.56 – 19,402.01)	0.36
Intubation ($CAD)	16,476.62 (40,344.62)	8,563.73 (21,423.41)	7,017.68 (-3,216.46 – 17,251.81)	0.175
Dialysis ($CAD)	450.98 (2,016.03)	315.77 (1,423.30)	90.04 (-467.59 – 647.67)	0.748
Feeds ($CAD)	446.15 (1,156.14)	373.36 (1,033.26)	-0.64 (-278.52 – 277.25)	0.996
Procedures in ICU ($CAD)	89.44 (281.51)	72.39 (279.20)	15.43 (-65.81 – 96.67)	0.705

1 adjusted for age at transplant, MELDNa at transplant, chronic liver failure, and matched participants
$ in 2020 Canadian Dollars

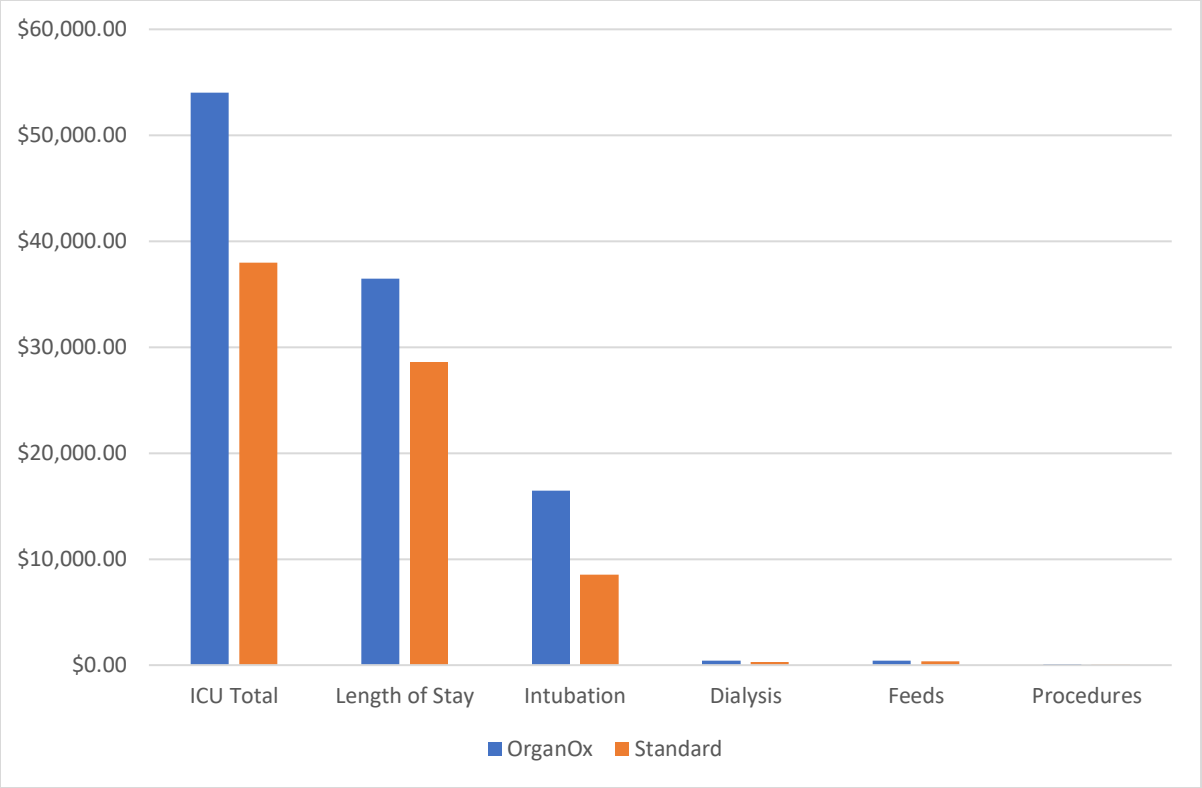

Figure 5-5: Intensive Care Unit Total Cost and Breakdown of Individual Costs

Table 5-4: Radiology Cost Breakdown

	Mean (SD)		Mean Adjusted Difference (95% Confidence Interval)[1]	P Value
	OrganOx Liver Transplant (n=59)	**Static Cold Storage Liver Transplant (n=176)**		
Total ($CAD)	1,301.74 (1,251.84)	1,249.74 (1,383.45)	34.36 (-282.18 – 350.91)	0.829
X-ray ($CAD)	340.87 (385.23)	287.71 (340.97)	51.93 (-45.12 – 148.78)	0.289
Chest	300.15 (351.18)	254.09 (307.56)	44.77 (042.47 – 131.98)	0.308
Abdomen	31.45 (57.48)	22.96 (37.59)	7.18 (-8.17 – 22.53)	0.353
Ultrasound ($CAD)	721.49 (557.28)	702.20 (674.87)	13.90 (-156.08 – 183.89)	0.871
Abdominal	661.70 (485.09)	634.07 (590.83)	19.87 (-131.87 – 171.61)	0.794
CT ($CAD)	87.86 (167.65)	60.53 (116.29)	23.49 (-19.04 – 66.02)	0.273
Abdominal	60.30 (111.49)	38.78 (92.37)	20.45 (-6.69 – 47.58)	0.137
MRI ($CAD)	35.68 (107.67)	44.10 (99.38)	-9.17 (-36.07 – 17.73)	0.498
Abdominal	11.18 (41.98)	28.92 (80.65)	-17.07 (-32.19 – -1.94)	**0.028**
Interventional Radiology ($CAD)	11.35 (57.69)	33.87 (135.53)	-23.34 (-42.79 – -3.94)	**0.019**
Other ($CAD)	104.50 (242.00)	121.32 (328.90)	-22.32 (-87.01 – 42.36)	0.492
VFSS	16.40 (57.57)	27.49 (108.28)	-20.11 (-43.49 – 3.28)	0.091
PICC	48.99 (92.95)	50.54 (122.27)	-2.15 (-31.21 – 26.91)	0.883

1 adjusted for age at transplant, MELDNa at transplant, chronic liver failure, and matched participants
$ in 2020 Canadian Dollars

CT – computed tomography
MRI – magnetic resonance imaging
VFSS – video fluoroscopic swallow study
PICC – peripherally inserted central catheter

Table 5-5: Blood Product Cost Breakdown

	Mean (SD)		Mean Adjusted Difference (95% Confidence Interval)[1]	P Value
	OrganOx Liver Transplant (n=59)	Static Cold Storage Liver Transplant (n=176)		
Total ($CAD)	9,538.41 (10,120.51)	9,995.59 (12,583.00)	-746,29 (-3,637.60 – 2,145.02)	0.607
Albumin ($CAD)	938.14 (893.94)	787.84 (802.88)	171.80 (-73.53 – 417.13)	0.166
Packed red blood cells ($CAD)	4,858.98 (6,129.74)	5,732.46 (8,586.07)	-955.46 (-2,794.67 – 883.74)	0.303
Platelets ($CAD)	598.60 (844.03)	547.29 (895.12)	-6.68 (-197.57 – 184.21)	0.944
Plasma ($CAD)	1,330.62 (1,216.63)	1,555.07 (2,196.89(	-234.25 (-639.97 – 171.46)	0.253
Cryoprecipitate ($CAD)	84.70 (320.14)	240.63 (672.30)	-201.75 (-372.76 - -30.74)	**0.022**
Fibrinogen ($CAD)	316.78 (818.25)	336.28 (1,109.82)	-104.40 (-446.99 – 238.18)	0.544
Other ($CAD)	1,410.56 (5,112.48)	796.02 (3,465.01)	584.41 (-903.96 – 2,072.77)	0.435

1 adjusted for age at transplant, MELDNa at transplant, chronic liver failure, and matched participants
$ in 2020 Canadian Dollars

Table 5-S1: Cost breakdown for LOS, ICU interventions, and procedures

Variable	Cost (2020 CAD$)	Source
ICU LOS		Evans et al. [33, 77]
Day 1	5,742.45	
Day 2	4,088.70	
Day 3	3,706.50	
Day 4	3,613.05	
Day 5 +	3,513.30	
Ward LOS		Evans et al. [33, 77]
Day 1	2,042.25	
Day 2	1,698.90	
Day 3	1,735.65	
Day 4	1,579.20	
Day 5 +	1,381.80	
Intubation (per day)	3,251.61	Dasta et al. [33, 34, 79]
Continuous Rental Replacement (per day)		Manns et al. [33, 80]
No anticoagulation	870.24	
Citrate	1,074.57	
Heparin	774.69	
Intermittent Hemodialysis (per run)	505.68	Manns et al.[33, 80]
Physician Consultation	184.62	AMA Fee Navigator[65]
Most Responsible Physician Rounding	82.67	AMA Fee Navigator[65]
Consultation Physician Rounding	42.26	AMA Fee Navigator[65]
Bronchoscopy	132.62	AMA Fee Navigator[65]
Tracheostomy	390.89	AMA Fee Navigator[65]
Gastroscopy	113.99	AMA Fee Navigator[65]
Endoscopic retrograde cholangiopancreatography	262.18	AMA Fee Navigator[65]
Lumbar Puncture	127.45	AMA Fee Navigator[65]
Colonoscopy	180.21	AMA Fee Navigator[65]
Coronary Catheterization	288.75	AMA Fee Navigator[65]
Electroencephalogram	132.56	AMA Fee Navigator[65]
Transthoracic Echocardiogram	230.00	AMA Fee Navigator[65]
Transesophageal Echocardiogram	288.75	AMA Fee Navigator[65]
Pericardiocentesis	218.04	AMA Fee Navigator[65]
Holter Monitor	57.75	AMA Fee Navigator[65]

AMA – Alberta Medical Association
ICU – intensive care unit
LOS – length of stay

Table 5-S2: Medication costs

Variable	Cost (2020 CAD$)	Source
Basiliximab per dose	1790.00	UofA Pharmacy
Thymoglobulin 25mg vial	314.00	UofA Pharmacy
Total Parenteral Nutrition Lipids 500ml Amino acid dextrose 3L	 16.90 76.39	UofA Pharmacy
Enteral Nutrition	70.79	UofA Pharmacy
Epinephrine 1ml vial	1.24	UofA Pharmacy
Norepinephrine 4ml vial	2.60	UofA Pharmacy
Phenylephrine 10ml vial	1.70	UofA Pharmacy
Isoproterenol 0.2ml vial	10.86	UofA Pharmacy
Milrinone 10ml vial	4.74	UofA Pharmacy
Vasopressin 1ml vial	17.52	UofA Pharmacy
Dobutamine 20ml vial	2.40	UofA Pharmacy
Normal Saline 100ml bag 250ml bag	 1.28 1.20	UofA Distribution Center

UofA – University of Alberta

Table 5-S3: Radiology costs

Variable	Cost (2020 CAD$)	Source
X-ray		UofA Radiology Department
Chest	38.92	
Abdomen	41.24	
Panorex	45.86	
Kidney, ureter, bladder	45.86	
Shoulder - unilateral	54.72	
Humerus - unilateral	36.61	
Elbow - unilateral	33.14	
Radius and Ulna - unilateral	36.61	
Hand - unilateral	32.37	
Spine (C, T, and L each individually)	68.98	
Hip - unilateral	47.40	
Pelvis	47.40	
Hip and Pelvis	61.27	
Knee - unilateral	42.01	
Ankle - unilateral	37.00	
Foot - unilateral	32.37	
Ultrasound		UofA Radiology Department
Complete abdomen	200.39	
Limited abdomen	102.90	
Abdominal doppler	242.78	
Abdominal paracentesis	121.62	
Liver biopsy	102.90	
Chest		
Unilateral	84.78	
Bilateral	161.08	
Chest thoracentesis	84.78	
Upper limb doppler		
Unilateral	121.17	
Bilateral	241.62	
Lower limb doppler		
Unilateral	121.17	
Bilateral	241.62	
Groin doppler		
Pelvis	127.17	
Kidney/Bladder	173.03	
ABI	84.78	
Wrist	115.23	
Scrotum	127.17	
Carotid		
Unilateral	127.37	
Bilateral	254.73	

Computed Tomography		UofA Radiology Department
Abdomen	121.62	
Abdomen with angiography	147.48	
Head	55.03	
Head with angiography	147.48	
Chest	121.62	
Chest with angiography	147.48	
Pulmonary embolism protocol	147.48	
Chest, abdomen, and pelvis	218.91	
Chest and abdomen	145.94	
Magnetic Resonance Imaging		UofA Radiology Department
Abdomen	188.54	
Abdomen with angiography	157.12	
Brain	157.12	
Brain with angiography	157.12	
Lumbar spine	188.54	
Nuclear Medicine		UofA Radiology Department
SPECT Ventilation Scan	286.15	
SPECT Perfusion Scan	296.17	
Liver	311.77	
Interventional Radiology		UofA Radiology Department
Cholangiogram	173.42	
Transjugular liver biopsy	197.31	
Venous catheter placement	197.31	
Biliary catheter placement	197.31	
Chest embolization		
1 hour	290.19	
2 hours	386.92	
3 hours	483.65	
4 hours	580.38	
Other		UofA Radiology Department
Videofluoroscopic swallowing study	161.28	
Peripherally inserted central catheter	222.36	
Flouro guided gastrostomy tube placement	187.29	
Flouro of upper gastrointestinal system	107.52	
Endoscopic retrograde cholangiopancreatography	197.31	
Lumbar puncture/myelogram	197.31	

Table 5-S4: Blood product costs

Variable	Cost (2020 CAD$)	Source
Albumin		Verbal
25% 50ml	30	
25% 100ml	60	
5% 250 ml	30	
5% 500ml	60	
Packed red blood cells		Alberta Precision Labs, Verbal, and Lagerquist et al. [33, 81]
Regular	702.31	
Irradiated	752.31	
Platelets		Alberta Precision Labs, Verbal, and Lagerquist et al. [33, 81]
Regular	317.35	
Irradiated	367.35	
Irradiated apheresis	367.35	
Plasma		Alberta Precision Labs, Verbal, and Lagerquist et al. [33, 81]
Regular	191.64	
Apheresis	540.82	
Cryosupernatant	110.59	
Fibrinogen	445	Verbal
Cryoprecipitate	110.59	Alberta Precision Labs [33]
HepaGam B® 5ml	875	Verbal
Octaplex® 1000 IU	580	Verbal
Beriplex® 1000 IU	580	Verbal
Factor XIIIA Subunit 2500 IU	27,000	Verbal
Elocate®		Verbal
500 IU	399	
750 IU	465	
1000 IU	620	
Hepatitis B Immune Globulin 5ml	720	Verbal

Table 5-S5: Baseline characteristics of study population excluding deaths and hospital transfers

	OrganOx Liver Transplant	**Static Cold Storage Liver Transplant**	**P Value**
Participants	56	164	
Age at Transplant (SD)	54.30 (10.91)	54.75 (9.69)	0.692
Sex **Male (%)** **Female (%)**	 44 (78.57) 12 (21.43)	 132 (80.49) 32 (19.51)	 0.704
MELDNa at Transplant (SD)	18.68 (9.15)	18.57 (8.97)	0.918
Re-Transplants (%)	5 (8.93)	15 (9.15)	**0.042**
Liver Failure **Acute (%)** **Chronic (%)**	 4 (7.14) 52 (92.86)	 5 (3.05) 159 (96.95)	 0.094
Procurement Location **Alberta (%)** **Outside Alberta (%)**	 35 (62.50) 21 (37.50)	 119 (72.56) 45 (27.44)	 0.17

MELDNa – Model for End-stage Liver Disease Sodium

Table 5-S6: Overview of Length of Stay and Major Cost Regions for study population excluding deaths and hospital transfers

	Mean (SD)		Mean Adjusted Difference (95% Confidence Interval)[1]	P Value
	OrganOx Liver Transplant (n=59)	Static Cold Storage Liver Transplant (n=176)		
Length of Stay				
Total	24.0 (20.54)	24.73 (23.48)	-1.15 (-6.91 – 4.60)	0.69
ICU	8.47 (14.08)	6.70 (9.96)	1.57 (-1.79 – 4.93)	0.352
Ward	15.53 (10.20)	18.03 (16.72)	-2.73 (-6.78 – 1.32)	0.183
Total Cost ($CAD)	141,004.00 (92,916.41)	115,538.30 (95,009.66)	23,597.05 (-2,357.23 – 49,531.32)	0.074
Length of Stay Cost ($CAD)				
Total	53,636.73 (51,176.78)	52,704.15 (52,122.19)	-294.03 (-15,934.93 – 15,346.86)	0.97
ICU	29,419.36 (39,768.67)	26,643.44 (35,765.71)	1,815.03 (-9,910.06 – 13,540.11)	0.758
Ward	24,217.38 (16,873.64)	26,060.71 (23,532.83)	-2,109.06 (-8,110.43 – 3,892.31)	0.484
Transplant Operation ($CAD)	57,772.52 (6,843.11)	36,016.02 (6,612.30)	21,629.02 (19,419.23 – 23,838.81)	**<0.001**
ICU Interventions ($CAD)	13,092.69 (35,237.59)	8,383.05 (21,150.96)	4,398.25 (-4,891.18 – 13,687.68)	0.347
Takeback Operations ($CAD)	784.75 (2,020.37)	1,472.88 (8,439.24)	-720.45 (-1,986.84 – 545.93)	0.259
Procedures ($CAD)	95.03 (278.81)	113.23 (344.01)	-12.01 (-86.99 – 62.97)	0.749
Physician Billing ($CAD)	4,060.02 (5,042.92)	4,077.18 (5,222.10)	-101.14 (-1,485.61 – 1,283.34)	0.884
Radiology ($CAD)	1,172.79 (1,126.98)	1,181.64 (1,259.57)	-5.99 (-326.44 – 314.47)	0.97
Blood Product ($CAD)	8,743.84 (9,386.22)	9,711.01 (12,724.93)	-1,086.07 (-4,077.28 – 1,905.14_	0.47

1 adjusted for age at transplant, MELDNa at transplant, chronic liver failure, and matched participants

$ in 2020 Canadian Dollars ICU – Intensive Care Unit

Table 5-S7: Overview of Length of Stay and Major Cost Regions for comparing the main analysis, status 1&2 transplant patients, and status 3&4 transplant patients

	Main Analysis		**Status 1 & 2**		**Status 3 & 4**	
	Mean Adjusted Difference (95% Confidence Interval)[1]	**P Value**	**Mean Adjusted Difference (95% Confidence Interval)[2]**	**P Value**	**Mean Adjusted Difference (95% Confidence Interval)[2]**	**P Value**
Length of Stay						
Total	0.39 (-5.48 – 6.26)	0.894	-0.78 (-7.51 – 5.95)	0.82	17.65 (-6.40 – 41.69)	0.14
ICU	2.73 (-1.09 – 6.54)	0.158	2.36 (-1.47 – 6.19)	0.226	10.99 (-2.67 – 24.65)	0.108
Ward	-2.34 (-6.37 – 1.70)	0.251	-3.14 (-7.67 – 1.39)	0.173	6.66 (-15.24 – 28.56)	0.53
Total Cost ($CAD)	32,220.61 (4,540.56 – 59,900.66)	**0.023**	28,230.52 (-1,311.69 – 57,772.72)	0.061	104,416.30 (23,879.25 – 184,962.30)	**0.015**
Length of Stay Cost ($CAD)						
Total	4,450.70 (-11,638.65 – 20,540.04)	0.582	1,857.50 (-15,367.19 – 19,082.19)	0.83	48,447.01 (11,700.96 – 85,193.06)	**0.013**
ICU	6,117.72 (-7,166.56 – 19,402.01)	0.36	4,465.50 (-9,319.39 – 18,250.39)	0.519	39,536.69 (-5,072.37 – 84,145.75)	0.078
Ward	-1,667.03 (-7,733.53 – 4,399.48)	0.584	-2,608.00 (-8,961.38 – 3,745.37)	0.415	8,910.32 (-15,353.00 – 33,173.64)	0.444
Transplant Operation ($CAD)	21,673.43 (19,571.48 – 23,775.38)	**<0.001**	21,536.83 (19,379.85 – 23,693.81)	**<0.001**	23,028.75 (14,781.11 – 31,276.39)	**<0.001**
ICU Interventions ($CAD)	7,121.12 (-3,431.42 – 17,673.65)	0.182	7,629.63 (-3,056.23 – 18,315.49)	0.158	12,645.42 (-26,114.97 – 51,405.81)	0.496

Takeback Operations ($CAD)	-960.32 (-2,154.51 – 233.87)	0.113	-1,198.27 (-2,544.28 – 147.73)	0.08	932.41 (-1,166.50 – 3,031.32)	0.357

1 adjusted for age at transplant, MELDNa at transplant, chronic liver failure, and matched participants
2 adjusted for age at transplant, MELDNa at transplant, and chronic liver failure
$ in 2020 Canadian Dollars
ICU – Intensive Care Unit

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6 Cost-Utility Analysis of the OrganOx Normothermic Machine Perfusion Compared to Static Cold Storage in Liver Transplantation in the Canadian Setting

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6.1 Abstract

Objective: To estimate the incremental cost-effectiveness of a liver transplant program that utilizes normothermic machine perfusion (NMP) in concert with static cold storage (SCS) compared to one that uses SCS alone (control).

Methods: A Markov model compared approaches (NMP vs control) using a 1-year cycle length over a 5-year time horizon from the public health care payer perspective. Primary micro-costing data ($CAD 2020) from a single center retrospective trial were applied along with European Quality of Life 5 Dimension (EQ-5D) utility values from literature sources. Transition probabilities were deduced using the retrospective cohort and supplemented by literature values for sensitivity analysis. Scenario and probabilistic sensitivity analysis (PSA) were conducted.

Results: The NMP approach was both cost-saving and cost-effective in comparison to the control approach, which was dominated. The cumulative costs for NMP was $5.57 billion and the control was $6.39 billion over 5 years. The mean cost of NMP was $557,450 and the control was $634,106. The NMP program had greater incremental quality adjusted life years (QALYs) gains over 5 years compared to control, with 3.48 versus 3.17. The overarching results remained unchanged in scenario analysis. In PSA, NMP was cost-effective 63% of the time at the conventional willingness-to-pay threshold of $50,000.

Conclusion: The addition of NMP to a liver transplant program results in greater QALY gains and is cost-effective from the public health care payer perspective.

6.2 Introduction

In 2019 chronic liver disease and cirrhosis were the fifth leading cause of death in Canada for ages 25 through 64 with liver transplantation being the only curative treatment for end stage disease [1]. As the prevalence of metabolic syndrome increases, along with the mean age of the population, there has been a decrease in the number of liver grafts available for transplantation [4, 5]. Corollary to this, there has been an increase in waitlist mortality: as per the Canadian Institute for Health Information (CIHI) the waitlist mortality rate has risen from 22% in 2018 to 27% in 2019 [3, 21]. This mismatch between supply and demand for liver grafts has led to the increased use of extended criteria donors (ECD) [7, 8]. However, ECD are more susceptible to the impacts of static cold storage (SCS) putting recipients at higher risk of post-transplantation complications [7, 8].

Normothermic machine perfusion (NMP), by the OrganOx machine, perfuses liver grafts at physiologic temperature, blood pressure, blood flow, and oxygenation [12]. Transplant surgeons are able to assess synthetic and metabolic parameters to ensure viability of the graft prior to transplantation [12]. There have been seven clinical studies published on the use of the OrganOx machine, with the only randomized control trial (RCT) from Nasralla et al. [13-16, 18, 19, 23]. Safety and feasibility of the OrganOx machine has been demonstrated in three different clinical settings: NMP immediately after procurement, NMP after time period of SCS, and NMP in the use of rescuing grafts initially deemed unsuitable for transplantation [13-16, 18, 19, 23]. The Nasralla et al. RCT showed no statistically significant difference in graft survival, patient survival, re-transplantation,

length of stay, major complications, primary non-function, and biliary complications with the OrganOx machine versus SCS [23]. The OrganOx treatment arm was found to have a significantly lower rates of discard, early allograft dysfunction, and peak aspartate aminotransferase levels in comparison to SCS [23]. The promising clinical outcomes of the OrganOx machine indicates that the costs of this technology are worth investigating.

The cost of the OrganOx machine has been explored in two studies. This author group performed micro-costing and calculated the cost per run of the OrganOx machine in the Canadian setting from the public health care payer perspective to be $18,593.02 to $20,241.35 (CAD$ 2019) [78]. This upfront cost must be considered within the context of the entire liver transplantation process, patient health related quality of life (utility), and clinical outcomes. One economic evaluation of the OrganOx machine has been completed, funded by OrganOx UK, by Javanbakht et al. [20]. The cost-utility analysis (CUA) compared liver transplantation by SCS to liver transplantation with use of the OrganOx machine [20]. Their CUA showed the OrganOx machine (metra) to be a cost-effective strategy with an incremental cost-effectiveness ratio (ICER) of £7,876 per quality adjusted life year (QALY) gained with a 99% probability of being cost-effective with a willingness-to-pay (WTP) threshold of £20,000 in 2018 pounds sterling over a lifetime horizon [20]. It is important to assess the cost-effectiveness of adding the OrganOx machine to a transplant program rather than the OrganOx machine on its own. This allows for assessment using real-world evidence in a model closer to the real usage of the OrganOx machine in a transplant centre therefore providing a more realistic understanding of the costs of implementing this technology.

This economic evaluation will compare two transplant programs, one using SCS alone and a second using SCS and the OrganOx machine, to assess the cumulative costs and incremental cost-effectiveness of adding the OrganOx machine to a Canadian liver transplant program.

6.3 Methods

6.3.1 Model Overview

A decision analytic model using a Markov model was created comparing two different transplant strategies to estimate the costs and outcomes over a 5-year time horizon for patients on the Canadian liver transplantation waiting list from the public health care payer perspective. A one-year cycle length was applied. Strategy one (control) is a transplant program utilizing only static cold storage (SCS) (**Figure 6-1**). Strategy one has four health states: waitlist, transplanted with a SCS graft, survive post-transplant, and dead. Strategy two (NMP) is a transplant program that has liver transplantation using both SCS and the OrganOx machine. Strategy two has five health states: waitlist, transplanted with a NMP graft, transplanted with a SCS graft, survive post-transplant, and dead (**Figure 6-1**). Patients were initially allocated to a health state based on Alberta liver transplantation data and transitioned from one health state to another each cycle (**Table 6-1**). The outcomes in the model were the cumulative cost and QALYs, resulting in calculating the incremental cost-utility. Costs and outcomes were discounted at a rate of 1.5% as per the guidelines from the Canadian Agency for Drugs and Technology in Health (CADTH) [83]. Half cycle correction was applied. A re-

transplantation state was not included, as the cost of an immediate re-transplantation within the transplantation admission period was included in the micro-costing and thus accounted for in the mean cost and in the probabilistic sensitivity analysis (PSA).

6.3.2 Transition Probabilities

The transition probabilities were calculated from data collected from the Alberta liver transplantation program and supplemented by critically assessed literature data (**Table 6-1**). The transition probabilities for transplantation and death on the waitlist were calculated from the 2016 year with standard deviation (SD) from 2008 through 2012, all of which had no transplantations with the OrganOx machine. The probability of staying on the waitlist being the difference between 1 and the sum of the probability of death on the waitlist and transplantation. The survival and death probabilities in the first-year post-transplantation was derived from the RCT of the OrganOx machine [23]. The survival and death probabilities beyond 1 year was derived from the 5-year survival data for liver transplantation from CIHI [84]. The additional transplants completed by NMP was a conservative estimate of additional transplants based on 15 transplants per year with a decrease in waitlist mortality by 4 people (26.7%) and decrease in number awaiting transplant by 11 people (73.3%). It was assumed that initial and long-term survival was the same for transplantation with a NMP grafts and a SCS graft, based on clinical studies showing no statistically significant differences in graft and patient survival [14, 18, 19, 23].

6.3.3 Health Utility Values

The health utility values used were the European Quality of Life 5 Dimension (EQ-5D) utilities based on a study by Ratcliffe et al., as published in the CUA of the OrganOx machine in the United Kingdom (UK) (**Table 6-2**) [20, 85]. The Ratcliffe et al. study compared health utility pre-transplantation and post-transplantation at 1 year and 2 years [85]. In our model, the utility of being on the waitlist was assumed to be the pre-transplantation utility of 0.53. The utility of transplantation was initially set to the waitlist utility of 0.53. The utility of survival at the first-year post-transplantation was 0.69. The utility of survival post-transplant beyond 1 year was 0.76. The utility of death was 0. It was assumed that the utility post-transplantation is the same for transplant with a NMP graft and a SCS graft. It was assumed that the health utility after 2 years was the equal to the health utility at 2 years.

6.3.4 Costs

All costs are presented in 2020 Canadian dollars. For the control, the mean waitlist cost was estimated at $185,375.70 (**Table 6-3**) [33]. This was deduced from the data of the 62 patients transplanted in 2016, when no OrganOx transplantations were completed. Physician billings, inpatient and outpatient care for the 1 year prior to transplantation were included, as provided by Data Integration, Measurement and Reporting (DIMR) from Alberta Health Services, this is the Medical Services Incorporated data sent to CIHI. It was assumed that death on the waitlist had the same cost as being on waitlist. The cost of transplant, from admission to discharge, was calculated via micro-costing [86]; the mean cost of transplant was $114,508. The mean cost of dying after transplant

during the same admission was $145,507; there were only 2 deaths in this manner. The mean cost for the initial year post-transplantation was based on the 365 days after discharge from transplant admission for the 62 patients transplanted in 2016 using costs from DIMR, estimated at $45,805.15 (**Table 6-3**) [33]. The annual cost of survival per annum after the initial first-year post-transplantation was a conservative estimate of half the cost of the initial year, based on literature review [36, 42]. The cost of death after initial survival was assumed to be the same as the cost of survival.

For NMP, the costs were determined using the same methods. The mean cost of transplantation was $144,797(SD) and the cost of death was $396,459(SD) (**Table 6-3**). It was assumed that the survival costs after transplant with NMP is the same as after transplant with SCS. Clinical outcomes are not statistically significantly different between NMP and SCS and therefore costs should be the same [14, 18, 19, 23].

6.3.5 Analysis

Analysis was completed in TreeAge Pro 2018 (TreeAge Software LLC, Williamstown, Massachusetts, USA). A PSA with Monte Carlo simulation with 10,000 iterations was performed to address parameter uncertainty. The conventional willingness-to-pay threshold of $50,000 CAD$ was used.

Multiple scenario analyses were completed including discounting at a rate of 0% and 3%, death rate on the waitlist of 0.095 and 0.26, decreasing transplantation by NMP to 0.11 with a decrease in the waitlist by 0.08 and death on the waitlist by 0.03, increasing

transplantation by NMP to 0.20 with a decrease in the waitlist by 0.15 and death on the waitlist by 0.05, and increasing the cost of survival post-transplantation to be the same as the cost of the waitlist.

6.4 Results

The cumulative cost over 5-years for NMP was $5,567,937,306 in comparison to the control at $6,385,154,452. The mean cost for NMP was $557,450 versus $634,106 for the control. The incremental effectiveness of NMP was 3.48 QALY versus 3.17 for the control. The higher number of QALYs accumulated in the NMP program is from the additional livers transplanted from the addition of the OrganOx machine, which leads to a subsequent decrease in both waitlist death and patients awaiting transplantation. The control strategy was dominated by the NMP strategy due to NMP being less costly and more effective with a negative ICER of -$242,514 (**Table 6-4**). Over a 5-year time horizon the NMP strategy was found to be both cost-saving and cost-effective in comparison to the control.

In PSA, the NMP program was cost-effective at a WTP threshold of $50,000 in 63% of iterations (**Figure 6-2 and 6-3**). In scenario analysis, replacing survival cost beyond one year with the waitlist cost resulted in the NMP strategy being cost-effective (ICER $4,588). These results were robust to other scenario analysis (**Table 6-4**).

6.5 Discussion

This study showed that from the public health payer perspective, the addition of the OrganOx machine to a transplant program is a cost-effective, and likely cost-saving, strategy when compared to a transplant program using SCS alone. The NMP strategy increases the number of lives saved and decreases waitlist numbers and mortality rate. While liver transplant is resource intensive, an increase in its use via application of NMP is offset by a reduction in waitlist and death costs. The NMP strategy remains cost-effective even when the survival cost post-transplantation was made substantially higher than the estimated cost.

As per the Canadian Agency for Drugs and Technology in Health guidelines the base case for an economic evaluation does not include societal costs [83]. The cost are likely substantial, and if this analysis was conducted from that perspective, it would likely show an even wider cost gap between the program approaches. Societal cost has a wide breadth, and includes but is not limited to the costs associated with, travel/accommodation, loss of work or decreased productivity at work for patients and caregivers, and replacement/training of a new employee [83]. Informal caregivers, usually a family member, have been shown to experience impacts from the burden of care through the pre-transplantation period to post-transplantation [87-89]. This can lead to depression, decreased life satisfaction, and poorer physical health [87-90]. It has also been noted that maintaining employment for informal caregivers during the pre-transplant period can be increasingly difficult as the care required for their loved one becomes more demanding with rising severity of disease [89]. The impact of caregiver burden likely

leads to a decrease in work productivity or unemployment for these individuals. This is in addition to the employment impacts for patients, as return to employment post-transplantation ranges from 22% to 55%, which is influenced by pre-transplantation employment [54, 57]. It would be difficult to adequately acquire data to capture these societal costs for this study.

Other costs and outcomes that were not considered in this study were the external effects that can apply in a NMP program. For instance, in the SCS program approach, the majority of liver transplantations occur during nighttime hours. However, with the addition of NMP transplantations can be transitioned to daytime [13]. This likely has cost and quality of life implications for the operating room team. It has been documented by this author group that the transition of transplantations from nighttime to daytime could save up to $2,347 per night (2019 CAD$) from the premium night-time salaries for staff [78]. Additionally, it has been shown that work-life balance concerns, night-time work, and number of hours worked per week are factors that influence burnout [91, 92]. Burnout impacts health care costs, with increases in medical errors in patient care and a reduction in physician productivity with increased physician turnover [74, 91, 93]. Increased turnover rates translate to increased number of friction periods, and thus friction costs [94].

One prior economic evaluation was completed in the United Kingdom comparing transplantation using the OrganOx machine to transplantation using SCS, funded by the OrganOx Company [20]. Javanbakht et al. showed that the OrganOx machine was more

costly and the cost-effective strategy over SCS with an ICER of £7,876 per QALY gained in 2018 pound sterling and a 99% probability of being cost-effective at a WTP threshold of £20,000 [20]. Their CUA compared liver transplantation using the OrganOx machine in comparison to SCS. The model was based on an RCT, which induces bias as the study population is required to fit specific inclusion criteria and results may not be reflective of the entire population awaiting liver transplantation. Their study applies a lifetime horizon: however, it does not model important outcomes that would be expected over that timeframe, such as hepatic artery thrombosis, ischemic cholangiopathy, or primary non-function [20]. The approach for our model was a more real-life comparison of 2 transplant programs rather than individual transplantation strategies: it is unlikely that a center would apply NMP to all grafts, rather than to select ones. Moreover, our cost estimates reflect the program cost as a whole, therefore reducing bias in our model. Additionally, the cost of any immediate post-transplantation complications and management or re-transplantations were captured in the micro-costing of the transplantation admission for this economic evaluation. These are important considerations as complications have been shown to be a driving factor of cost due to requiring further interventions and increasing length of stay [44, 45].

The results of this study must be interpreted within the limitations of its design. For instance, the healthy utility values employed were collected in the UK. The health care system in the UK is more in likeness to the Canadian system than others, such as the United States. In comparison of the indications for transplantation between the study population in the United Kingdom and the Canadian study population there are minimal

differences: the Canadian cohort had less alcoholic liver disease and primary biliary cholangitis, with more hepatocellular carcinoma. Other transplantation indications were comparable. Therefore, the health utility values from EQ-5D data are currently the best estimation of the Canadian population but may not be fully representative. Prospective collection of EQ-5D data in the Canadian setting should be undertaken with completion of another economic evaluation in the future. As per the CADTH guidelines, the time horizon for the base case should be for a lifetime [83]. However, in this circumstance, creating a model to account for all costs and outcomes over a lifetime would introduce many limitations: for instance, rate of re-transplantation. As well, there are limitations in the current cost data available post-transplantation to account for all possible costs. The five-year time horizon in this study has costs that likely appropriately capture all possible costs and outcomes in the PSA: extrapolating these costs out to a lifetime would likely not be representative of the lifetime costs to these medically complex patients.

Further to this study, data for health utility throughout the transplantation process as well as costs and outcomes of long term follow up of liver transplantation patients in Canadian transplant programs should be acquired. Transplant programs using this NMP technology should continue to capture the quantity of additional liver grafts successfully transplanted, changes in waitlist numbers and morality rate, and their long-term outcomes. This additional data would increase our confidence in the validity of the model, especially for health utility, and allow for extrapolation out to a lifetime to ensure long term cost-effectiveness.

In conclusion, the addition of the OrganOx machine to a transplant program is a cost-saving and cost-effective strategy when compared to a transplant program only using SCS: these savings are likely underestimated from the health payer perspective, relative to the societal perspective. The additional lives saved from use of the OrganOx machine leads to a decrease in waitlist mortality and in the number of patients awaiting transplant: this helps to address the current mismatch in supply and demand.

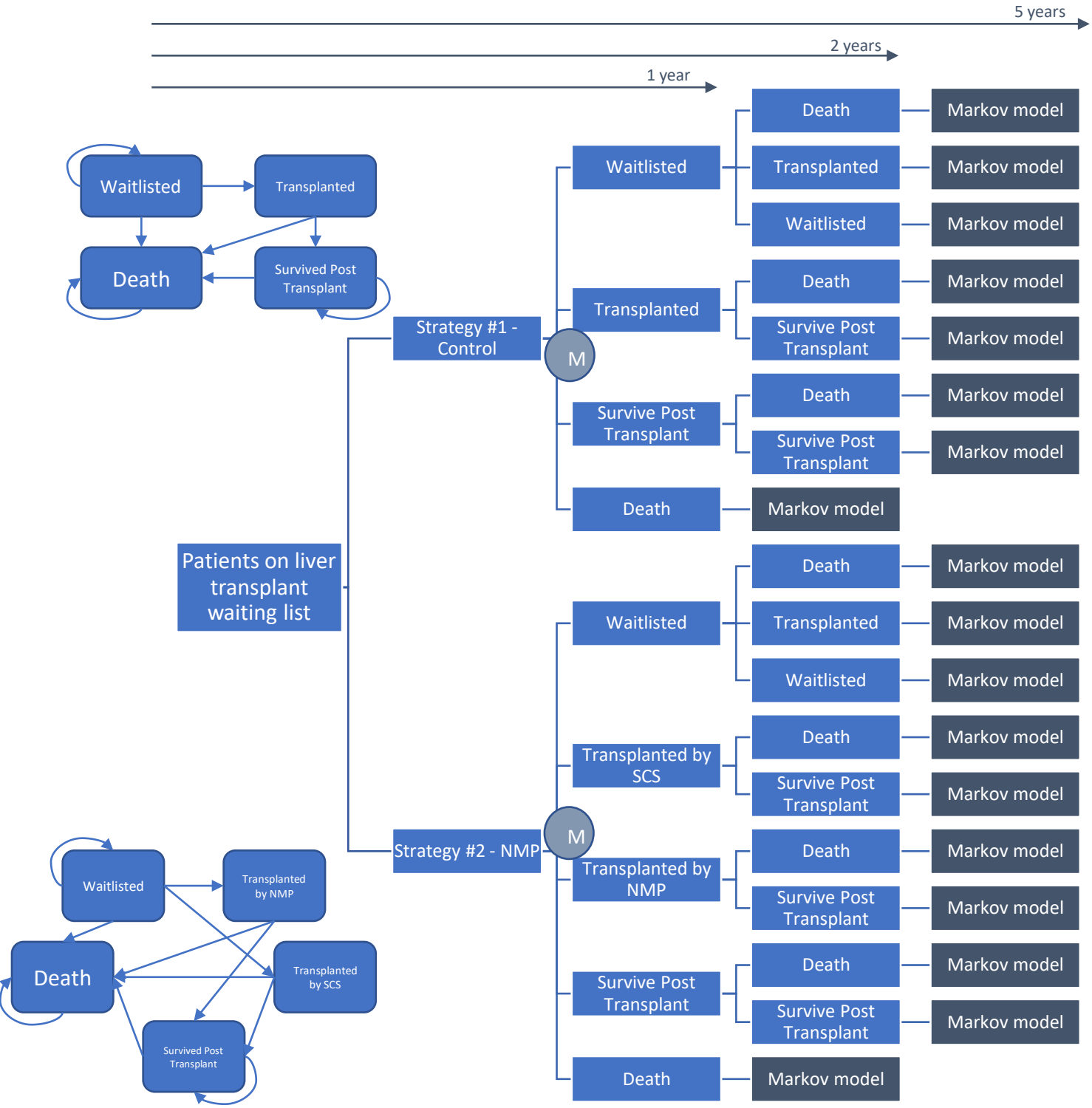

Figure 6-1: Decision Tree and Markov Model for Strategy #1 using static cold storage (SCS) alone and Strategy #2 using SCS and normothermic mahine perfusion (NMP)

Table 6-1: Health State Transition Probabilities

Variable	Distribution	Base Case	Standard Deviation for Sensitivity Analysis	Reference
Strategy #1 – Control				
Waitlist	Beta	0.41	-	AB Tx database
Die from waitlist	Beta	0.11	0.046	AB Tx database
Transplant by SCS	Beta	0.48	0.05	AB Tx database
Survive post-transplant	Beta	0.96	0.001	Nasralla et al. [23]
Die post-transplant	Beta	0.04	0.001	Nasralla et al. [23]
Survive post-initial survival	Beta	0.96	0.001	CIHI [4]
Die post-initial survival	Beta	0.04	0.001	CIHI [4]
Strategy #2 – NMP				
Waitlist	Beta	0.3	-	AB Tx database
Die from waitlist	Beta	0.07	0.01	AB Tx database
Transplant by NMP	Beta	0.15	0.01	AB Tx database

NMP – normothermic machine perfusion
CIHI – Canadian Institute for Health Information
AB Tx – Alberta Transplant

Table 6-2: Health Utility Inputs

Variable	Distribution	Base Case	Standard Deviation	Reference
Strategy #1 - Control				
Waitlist	Beta	0.53	0.22	Ratcliffe et al. [85]
Transplant by SCS	Beta	0.53	0.22	Ratcliffe et al. [85]
Survival post-transplant at 1 year	Beta	0.69	0.33	Ratcliffe et al. [85]
Survive post-transplant after 1 year	Beta	0.76	0.33	Ratcliffe et al. [85]
Death	Beta	0	0	Ratcliffe et al. [85]
Strategy #2 – NMP				
Transplant by OrganOx	Beta	0.53	0.22	Ratcliffe et al. [85]
Survival post-transplant by NMP at 1 year	Beta	0.69	0.33	Ratcliffe et al. [85]
Survive post-transplant by NMP after 1 year	Beta	0.76	0.33	Ratcliffe et al. [85]

NMP – normothermic machine perfusion

Table 6-3: Cost Inputs

Variable	Distribution	Base Case	Standard Deviation for Sensitivity Analysis	Reference
Strategy #1 - Control				
Waitlist	Gamma	185,375.70	183,788.20	Alberta data
Die from waitlist	Gamma	185,375.70	183,788.20	Alberta data
Transplant by SCS	Gamma	114,507.80	98,404.17	Micro-costing
Rest of transplant year	Gamma	45,805.15	70,171.69	Alberta data
Survive post-transplant	Gamma	22,902.58	35,086.85	
Die post-transplant	Gamma	145,506.80	4,456.62	Micro-costing
Strategy #2 - NMP				
Transplant by OrganOx	Gamma	144,797.30	102,786.20	Micro-costing
Die post-transplant OrganOx	Gamma	396,459.10	7,517.19	Micro-costing

NMP – normothermic machine perfusion

Table 6-4: Base Case Costs, Quality Adjusted Life Years, and Incremental Cost-effectiveness Ratio

	Total		Incremental		Incremental Cost-effectiveness Ratio
Strategy	**Cost ($CAD 2020)**	**QALY**	**Cost ($CAD 2020)**	**QALY**	**($/QALY)**
Strategy #1 – Control	634,106	3.17	76,656	-0.32	-242,514 (dominated)[a]
Strategy #2 – NMP	557,450	3.48			

[a] Dominated ICER results when Strategy #1 – Control is both less effective and more costly than Strategy #2 – NMP

QALY – quality adjusted life years
NMP – normothermic machine perfusion

Table 6-5: Scenario Analyses Costs, Quality Adjusted Life Years, and Incremental Cost-effectiveness Ratio

		Total		Incremental		Incremental Cost-effectiveness Ratio
Scenario	**Strategy**	**Cost ($CAD 2020)**	**QALY**	**Cost ($CAD 2020)**	**QALY**	**($/QALY)**
Discounting 0%	Strategy #1 – Control Strategy #2 – NMP	645,515 566,425	3.25 3.57	79,090	-0.32	-243,900 (dominated)[a]
Discounting 3%	Strategy #1 – Control Strategy #2 – NMP	623,333 548,979	3.09 3.4	79,090	-0.31	-241,122 (dominated)[a]
Waitlist death probability at 0.095 for control and 0.055 for NMP	Strategy #1 – Control Strategy #2 – NMP	626,942 549,559	3.24 3.55	77,382	-0.31	-246,931 (dominated)[a]
Waitlist death probability at 0.26 for control and 0.22 for NMP	Strategy #1 – Control Strategy #2 – NMP	697,068 626,878	2.56 2.9	70,191	-0.33	-212,121 (dominated)[a]
NMP probability 0.11 with waitlist probability decreasing by 0.08 and waitlist death probability decreasing by 0.03	Strategy #1 – Control Strategy #2 – NMP	634,106 570,484	3.17 3.45	63,622	-0.29	-221,217 (dominated)[a]

NMP probability 0.20 with waitlist probability decreasing by 0.15 and waitlist death probability decreasing by 0.05	Strategy #1 – Control Strategy #2 – NMP	634,106 542,996	3.17 3.52	91,110	-0.35	-261,484 (dominated)[a]
Survival cost at waitlist cost of $185,375.70	Strategy #1 – Control Strategy #2 – NMP	1,073,643 1,075,094	3.17 3.48	1,450	0.32	4,588

[a] Dominated ICER results when Strategy #1 – Control is both less effective and more costly than Strategy #2 – NMP

QALY – quality adjusted life years
NMP – normothermic machine perfusion

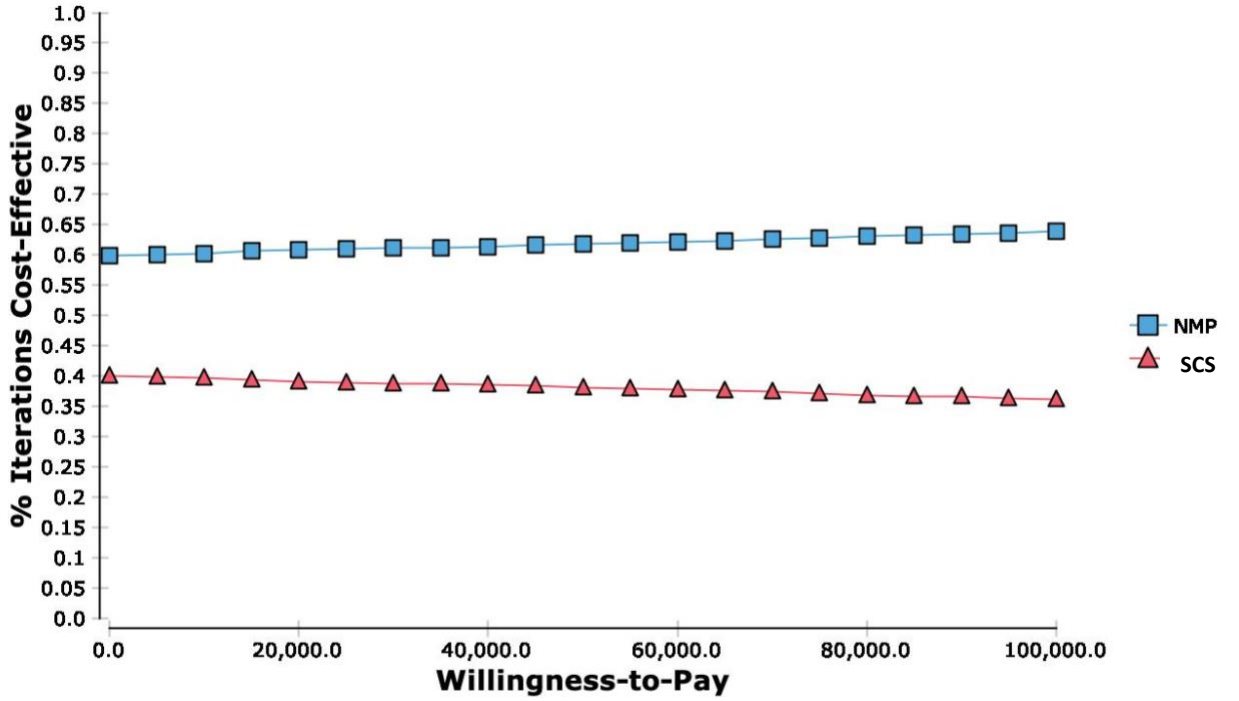

Figure 6-2: Cost-effectiveness acceptability curve at a range of willingness-to-pay thresholds ($0-$100,000), compares the probability of Strategy #2 – NMP being cost-effective when compared to Strategy #1 – control over a range of values for the willingness-to-pay for the gain of 1 quality-adjusted life year

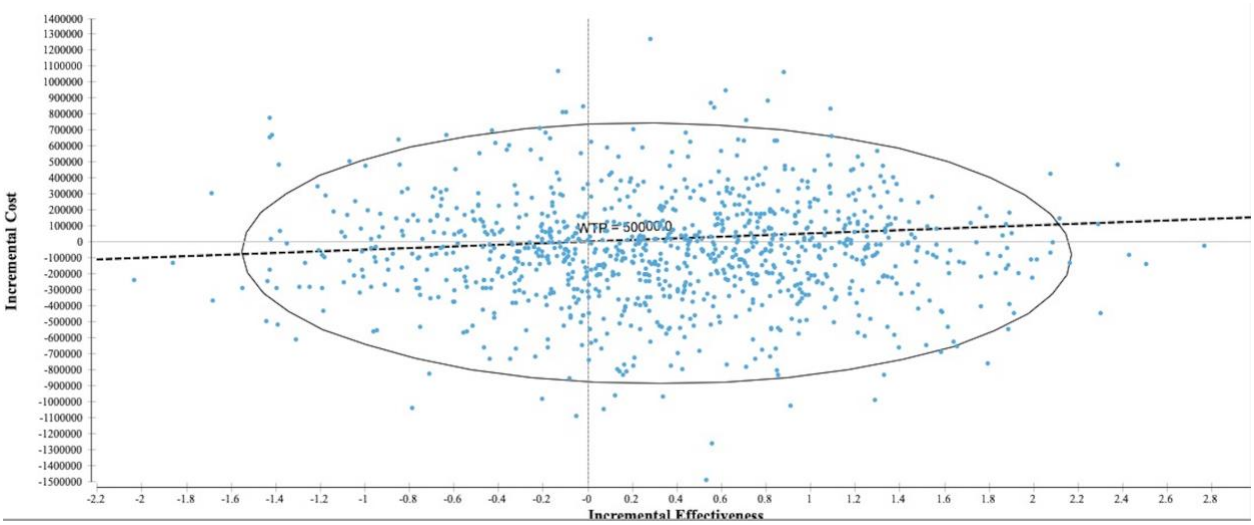

Figure 6-3: Scatter plot of incremental cost and incremental effectiveness for 10,000 Monte Carlo iterations with $50,000 willingness to pay threshold

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7 Impact of the OrganOx Normothermic Machine Perfusion on the Clinical Liver Transplantation Operating Room Team

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7.1 Abstract

Introduction: The addition of the OrganOx normothermic machine perfusion (NMP) to a liver transplantation program has impacts on more than just the patient. The objective of this study was to identify the impacts from the addition of the OrganOx machine to a long-standing liver transplant program.

Methods: A single clinical liver transplant operating room team completed a survey about the time before and after implementation the OrganOx machine focused on wellbeing. The survey contained questions from the validated Psychological General Well-Being Index (PGWBI), the validated Maslach Burnout Inventory – Human Services Survey (MBI-HSS), and open-ended questions. The median score pre- and post-OrganOx was calculated and common concepts from open ended questions were identified using content analysis.

Results: A total of 13 full responses were returned with a response rate of 72.22%. The majority of participants reported that the addition of the OrganOx machine benefited the clinical team, both personally and professionally, and to patients. The OrganOx machine addition leads to less nighttime transplantations with more sleep for staff, improved work-life balance and job satisfaction, more efficient use of staffing. Participants reported improved patient safety including increase in the number of liver transplantations, ensuring liver grafts are viable prior to transplantation, the team being better rested, and having the full complement of allied health professionals available during daytime hours.

Discussion: The addition of the OrganOx machine firstly was felt to improve patient safety in numerous ways. It also improved multiple factors that play a role in burnout of the clinical team with improvement of both personal and professional life.

7.2 Introduction

Over the last decade the development and use of machine perfusion in liver transplantation has been prominent in transplant research. Appropriately the focus of research has been on the safety and feasibility of this technology and on patient outcomes. Multiple studies, including a randomized control trial, have proven safety and feasibility of the OrganOx machine, but show no statistically significant differences in patient survival, graft survival, or complications [13-16, 18, 19, 23]. The promising clinical outcomes from trials with the OrganOx machine indicates that the costs related to this technology is important to explore.

The first economic evaluation of the OrganOx machine was completed in 2020 in the United Kingdom, which showed the OrganOx machine to be a cost-effective strategy over static cold storage (SCS) [20]. The incremental cost-effectiveness ratio was £7,876 per quality adjusted life year (QALY) gained in 2018 Great British pounds sterling. A cost analysis of the cost per run of the OrganOx machine in the Canadian setting was completed and showed the cost to be $18,593 to $20,241 ($CAD 2019) [78]. These economics studies are important but they do not consider the societal costs from the use of this technology, such as loss of work or decreased work productivity and replacement/training of a new employee [83].

The clinical liver transplant operating room team is a component of the society impacted by the OrganOx machine. The use of the OrganOx machine facilitates a switch of transplants from nighttime to daytime. In a study by Bral et al., 84% of transplants using the OrganOx machine were completed during daytime hours compared to 65% for transplantation using SCS [13]. This switch has potential impacts on burnout rates of the clinical team, which impacts societal cost as burnout can lead to decreased work productivity and increased personnel turnover. However, the impact of the OrganOx machine on this population has not been captured. The objective of this study was to determine the impacts of the OrganOx machine on a clinical operating room team.

7.3 Methods

Ethics approval was obtained through the Health Research Ethics Board – Health Panel. A survey used questions from the validated Psychological General Well-Being Index (PGWBI), the validated Maslach Burnout Inventory – Human Services Survey (MBI-HSS), and open-ended questions (see Appendix) [95, 96]. The survey was sent by email recruitment to 18 participants at an urban transplant hospital who are a part of the liver transplant operating room clinical team, which is comprised of operating room nurses, anesthesia technicians, transplant anesthesiologists, and liver transplant surgeons. The recruitment email contained an informed consent form where completion and submission of the survey is considered participant consent. The survey was delivered online and data was collected by Qualtrics. Eligible participants had to be a part of the clinical team for both the time prior and post implementation of the OrganOx

machine. One survey participant who did not complete responses for both pre- and post-OrganOx was excluded.

The median response for pre- and post-OrganOx, frequency of responses per question, the change in response, and frequency of changed response per question and by participant was calculated. The median answer for willingness-to-pay for OrganOx was calculated. The open-ended responses were compiled in Excel and analyzed using summative content analysis by two researchers (ANW and LAW). The researchers independently read and re-read the responses by question and by participant and assigned codes to relevant text based on the research question. Next, we reviewed the coding scheme at research team meetings and discussed discrepancies to reach consensus. Finally, common content across responses was summarized.

7.4 Results

Out of the 18 eligible clinical team members, 13 completed the survey for a response rate of 72.2%. Responses included nurses (8), transplant anesthesia (2), and transplant surgeons (3) (**Table 7-1**). A total of 6 (46.2%) participants, representing all three clinical roles, had a change in response to at least one question (**Table 7-2**). Each question had between 1 (7.7%) to 3 (23.1%) participants change their response (**Table 7-3**). Overall, clinical team members reported that the addition of the OrganOx machine reduced the frequency of feeling emotionally drained, burned out, or frustrated by work, and feeling healthy enough to carry out things that people like to do or had to do (**Table 7-4**).

While a couple of participants disagreed or reported no change, the majority of participants reported the addition of the OrganOx machine added benefit to them personally and professionally, to the clinical team, and for the patients (**Figure 7-1**). The majority of participants (12) agreed that the OrganOx machine should continue to be used and 1 (7.7%) participant somewhat disagreed (**Figure 7-1**). Participants suggested the health care system should be willing to pay an additional $19,000 (median) per transplantation for use of the OrganOx machine, with responses ranging from $5,000 to $100,000.

Open-ended responses identified four benefits as a result of the OrganOx machine. 1. decrease in nighttime work leading to more sleep; 2. improved work-life balance and improved job satisfaction; 3. improved staffing logistics with more staff available during daytime transplants and easier scheduling; and 4. improved patient safety. Less nighttime work, improved work-life balance and job satisfaction were noted to decrease burnout. The four benefits are described below with illustrative quotes from participants. The role of participants has not been included with quotes to maintain anonymity.

The majority of participants described less nighttime work resulting in more sleep as a result of the OrganOx machine. For example, a participant commented that the OrganOx machine offers *"flexibility to allow most liver transplants to be done during the day when teams are at their best"* (participant 11). Increased sleep was identified as a personal benefit. It was also noted that being well rested improved the professional environment with it being a "*more conducive and supportive atmosphere. More*

integrated team" (participant 9). Additionally, it was noted that the *"move to mostly day-time transplants has meant that it is less disruptive to the working week and is a buffer against burnout"* (participant 8). However, it was noted that the shift from nighttime to daytime transplantations resulted in two unintended consequences including decreased salary from loss of the nighttime premiums and the impact on scheduled hepatobiliary patients: if *"an elective patient is bumped to do a daytime transplant, obviously it does not benefit them"* (participant 5).

The OrganOx machine has allowed for an improvement of work-life balance and job satisfaction in the majority of participants. The OrganOx machine has *"vastly improved work-life balance, major improvement in physical and psychological wellbeing…the positive impact that the OrganOx has had on my personal wellbeing is immeasurable"* (participant 7). It has also improved job satisfaction leading to "*much better team dynamics"* (participant 10). Improvement in these areas were noted to impact burnout: *"burnout and exhaustion are very real threats to our subspecialty, and the OrganOx has been instrumental in physician retention within our group"* (participant 7).

Participants varied in their opinions as to whether the OrganOx machine improved staffing. The majority of participants said it allowed for more efficient staff planning: *"allows for more notice and planning of a transplant on shift"* (participant 5). Daytime transplantation also means there is *"additional help and resources readily available (RNs, anesthesia techs, service attendants [i.e. for blood product pickup], larger number of lab/blood bank/transfusion medicine staff) during these challenging cases is also*

crucial and reduces the overall stress of these challenging cases" (participant 7). However, not all staff benefitedx from a shift to daytime transplantations as "*fellows still have to hook up the organ to machine in the middle of the night. [This is] not always a quick process [as] someone must sit, monitor, and stabilize machine during all hours [that the liver graft] sits in OrganOx"* (participant 2). Regardless, it was argued that "*the OrganOx helps during night shift because we use less resources in terms of nursing staff compared to performing a liver transplant the night of organ arrival"* (participant 12). This was countered with *"on night shift - this has added additional workload to a shift with minimal staff resources"* (participant 13).

Lastly, participants reported that the OrganOx machine benefited patient safety in four ways. Firstly, the OrganOx machine *"allows more patients to receive liver transplants"* (participant 1). Secondly, the OrganOx machine allows for an *"additional opportunity to evaluate borderline livers"* (participant 11) leading to *"safer use of marginal and DCD* [donation after cardiac death] *grafts - tested for safety on a wet run on the machine first"* (participant 9). Thirdly, the OrganOx machine allows for more sleep and *"a well rested team can only benefit the patients as people make less mistakes when well rested and can think clearer"* (participant 4). Fourthly, daytime transplantations allows for the full complement of allied health care professionals to be available making it "*[feel] safer to do complicated transplants during the day when more resources are available"* (participant 5).

7.5 Discussion

Overall, the addition of the OrganOx machine was perceived by participants as beneficial for the clinical team, both personally and professionally, and for the patients. The addition of the OrganOx machine led to more sleep, higher job satisfaction, and better work-life balance for the clinical team. Improvement in these three areas created more collegiality in the operating room and better team dynamics. This could improve burnout among the clinical team and lead to higher retention. A study by Sillero et al. showed that nursing burnout was reduced through better relationships between physicians and nurses [97]. This could also improve physician burnout as it has been documented for both surgeons and anesthesiologists that nighttime work, total hours worked per week, and difficulties with work-life balance are factors that influence the high burnout rates found in physicians [91, 92]. Therefore, improvement of these factors could allow for longer lasting impacts both for longevity of career and personal wellbeing [98]. This could also improve patient safety as burnout and poor quality of life have been shown to increase medical errors, which have substantial costs to the health care system [74, 91, 99].

Additionally, liver transplantation is a sub-specialized area for both surgery and anesthesiology. A 2009 study found that the number of liver transplant surgeons being trained was going to meet the need, as projected to 2020 [100]. However, there is not an abundance of transplant surgeons or anesthesiologists and if burnout leads to physician turnover or decreased work hours this would have far reaching impacts with colleagues being required to fill the clinical gap, thereby increasing their risk of burnout. It was

documented that the estimated annual attributable cost of burnout in US physicians due to decreased productivity and physician turnover was $4.6 billion in 2019 US dollars [93]. The attributable cost of transplant team burnout is unknown but if the upfront cost of the OrganOx machine allows for better quality of life, less nighttime hours, improved job satisfaction, and better work-life balance it may be worth the cost. Decreasing known risk factors for burnout leading to better patient care and longevity of the clinical team, which are not captured by a traditional cost analysis, play a crucial role in the ongoing success of transplant programs.

The facilitation of shifting liver transplantation from nighttime to daytime also impacts staffing from two perspectives. The first is a more efficient use of peri-operative nursing staff. If a liver transplantation occurs overnight the liver transplant nursing team is called in to work the night shift, which leads to a loss of those nursing staff the next day and requires other nursing staff scheduled as off to come in for the next day. When transplants are shifted to the day the nursing staff work as scheduled, thereby ensuring staffing adequacy, which is also a factor that impacts nursing burnout [97]. The second is daytime transplantations ensure that the full complement of allied health professionals, such as blood bank, laboratory medicine, and service attendants, are available in comparison to the during the nightshift. This allows for additional help during a complex surgery. However, the transition to daytime transplantation also removes the premiums of nighttime salaries for staff, which can be up to $2,347 ($CAD 2019) [78].

Participants also identified some unintended consequences from the addition of OrganOx. Firstly, the OrganOx machine does not entirely eliminate nighttime work. Transplantations may be shifted to daytime, but the liver graft is typically procured and attached to the machine during nighttime hours. This still requires staffing, including nursing, anesthesia technicians, and the liver transplant fellows. Typically, the nursing staff that help with OrganOx attachment are the scheduled nursing staff as opposed to calling in nursing staff from the liver transplantation team, which ensures adequate staffing for the dayshift. It was likely known at the time of implementation that nighttime work would still be required but some may feel the nighttime staffing impacts are larger than expected.

Secondly, an unintended consequence of switching to daytime transplantation is the loss of salary that comes with nighttime premiums for all staff. This potentially would decrease the incentive for some to participate in liver transplant call. Thirdly, the switch to daytime transplantation can lead to cancellation of elective daytime hepatobiliary procedures. This means that patients would need to be rescheduled for their operation, potentially creating a delay in their care and patients feeling frustrated with the health care system. However, this consequence may not be a consideration for some transplant centers. Fourthly, there is potential for disappointment of the transplant recipient if the graft is deemed unsuitable after NMP, but this is a reality in transplantation despite NMP use.

The main limitation of this study is the small sample size. This is a reflection of the small group of specialized people working in a busy transplant center. There were also no full responses from the anesthesia technicians, who play a role both in running the OrganOx machine and in the liver transplantation operation. Therefore, their perspectives have not been captured. Another limitation of this study is that burnout is a complex issue related to multiple factors and this survey may not have captured all aspects of burnout. Additionally, the OrganOx machine was not implemented to be the solution to burnout in this clinical group.

In conclusion, the majority of survey participants felt that the OrganOx machine should continue to be used. The addition of the OrganOx machine allows for a shift from nighttime to daytime transplantation leading to more sleep, an improvement of work-life balance and job satisfaction, an improvement in logistical organization and efficient use of staff, and improved patient safety. These improvements have implications for decreasing burnout, leading to an increase in work productivity and less personnel turnover, which is a societal cost not captured in the traditional economic evaluations of the OrganOx machine.

Table 7-1: Survey Participant Characteristics

Survey Participant Characteristics	**Number (%)**
Role	
Nurse	8 (61.54)
Anesthesia	2 (15.38)
Transplant Surgeon	3 (23.08)
Liver Transplantation Experience	
3-5 years	3 (23.08)
6-9 years	2 (15.38)
10 years or more	6 (46.15)
Missing	2 (15.38)
Age	
40 years or less	5 (38.46)
41-50 years	3 (23.08)
51-59 years	3 (23.08)
60 years or more	2 (15.38)
Gender	
Female	8 (61.54)
Male	5 (38.46)

Table 7-2: Characteristics of responses that changed from pre-OrganOx to post-OrganOx

	Changed Response from Pre to Post OrganOx n (%)
Total Reponses (n=117)	20 (19.66)
Changed Response by Role (n=20) Nurse Anesthesia Transplant Surgeon	 8 (40) 9 (45) 3 (15)
Changed Responses by Individual (n=13) Change No change	 6 (46.15) 7 (53.85)
Number of Questions with Changed Response per Individual (n=6)	2 (1-9)[a]
Changed Responses by Question (n=9) Change No change	 9 (100) 0 (0)
Number of Individuals with Changed Response per Question (n=9)	3 (1-3)[a]

[a] Median (range)

Table 7-3: Participant changes in response per question

Question	Pre-OrganOx	Change	Post-OrganOx
I feel emotionally drained from my work			
a) Never	a) 2		a) 2
b) A few times a year	b) 4		b) 6
c) Once a month or less	c) 2	n=1 -1	c) 1
d) A few times a month	d) 0		d) 0
e) Once a week	e) 1	n=1 -3	e) 0
f) A few times a week	f) 3		f) 3
g) Everyday	g) 1		g) 1
I feel used up at the end of the workday			
a) Never	a) 0		a) 0
b) A few times a year	b) 3		b) 3
c) Once a month or less	c) 1		c) 3
d) A few times a month	d) 3	n=1 -1	d) 3
e) Once a week	e) 1	n=1 -2	e) 0
f) A few times a week	f) 3	n=1 -2	f) 2
g) Everyday	g) 2		g) 2
I feel burned out from my work			
a) Never	a) 2		a) 2
b) A few times a year	b) 2		b) 5
c) Once a month or less	c) 4	n=2 -1	c) 2
d) A few times a month	d) 2	n=1 -2	d) 1
e) Once a week	e) 0		e) 0
f) A few times a week	f) 2		f) 2
g) Everyday	g) 1		g) 1
I feel I'm positively influencing other people's lives through my work			
a) Never	a) 0		a) 0
b) A few times a year	b) 0		b) 0
c) Once a month or less	c) 0		c) 0
d) A few times a month	d) 2	n=1 +2	d) 1
e) Once a week	e) 0		e) 0
f) A few times a week	f) 7		f) 8
g) Everyday	g) 4		g) 4
I feel energetic			
a) Never	a) 1		a) 1
b) A few times a year	b) 0		b) 0
c) Once a month or less	c) 0		c) 0
d) A few times a month	d) 0		d) 0
e) Once a week	e) 3	n=1 +1	e) 2
f) A few times a week	f) 8	n=2 +1	f) 7
g) Everyday	g) 1		g) 3

I feel frustrated by my job a) Never b) A few times a year c) Once a month or less d) A few times a month e) Once a week f) A few times a week g) Everyday	 a) 0 b) 3 c) 2 d) 2 e) 1 f) 4 g) 1	 n=2 -1 n=1 -3 	 a) 0 b) 3 c) 5 d) 0 e) 1 f) 3 g) 1
How happy, satisfied or pleased were you with your personal life? a) Extremely happy b) Very happy most of the time c) Generally satisfied d) Sometimes fairly happy, sometimes fairly unhappy e) Generally dissatisfied, unhappy f) Very dissatisfied or unhappy most or all of the time	 a) 2 b) 2 c) 5 d) 2 e) 0 f) 1	 n=2 +1 -1 n=1 -2 	 a) 2 b) 4 c) 3 d) 2 e) 0 f) 1
Did you feel healthy enough to carry out the things you like to do or had to do? a) Yes b) For the most part c) Health problems limited me in some important ways d) I was only healthy enough to take care of myself e) I needed some help in taking care of myself f) I needed someone to help me with most or all of the things I had to do	 a) 6 b) 3 c) 1 d) 1 e) 1 f) 0	 n=1 -3 	 a) 7 b) 3 c) 1 d) 0 e) 1 f) 0
My daily life was full of things that were interesting to me a) None of the time b) A little of the time c) Some of the time d) A good bit of the time e) Most of the time f) All of the time	 a) 0 b) 0 c) 1 d) 4 e) 7 f) 1	 n=1 +2 	 a) 0 b) 0 c) 0 d) 4 e) 8 f) 1

Table 7-4: The median response for pre-OrganOx and post-OrganOx feelings toward professional and personal life

Question	Pre-OrganOx[a]	Post-OrganOx[a]
I feel emotionally drained from my work	Once a month or less	A few times a year
I feel used up at the end of the workday	A few times a month	A few times a month
I feel burned out from my work	Once a month or less	A few times a year
I feel I'm positively influencing other people's lives through my work	A few times a week	A few times a week
I feel energetic	A few times a week	A few times a week
I feel frustrated by my job	A few times a month	Once a month or less
How happy, satisfied or pleased were you with your personal life?	Generally satisfied – please	Generally satisfied – please
Did you feel healthy enough to carry out the things you like to do or had to do?	For the most part	Yes – definitely so
My daily life was full of things that were interesting to me	Most of the time	Most of the time

[a] Median score

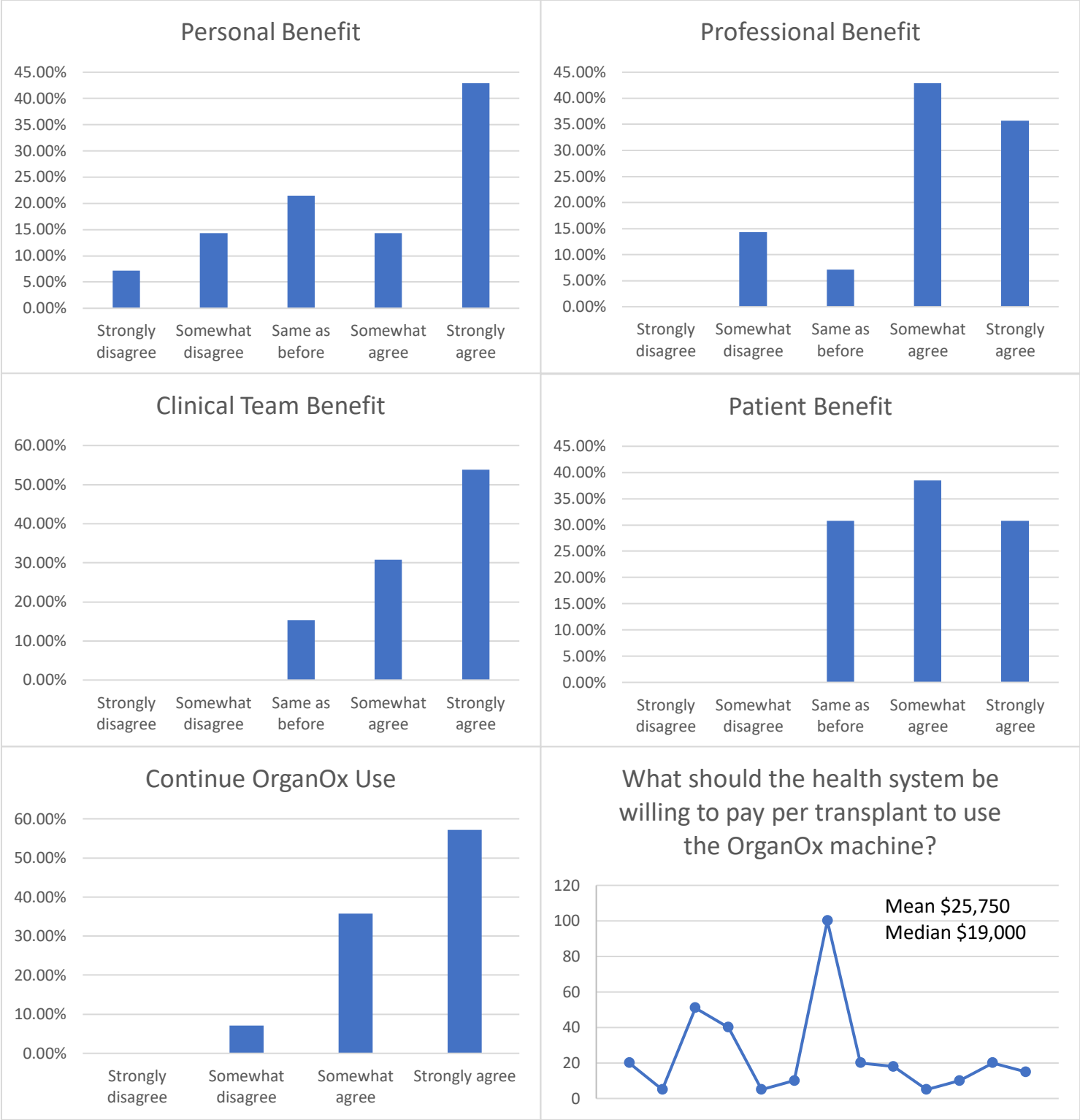

Figure 7-1: Opinions on whether the use of the OrganOx has led to benefits for participants personally and professionally, for the overall clinical operating room team, and for the patient. Opinion on whether the use of the OrganOx should continue and how much the health system should be willing to pay

7.6 References

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8 Summary

Over the last decade there has been ongoing research for the use of machine perfusion in the setting of liver transplantation. The focus of its use is to help fill the gap that has arisen between supply and demand and to assess viability of liver grafts, especially with the increased use of extended criteria grafts. Promising clinical benefits of normothermic machine perfusion (NMP) with the OrganOx machine have been proven safe and feasible in three clinical settings [13-16, 18, 19, 23]. The first is the use of NMP immediately after procurement to the time of transplantation [14, 18, 19, 23]. The second is the use of NMP after a period of static cold storage (SCS) [13, 15]. The third is the use of NMP to rescue liver grafts that have been deemed unsuitable for transplantation [16]. These studies have shown that the OrganOx machine allows for a lower discard rate of liver grafts leading to an increase in available grafts for transplantation. The cost of the OrganOx machine, the cost of liver transplantation with SCS, and these costs in relation to patient benefit is an area that required further research, especially in the Canadian setting.

It is well known that the process of liver transplantation is costly and resource intensive for the health care system, the patient, and their caregivers. The process has three distinct time periods to it: pre-transplantation, transplantation admission, and post-transplantation. Each of these periods have distinct costs that are driven by multiple factors and can range widely. The pre-transplantation period cost is influenced by longer waitlist times, the amount of inpatient care, poor overall functional status, and chronicity of liver failure [35-37, 39, 40, 42]. The transplantation admission is the most

expensive period. The driving factors include an increased length of stay (LOS), a higher model for end-stage liver disease (MELD) score at the time of transplantation, poor overall functional status, post-operative complications, and extended criteria grafts [35, 39, 40, 42-53]. The post-transplantation period ranges in time but the first year is usually the most expensive [42]. This period is influenced by overall functional status, the amount of inpatient care, and medication [35, 36, 42]. The identification of these driving factors allows for implementation of clinical interventions that may have upfront costs but lead to an overall cost savings in the liver transplantation process. Interventions could include standardized pre-transplantation frailty assessments followed by physical therapy as required and the use of machine perfusion.

Multiple cost analyses were completed to define the cost of the liver transplantation operation and admission for both SCS and the OrganOx machine. The cost of the liver transplantation operation for in-province procurement and transplantation ranges from $30,770 to $35,659 ($CAD 2019) and for out-of-province procurement and in-province transplantation ranges from $44,636 to $48,076. The cost per run of the OrganOx machine ranges from $18,593 to $20,241. The mean cost of the liver transplantation admission for SCS was $119,424 ($CAD 2020) and for OrganOx was $155,319, with a significantly higher mean adjusted difference of $32,221 (p=0.023). The higher costs for the OrganOx group were from the cost of using the OrganOx machine and longer length of stay in the intensive care unit (ICU) with more ICU interventions.

The costs of liver transplantation should be considered in relation to patient benefit. A cost-utility analysis comparing a transplant program using SCS alone (control) to a transplant program using SCS and the OrganOx machine (NMP) was completed. This showed the addition of the OrganOx machine to be both cost-saving and cost-effective when compared to the control approach, which was dominated. The cumulative cost over a five-year time horizon was $5.57 billion ($CAD 2020) for NMP and $6.39 billion for the control. The mean cost for the NMP approach was $557,450 with a quality adjusted life year (QALY) gain of 3.48. The mean cost for the control approach was $634,106 with a QALY gain of 3.17. The probabilistic sensitivity analysis showed the NMP approach to be cost-effective 63% of the time at the conventional willingness-to-pay threshold of $50,000.

The cost analyses and cost-utility analysis of the OrganOx machine do not account for the societal costs to the clinical team or the patient and their caregivers. The survey conducted suggested that the implementation of the OrganOx machine has led to decreased burnout in the clinical operating room team and improved patient safety. The societal cost of burnout in the form of decreased productivity, medical error, or physician turnover is not captured in cost analyses. However, the survey results suggest that the addition of the OrganOx machine helps improve sleep, work-life balance, and job satisfaction which could improve burnout in the clinical liver transplantation operating room team.

This research adds to the current knowledge of the OrganOx machine. From a clinical perspective, this research supports the implementation of the OrganOx machine into Canadian liver transplantation programs. Although, this technology has substantial upfront costs the increased patient benefit gained from increasing the number of liver transplantations, with subsequent decreases in the waitlist and death on the waitlist, is shown to be cost-saving and cost-effective. Therefore, the additional costs for the OrganOx machine leads to additional lives being saved and overtime will help address the increasing waitlist mortality from the supply and demand mismatch.

From a research perspective, the use of the OrganOx machine in a Canadian liver transplantation program should be followed prospectively to see whether the proposed benefits to patients and to the liver transplantation waitlist are as expected. Additionally, there is a lack of data on the health utility of patients as they progress through the transplantation process in the Canadian setting. Further research to collect data for health utility will allow for better understanding of the patient benefit from liver transplantation and for use in further Canadian economic evaluations. Long term post-transplantation costs and outcomes for both SCS and the OrganOx machine are required to help address future economic evaluations with a time horizon of a lifetime. Additionally, micro-costing of liver transplantation patients for the duration of their time on the waitlist should be captured. These two areas of cost, in conjunction with our transplant admission cost data, will help address whether the identified driving factors from the literature are at play in the Canadian setting, whether there are additional

clinical interventions that can be applied to help address these, and provide cost data for future economic evaluations in the area of liver disease and transplantation.

In conclusion, the addition of liver transplantation with the OrganOx machine to a Canadian liver transplant program is cost-saving and cost-effective when compared to liver transplantation with SCS alone. The benefit from the OrganOx machine is a reflection of an increase in the number of lives saved from additional transplants above those from SCS. The use of the OrganOx machine will help address the increasing waitlist morality rate due to the supply and demand mismatch.

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Appendix

Clinical Operating Room Team Survey

Liver Transplant Team OrganOx Machine Survey

This survey is anonymous. Please do not include any personal identifiers in the open-ended questions.

1) Role:
    a) Nurse
    b) Anesthesia
    c) Transplant Surgeon
    d) Other
        i) Box to write in role

2) How many years have you worked as a member of the liver transplant team?
    a) 3-5 years
    b) 6-9 years
    c) 10 years or more
3) Age:
    a) 40 years or less
    b) 41-50 years
    c) 51-59 years
    d) 60 years or more
4) Sex:
    a) Male
    b) Female
    c) Prefer not to answer

Please answer these questions in relation to how you felt about your job as a member of the liver transplant team in the time **prior** to the addition of the OrganOx machine

5) I feel emotionally drained from my work
   a) Never
   b) A few times a year
   c) Once a month or less
   d) A few times a month
   e) Once a week
   f) A few times a week
   g) Everyday

6) I feel used up at the end of the workday
   a) Never
   b) A few times a year
   c) Once a month or less
   d) A few times a month
   e) Once a week
   f) A few times a week
   g) Everyday

7) I feel burned out from my work
   a) Never
   b) A few times a year
   c) Once a month or less
   d) A few times a month
   e) Once a week
   f) A few times a week
   g) Everyday

8) I feel I'm positively influencing other people's lives through my work
   a) Never
   b) A few times a year
   c) Once a month or less
   d) A few times a month
   e) Once a week
   f) A few times a week
   g) Everyday

9) I feel very energetic
   a) Never
   b) A few times a year
   c) Once a month or less
   d) A few times a month
   e) Once a week
   f) A few times a week
   g) Everyday

10) I feel frustrated by my job
   a) Never
   b) A few times a year
   c) Once a month or less
   d) A few times a month
   e) Once a week
   f) A few times a week
   g) Everyday

Please answer these questions in relation to how you feel about your job as a member of liver transplant team during the time **after** the addition of the OrganOx machine

11) I feel emotionally drained from my work
   a) Never
   b) A few times a year
   c) Once a month or less
   d) A few times a month
   e) Once a week
   f) A few times a week
   g) Everyday

12) I feel used up at the end of the workday
   a) Never
   b) A few times a year
   c) Once a month or less
   d) A few times a month
   e) Once a week
   f) A few times a week
   g) Everyday

13) I feel burned out from my work
   a) Never
   b) A few times a year
   c) Once a month or less
   d) A few times a month
   e) Once a week
   f) A few times a week
   g) Everyday

14) I feel I'm positively influencing other people's lives through my work
   a) Never
   b) A few times a year
   c) Once a month or less
   d) A few times a month
   e) Once a week
   f) A few times a week
   g) Everyday

15) I feel very energetic
   a) Never
   b) A few times a year
   c) Once a month or less
   d) A few times a month
   e) Once a week
   f) A few times a week
   g) Everyday

16) I feel frustrated by my job
   a) Never
   b) A few times a year
   c) Once a month or less
   d) A few times a month
   e) Once a week
   f) A few times a week
   g) Everyday

Please answer these questions in relation to how you felt about your personal life in the context of your responsibilities as a member of the liver transplant team in the time **prior** to the addition of the OrganOx machine

17) How happy, satisfied, or pleased were you with your personal life?
    a) Extremely happy – could not have been more satisfied or please
    b) Very happy most of the time
    c) Generally satisfied – please
    d) Sometimes fairly happy, sometimes fairly unhappy
    e) Generally dissatisfied, unhappy
    f) Very dissatisfied or unhappy most or all of the time

18) Did you feel healthy enough to carry out the things you like to do or had to do?
    a) Yes – definitely so
    b) For the most part
    c) Health problems limited me in some important ways
    d) I was only healthy enough to take care of myself
    e) I needed some help in taking care of myself
    f) I needed someone to help me with most or all of the things I had to do

19) My daily life was full of things that were interesting to me
    a) None of the time
    b) A little of the time
    c) Some of the time
    d) A good bit of the time
    e) Most of the time
    f) All of the time

Please answer these questions in relation to how you felt about your personal life in the context of your responsibilities as a member of the liver transplant team during the time **after** the addition of the OrganOx machine

20) How happy, satisfied, or pleased were you with your personal life?
    a) Extremely happy – could not have been more satisfied or please
    b) Very happy most of the time
    c) Generally satisfied – please
    d) Sometimes fairly happy, sometimes fairly unhappy
    e) Generally dissatisfied, unhappy
    f) Very dissatisfied or unhappy most or all of the time

21) Did you feel healthy enough to carry out the things you like to do or had to do?
    a) Yes – definitely so
    b) For the most part
    c) Health problems limited me in some important ways
    d) I was only healthy enough to take care of myself
    e) I needed some help in taking care of myself
    f) I needed someone to help me with most or all of the things I had to do

22) My daily life was full of things that were interesting to me
    a) None of the time
    b) A little of the time
    c) Some of the time
    d) A good bit of the time
    e) Most of the time
    f) All of the time

Please answer these questions in relation to your perspective on the addition of the OrganOx machine

23) Do you think that you have had benefit from the addition of the OrganOx machine personally?
    a) Strongly disagree
    b) Somewhat disagree
    c) Same as before
    d) Somewhat agree
    e) Strongly agree

24) Please describe how you have personally benefited from the addition of the OrganOx machine (OPEN ENDED)

25) Do you think that you have had benefit from the addition of the OrganOx machine professionally?
    a) Strongly disagree
    b) Somewhat disagree
    c) Same as before
    d) Somewhat agree
    e) Strongly agree

26) Please describe how you have professionally benefited from the addition of the OrganOx machine (OPEN ENDED)

27) Do you think that the clinical team has had benefit from the addition of the OrganOx machine?
    a) Strongly disagree
    b) Somewhat disagree
    c) Same as before
    d) Somewhat agree
    e) Strongly agree

28) Please describe how the clinical team has or has not benefited from the addition of the OrganOx machine (OPEN ENDED)

29) Do you think that that patients have had clinical benefit from the addition of the OrganOx machine?
    a) Strongly disagree
    b) Somewhat disagree
    c) Same as before
    d) Somewhat agree
    e) Strongly agree

30) Please describe how patients have or have not benefited clinically (OPEN ENDED)

31) Do you think the transplant team should continue using the OrganOx machine?
    a) Strongly disagree
    b) Somewhat disagree
    c) Somewhat agree
    d) Strongly agree

32) Please explain your answer (OPEN ENDED)

33) Given that on average a liver transplant costs the system $35,000, what should the health system be willing to pay per transplant to use the OrganOx machine?
    a) Slider $0 to $100+ K

34) Is there anything else you would like to tell us about how the addition of the OrganOx machine has changed your experience and/or your job satisfaction as a member of the liver transplant team? (OPEN ENDED)