COMPARISON OF GRAFT SURVIVAL AFTER LIVER TRANSPLANTATION BETWEEN SÃO PAULO, BRAZIL, AND THE UNITED STATES

by

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A thesis submitted in conformity with the requirements for the degree of Master of Science
Institute of Health Policy, Management, and Evaluation
University of Toronto

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Abstract

This study compared graft failure or patient mortality after primary liver transplantation, between São Paulo (SP), Brazil, and the USA. Cox proportional hazards model was used to evaluate the impact of covariates; secondary analysis used propensity score matching. Among 2,256 SP and 27,902 US transplant recipients, risk of graft failure for SP patients was higher during the early post-transplant period: hazard ratio (HR) at 30 days, 3 months and 6 months: 4.65 (95% CI: 4.21, 5.14), 2.34 (95% CI: 1.91, 2.87) and 1.49 (95% CI: 1.17, 1.90) respectively. Between 1 to 3 years and 3 to 5 years, a lower relative hazard was seen in SP: 0.67 (95% CI: 0.54, 0.83) and 0.53 (95% CI: 0.35, 0.80) respectively. Liver transplant recipients in SP face higher relative risk for graft failure or patient mortality in the first 6 months post-transplant, with a tendency toward lower relative risk beyond 1-year after transplant.
Acknowledgments

I would like to dedicate this thesis to my mother, Manavazhi Meenambika (in Memoriam) and to my father, Cheruparambil Sankarankutty, who by example has taught me the principles that have guided me through my life.

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Table of Contents

ACKNOWLEDGMENTS ........................................................................................................ III
TABLE OF CONTENTS ....................................................................................................... IV
LIST OF TABLES ............................................................................................................... VI
LIST OF FIGURES ........................................................................................................ VII
LIST OF APPENDICES ................................................................................................... VIII

CHAPTER 1 ..................................................................................................................... 1

1 INTRODUCTION ......................................................................................................... 1

1.1 BACKGROUND ....................................................................................................... 1

1.2 BRAZIL AND THE UNITED STATES ..................................................................... 5

1.2.1 Overview of the Health Care Systems in Brazil and the USA ......................... 7

1.2.1.1 The Brazilian Health Care System ............................................................. 7

1.2.1.2 The US Health System ............................................................................. 10

1.3 SÃO PAULO, BRAZIL ........................................................................................... 13

CHAPTER 2 ................................................................................................................... 16

2 METHODS ................................................................................................................ 16

2.1 DATA SOURCES ................................................................................................... 16

2.2 STUDY POPULATION ............................................................................................ 17

2.3 STUDY EXPOSURES .............................................................................................. 17

2.4 STUDY OUTCOMES ............................................................................................... 17

2.5 POTENTIAL CONFOUNDERS .............................................................................. 18

2.6 MISSING DATA ..................................................................................................... 18

2.7 SUBCOHORT ANALYSIS ...................................................................................... 19

2.8 SENSITIVITY ANALYSIS ..................................................................................... 20

2.9 STATISTICAL ANALYSIS ..................................................................................... 20

2.10 A NOTE ON SURVIVAL ANALYSIS AND TIME-DEPENDENT EFFECTS ........... 21

2.11 PROPENSITY SCORE MATCHING (PS) ................................................................. 22

2.11.1 Steps in PS analysis ....................................................................................... 23
CHAPTER 3 ........................................................................................................................................... 26

3 RESULTS ............................................................................................................................................. 26
  3.1 RESULTS FOR THE STUDY POPULATION .......................................................................................... 26
  3.2 RESULTS FOR THE SUBCOHORT WITH ACUTE HEPATIC NECROSIS .................................................. 31
  3.3 RESULTS FOR THE SUBCOHORT WITH HEPATOCELLULAR CARCINOMA ........................................... 35
  3.4 RESULTS FOR THE PROPENSITY SCORE-MATCHED COHORT ............................................................. 38
  3.5 SENSITIVITY ANALYSIS ...................................................................................................................... 41

CHAPTER 4 ............................................................................................................................................. 43

4 DISCUSSION ....................................................................................................................................... 43
  4.1 INTERPRETATION OF THE FINDINGS ................................................................................................. 43
  4.2 METHODOLOGICAL STRENGTHS AND LIMITATIONS ....................................................................... 48
  4.3 EXPLANATION FOR THE OBSERVED DIFFERENCES ......................................................................... 50
  4.4 CONCLUSIONS ..................................................................................................................................... 52

REFERENCES .......................................................................................................................................... 54

APPENDICES .......................................................................................................................................... 63
List of Tables

Table 1. Comparison of Economic and Social Indicators: Brazil, São Paulo and the USA... 6

Table 2. Characteristics of the Study Population ................................................................. 27

Table 3. Time-stratified unadjusted hazard ratios for graft failure or patient mortality for patients receiving liver transplants in São Paulo (SP) vs. United States (US) liver transplant recipients................................................................. 30

Table 4. Time-stratified adjusted hazard ratios for graft failure or patient mortality for patients receiving liver transplants in SP vs. US liver transplant recipients ....................... 30

Table 5. Characteristics of the subcohort of patients with Acute Hepatic Necrosis (AHN) 32

Table 6. Time-stratified unadjusted hazard ratios for the subcohort of patients with Acute Hepatic Necrosis......................................................................................... 34

Table 7. Time-stratified adjusted hazard ratios for the subcohort of patients with Acute Hepatic Necrosis......................................................................................... 34

Table 8. Characteristics of the subcohort of patients with Hepatocellular Carcinoma ...... 35

Table 9. Time-stratified unadjusted hazard ratios for the subcohort of patients with Hepatocellular Carcinoma ......................................................................................... 37

Table 10. Time-stratified adjusted hazard ratios for the subcohort of patients with Hepatocellular Carcinoma ......................................................................................... 38

Table 11. Characteristics of the Propensity Score-Matched Cohort ................................. 39

Table 12. Time-stratified hazard ratios for the Propensity Score-Matched cohort .......... 41

Table 13. Sensitivity analysis ................................................................................................ 42
List of Figures

Figure 1. Graft survival among the United States adult liver transplant recipients transplanted in 2007: deceased donors. ................................................................. 14

Figure 2. Unadjusted graft survival rates for São Paulo, Brazil, adult liver transplant recipients between 17/07/2006 and 31/06/2012. ........................................................................................................... 15

Figure 3. Time-stratified effects of fixed baseline risk factor on the outcome. ............ 22

Figure 4. Study Flow Diagram.............................................................................................................. 26

Figure 5. Kaplan-Meier 5-year Survival Estimate for the Study Population ................. 28

Figure 6. Kaplan-Meier 1-year Survival Estimate for the Study Population ............... 29

Figure 7. Kaplan-Meier 5-year survival estimate for the subcohort of patients with Acute Hepatic Necrosis........................................................................................................................................... 33

Figure 8. Kaplan-Meier 5-year survival estimate for the subcohort of patients with Hepatocellular Carcinoma ........................................................................................................................................... 36

Figure 9. Kaplan-Meier 5-year Survival Estimate for the Propensity Score-Matched Cohort ........................................................................................................................................... 40
List of Appendices

Appendix 1: University of Toronto Ethics Approval Letter ................................. 63
Chapter 1

1 Introduction

1.1 Background

Increasing emphasis is being placed on the assessment of outcomes in modern surgical practice, with direct applicability to daily clinical activity\(^1\). Patients, healthcare administrators, funders and the public expect the effective use of resources. Assessment of outcomes of surgical interventions is therefore important as it (i) provides patients with information regarding the procedures as well as the results of the surgical unit, (ii) informs the physicians on the adequacy of the results or whether improvements are required, and (iii) provides healthcare administrators with information regarding the results of the resources allocated, thereby informing all interested parties on the adequacy of the use of scarce resources. Despite the importance and the need for such evaluations, the methods of evaluation have inherent strengths and weaknesses that need to be kept in mind while making these comparisons. Healthcare administrators should undertake the responsibility for delivering such analysis and providing the public with this information.

Various countries are reporting health system performance statistics in an attempt to identify high performers and understand what drives their success. These comparisons provide an opportunity for benchmarking, allowing policy-makers and clinicians to identify areas in which different centers and countries can learn from each other.

While high-income countries routinely collect surgical mortality data, practically no middle- or low-income countries evaluate their outcomes on a routine basis\(^2\);\(^3\). Seventy percent of countries lack routine surgical surveillance systems. However, despite the paucity of transnational comparisons, international variation in the care provided to people has been reported\(^4\);\(^5\);\(^6\).

GlobalSurg, an international collaboration of surgical researchers, evaluated mortality of emergency abdominal surgery in high-, middle- and low-income countries. They reported that mortality rates after these procedures are two to three times higher in low- compared with high-income countries. Furthermore, the trend towards higher mortality (both at 24 hours and 30 days) remained after adjusting for observable prognostic factors\(^2\).
A poster presentation published in the Lancet, by Weiser and collaborators, reported on the variability of mortality after cesarean delivery, appendectomy, and groin hernia repair in low-income and middle-income countries. They reported exceedingly variable all-cause postoperative mortality rates within resource-constrained environments, substantially higher than those in middle-income and high-income settings, with case fatality estimates of 0.7 (central Europe) and 13.9 (central sub-Saharan Africa) per 1000 caesarean deliveries, 5.6 (central Asia) and 6.4 (central sub-Saharan Africa) per 1000 appendectomies, and 3.5 (tropical Latin America) and 33.9 (central sub-Saharan Africa) per 1000 hernia repairs.

These higher mortality rates are not restricted to surgical fields. Orlandini and collaborators have reported on the outcomes of patients in clinical trials with ST-segment elevation myocardial infarction among countries with different gross national incomes (GNI). They detected a large difference in the actual mortality rates seen across the three groups (12.1, 9.4, and 4.9% from low to high GNI). Even after adjustment for known risk factors, mortality was still higher in lower income countries, although the relationship was attenuated.

Similarly, Kämpfer J, et al. reported on the long-term outcomes (all-cause mortality) after acute myocardial infarction in countries with different socioeconomic environments. Mortality, at 3.5 years of follow-up, was almost twofold higher (8.5%) in Gdansk (Poland) and threefold higher (14.6%) in Lutsk (Ukraine), compared to the 4.6% in Bern (Switzerland).

Regarding the difficulties of transnational comparisons, Karanikolos et.al., reporting on health systems performance and cancer outcomes raised the issues of comparability among registries as well as the intrinsic characteristics of health systems that could impact the effectiveness of the care that is provided. For example, on the first issue (comparability of registries), even registries such as the US Surveillance, Epidemiology and End Results (SEER) program systematically underrepresents African Americans and poorer people, which could lead to an overestimate of national survival levels. On the second issue, there may be some systematic differences between health systems that can be linked to variation in outcomes, such as the existence, or otherwise, of a comprehensive, integrated approach to cancer management. They illustrate this point by comparing mortality related to cervical cancer in Germany and Finland. Acknowledging that early detection of cancer is crucial for increasing the chances of successful treatment and subsequent survival, a Finnish woman can expect to undergo seven smears in her lifetime, whereas a German woman may have 50 or more, yet cervical cancer mortality in Finland is half
that in Germany. The authors comment that countries vary in the extent to which their systems are organized or opportunistic, with consequences for the quality of the intervention\textsuperscript{5}.

Recently there has been an increasing interest in evaluating international surgical outcomes, starting with the standardization of perioperative outcome measures, an initiative of the European Society of Anaesthesiology and the European Society of Intensive Care Medicine joint task force\textsuperscript{7,8}.

The International Surgical Outcomes Study (ISOS) is an important initiative evaluating surgical outcomes worldwide. This study presents the patient outcomes after elective surgery from a prospective cohort study in 27 low, middle and high-income countries, however, they still have not reported transnational comparisons\textsuperscript{9}.

Surgery is part of the treatment for a wide range of conditions, however, it is estimated that less than a third of the world's population has access to safe, timely and affordable surgery. Furthermore, only 6\% of the procedures undertaken worldwide take place in middle- and low-income countries, where one-third of the world's population resides. Safe surgery requires considerable infrastructure, therefore increased coverage is not sufficient in itself, it should be accompanied by quality assurance\textsuperscript{2}.

International comparison of performance can be undertaken at a system-wide level, by disease, or at a sub-sector level (for example at a hospital level). Comparisons at the disease level reduce the heterogeneity of the population studied relative to the system-wide comparison\textsuperscript{10}. A disease-based approach is also attractive because it can produce measures at a country, regional, and hospital levels which can be compared across jurisdiction and therefore provide valuable information for improvement.

International survival comparisons help understand the relative contribution of different factors to outcome variations between the regions. These studies should be undertaken in middle- and low-income countries where scarce resources need to be carefully allocated and their impact constantly monitored. Reports of outcomes in middle- and low-income settings are therefore welcome and such studies are beginning to emerge. For example, rates of death and complications for emergency surgical procedures in a such a setting were observed to be 2.7\% and 6.6\%, respectively\textsuperscript{11}. Another recent publication reported the outcomes of eight surgical procedures and six clinical conditions for the State of São Paulo, Brazil, and compared it to the
values reported by the US Agency for Healthcare Research and Quality (AHRQ)\(^{11}\). For the year 2012, the surgical mortality rate (number of in-hospital deaths per 100 discharges) for the various procedures were reported as follows: coronary artery bypass graft (5.4), percutaneous coronary intervention (2.1), abdominal aortic aneurism repair (36.5), carotid endarterectomy (1.5), pancreatic resection (12.2), esophageal resection (14.3), craniotomy (16.7), and hip replacement (0.6). These values are 1.2 to 7.8 times greater than the values reported by the AHRQ in the US. Similarly, the mortality rate (year 2012) for the following clinical conditions was reported: acute myocardial infarctions (14.3), heart failure (13.3), acute stroke (19.1), gastrointestinal hemorrhage (9.1), hip fracture (4.1), and pneumonia (18.1). These values are 2.2 to 5.3 times greater than the values reported by AHRQ. These results are not risk-adjusted, but they seem to show worse outcomes in a lower income country. Reliable comparisons of outcomes across different jurisdictions and health care systems are therefore necessary and can encourage providers to improve their positioning in benchmarking.

Globally, cirrhosis of the liver ranks 17\(^{th}\) as the cause of years of life lost (YLLs). In North America, it ranks 9\(^{th}\) and in Tropical Latin America it ranks 10\(^{th}\).\(^{12}\) Liver transplantation, the treatment of choice for liver cirrhosis, is a highly standardized procedure worldwide, which permits international comparisons of outcomes if there is adequate accounting for case-mix. This provides a unique opportunity for benchmarking. However, very few studies have performed transnational comparisons. These studies have compared liver transplant outcomes between the USA, Canada, the United Kingdom and Ireland, all high-income countries\(^{13; 14}\). One-year survival was reported to be similar in the USA, UK, and Canada\(^{13}\). In the UK and Ireland, those who survived the first-year post-transplant presented a lower risk-adjusted mortality compared to their counterparts in the USA\(^{14}\). Based on these results the authors hypothesized that the observed differences in mortality reflected disparities in perioperative and long-term care between the healthcare systems.

Survival, or conversely mortality, is the frequently reported outcome measure. For the purpose of benchmarking, outcome measures should be context-sensitive both to the procedure and specialty in consideration, because most patients undergoing surgery do not die in the short-term. However, specifically in the case of liver transplantation, long-term survival can potentially be a measure of the effectiveness of the healthcare systems. Survival patterns encountered can help drive strategies and shape policies, as seen with cancer treatments in countries, such as Denmark, Northern Ireland, Wales, England, Australia, Norway, Canada, and Sweden \(^{15}\). Any country or
jurisdiction evaluating the overall effectiveness of its healthcare services must first verify its current status, compare its results with a reference, and investigate the potential causes for the differences encountered.

Global comparisons, especially of healthcare systems, is a complicated exercise. The World Health Report 2000 attempted to rank the world’s health care systems\(^\text{16}\). There were many criticisms of the report, but its greatest contribution was placing health care system performance firmly on the political and research agenda. Governments of countries that scored highly, such as France, were delighted, while others who scored lower, such as Brazil, formally expressed their displeasure to the WHO Executive Board.

When making these comparisons, it is important to keep in mind that, “while the healthcare system is expected to advocate for public health policies, health is influenced by many factors beyond the healthcare system, as exemplified by the apparently very good performance of countries, in the 2000 World Health Report, known to follow a Mediterranean diet” \(^\text{17}\). Nevertheless, such reports have made it difficult for politicians to dismiss comparative data on performance, and in some countries such as the United Kingdom, they have stimulated new policies on cancer\(^\text{17}\).

### 1.2 Brazil and the United States

Brazil is a democratic middle-income nation, with a surface area of 8,514,877 square kilometers and an estimated population of 198.7 million for the year 2012 (population density of 23.3 per square kilometer). While the USA is a leading nation in the world with a surface area of 9,629,091 square kilometers and an estimated population of 317.5 million for the year 2012 (population density of 33.0 per square kilometer). As health is influenced by factors beyond the formal healthcare system, it is important to consider the background of the two countries. However, the availability of data from Brazil was restricted to the State of SP, therefore this study compared the outcomes in SP with those in the USA. Table 1 illustrates some of the comparative economic and social indicators for each jurisdiction. Data relating to Brazil and São Paulo are presented in order to provide context for comparison of São Paulo with the USA. This table illustrates well the differences between the jurisdictions, notably the gross domestic product (GDP), GDP per capita, the proportion of the population above 60 years of age, infant mortality
rate, both the health expenditure per capita and as a proportion of the GDP, as well as each country’s ranking according to the human development index.

Table 1. Comparison of Economic and Social Indicators: Brazil, São Paulo and the USA

<table>
<thead>
<tr>
<th>Economic and Social Indicators</th>
<th>Brazil</th>
<th>SP</th>
<th>USA</th>
</tr>
</thead>
<tbody>
<tr>
<td>GDP: Gross domestic product (million US$)(^1,2,3)</td>
<td>2,254,109</td>
<td>722,514</td>
<td>16,244,600</td>
</tr>
<tr>
<td>GDP per capita (US$)(^1,2,3)</td>
<td>11,346.80</td>
<td>17,015.90</td>
<td>51,163.30</td>
</tr>
<tr>
<td>Individuals using the internet (%)(^1,2,4)</td>
<td>49.9</td>
<td>66.5</td>
<td>81</td>
</tr>
<tr>
<td>Population growth rate (average annual %)(^1,2,4)</td>
<td>0.9</td>
<td>0.92</td>
<td>0.8</td>
</tr>
<tr>
<td>Urban population (%)(^1,2,5)</td>
<td>85.2</td>
<td>95.9</td>
<td>82.9</td>
</tr>
<tr>
<td>Population aged 0 - 14 years (%)(^1,2,6)</td>
<td>24.1</td>
<td>21.5</td>
<td>19.6</td>
</tr>
<tr>
<td>Population aged 60+ (females and males, % of total)(^1,2,6)</td>
<td>12.2/10.1</td>
<td>6.6/5.1</td>
<td>21.3/18</td>
</tr>
<tr>
<td>Life expectancy at birth (females and males, years)(^1,2,4)</td>
<td>77.5/70.2</td>
<td>80.11/73.5</td>
<td>81.2/76.4</td>
</tr>
<tr>
<td>Infant mortality rate (per 1,000 live births)(^1,2,4)</td>
<td>19.5</td>
<td>15.7</td>
<td>6.1</td>
</tr>
<tr>
<td>Health expenditure per capita (US$)(^7)</td>
<td>1,078.00</td>
<td></td>
<td>8,845.00</td>
</tr>
<tr>
<td>Health expenditure, total (% of GDP)(^8)</td>
<td>9.5</td>
<td></td>
<td>17.0</td>
</tr>
<tr>
<td>Education: Government expenditure (% GDP)(^1,2)</td>
<td>5.8</td>
<td></td>
<td>5.6</td>
</tr>
<tr>
<td>PISA scores (Mathematics/Reading/Science)(^9)</td>
<td>391 / 410 / 405</td>
<td></td>
<td>481 / 498 / 497</td>
</tr>
<tr>
<td>Intentional homicides (females and males, per 100,000)(^1,2,10)</td>
<td>5.4/54.7</td>
<td>3.2/15.8</td>
<td>1.9/6.6</td>
</tr>
<tr>
<td>Human development index (index / world rank)(^11,12,13)</td>
<td>0.755 / 75</td>
<td>0.783 / -</td>
<td>0.915 / 8</td>
</tr>
</tbody>
</table>

Source:


1.2.1 Overview of the Health Care Systems in Brazil and the USA

1.2.1.1 The Brazilian Health Care System

Brazil is a federative republic which covers 47% of South America. The country has three levels of autonomous government – federal government, 26 states, one federal district, and 5563 municipalities. Its population is multi-ethnic. Brazil’s gross domestic product more than doubled between 1991 (US$ 600 billion) and 2008 (US$ 1.6 trillion). Its Gini coefficient* decreased from 0.637 to 0.547 but remains among the highest in the world. The leading causes of death in Brazil are diseases of the circulatory system, followed by cancer and external causes (mostly homicides and traffic accidents). The greatest contributor to the burden of disease are chronic diseases. Communicable diseases have decreased over time but it continues to affect a substantial proportion of the population. Chronic disease presents a great challenge to the health system as the public health system is organized to provide predominantly acute care.

Presently, the country's health system is a network of complementary and competitive service providers and purchasers, forming a public-private mix financed mainly by private funds. The public subsector offers services financed and provided by the state at the federal, state and municipal levels (health service to military personnel is entirely state-funded though provided separately through dedicated institutions). A private (for-profit and nonprofit) subsector provides services financed through public and private funds while a private health insurance subsector, offers services through varying health plans, insurance premiums and tax subsidies. These public and private components although distinct are interconnected and people can use services in all subsectors, according to their ease of access and ability to pay.

1.2.1.1.1 The public health subsystem

Brazil's public Unified Health System (Sistema Único de Saúde - SUS) was instituted by the constitution in 1988. It establishes health as every citizen’s right and the state’s duty. It is tasked with ensuring continuity of care to all citizens at the primary, specialist outpatient and hospital

* Gini coefficient – represents the distribution of income or wealth among a nation’s residents, and is commonly used as a measure of inequality.
levels, as well as health promotion, surveillance, vector control and health education. Decentralization is an important principle of SUS with the Family Health Program (PSF) at the base of its structure. Among the several initiatives undertaken at the national level were the development of a national HIV/AIDS prevention and control program, efforts for tobacco control, the creation of the national sanitary surveillance agency, development of the National Supplementary Health Agency, care for the Indigenous population and the initiation of a national transplant program.

1.2.1.1.2 The private health subsystem

The private health subsystem interfaces with the public sector by providing services contracted out by SUS, as well as with out-of-pocket hospital and ambulatory services, drugs and private health plans and insurances. Part of this supply is financed by SUS and the remaining by private sources. The demand for private health plans and insurance is mainly from employees of public and private companies that offer such coverage. In 2013, 27.9% of the population had health insurance (IBGE; https://www.ibge.gov.br/estatisticas-novoportal/sociais/saude/9160-pesquisa-nacional-de-saude.html). The private subsector continues to expand and is subsidized by the government, while the public subsector is often underfunded. Frequently, even the population with health insurance often receive vaccines, high-cost services and complex procedures such as hemodialysis and transplants through the SUS.

1.2.1.1.3 Financing

Funding for the SUS comes from tax revenues and social contributions from the federal, state and municipal budgets, which have not been sufficient to ensure stable financial resources for the public system. The public share of health care spending was 41%, in 2007, as compared to countries such as the UK (82%), Italy (77.2%), Spain (71.8%), and is lower than even the USA (48%). Private sources of funding - direct spending by families and companies, with direct and indirect government subsidies, fund most private health care plans, insurance policies and drug purchases.
1.2.1.1.4 Infrastructure (supply)

The supply of hospital beds financed by the public sector is insufficient. In 1993, Brazil had an inpatient bed density of 3.3 beds per 1000 population, this has decreased to 1.9 per 1000 population, which is lower than that of all the countries in the Organization for Economic Cooperation and Development, except Mexico (1.7 per 1000 population in 2007). The number of health professionals has, however, increased substantially in the past 10 years. In 2007, there were 1.7 doctors, 0.9 nurses and 1.2 dentists per 1000 population, although geographical distribution remained uneven.

1.2.1.1.5 Access to and use of healthcare

Access to health care has improved since the creation of the SUS. The number of people seeking primary health care in clinics increased by 450% between 1981 and 2008. In 2008, 76% of individuals in the highest income group reported visiting a doctor, compared with 59% of individuals in the lowest income group, which shows that socioeconomic inequity exists. However, such disparity does not exist among people who self-rate their health as poor, indicating that people with serious health disorders are able to seek health care and receive treatment, irrespective of their socioeconomic class.

The National Immunization Program, set up in 1973, stands out as one of Brazil's most successful public health programs, as shown by its high vaccination coverage and sustainability (vaccines are supplied by the National Self-Sufficiency Program in Immunobiological which guarantees free access).

In summary, SUS is under continual development and continues striving to enable universal and equitable coverage. Further challenges arise from the changing demographic and epidemiological characteristics of the Brazilian population, which needs a transition from a model of acute care to one based on intersectoral health promotion and health service integration. The greatest challenge facing the SUS is political as issues such as financing, the composition of the public-private mix, and the persistent inequities cannot be solved in the technical sphere only.
1.2.1.2 The US Health System

The US has the largest economy in the world with one the highest gross national incomes per head. It has a federal constitutional democracy. The US health-care system can be thought of as multiple systems that operate independently and, at times, in collaboration with each other. The organization is divided between the federal and state governments. The states fund and manage many public health functions and pay part of the Medicaid costs, while products such as drugs and medical devices are regulated at the federal level.

Senior citizens and some of the disabled receive care through Medicare, and Medicaid provides services for some of the poor and near-poor. Both the public and private payers purchase health-care services from providers subject to regulations enforced by the local, state and federal governments as well as by private regulatory organizations.

The Department of Health and Human Services (HHS) plays the largest administrative role in the US health-care system. HHS includes agencies such as the Centers for Medicare & Medicaid Services (CMS) that administer the public Medicare and Medicaid programs and the Children’s Health Insurance Program (CHIP). The Office of Veterans Affairs (VA), a federal agency independent of HHS, oversees the Veterans Health Administration (VHA) which provides care to military veterans. While the Department of Defense is responsible for the health care of active duty military personnel and their families through TriCare.

Medicare is the largest public purchaser of healthcare. The private sector plays a greater role in the health system than in other high-income countries. There are three main categories of private insurance: health maintenance organizations (HMOs), preferred provider organizations (PPOs) and high-deductible plans. Most of the Americans with private insurance obtain it through an employer. Health-care providers and services include hospitals, physicians, dentists, prescription drugs, home health and long-term care, mental health, other professional services and public health services.

1.2.1.2.1 Financing

Public sources contribute to 48% of health-care expenditure, private third-party payers contribute 40%, and the remaining 12% is paid for by individuals out of pocket. Even though the proportion
of public and private spending on health care is roughly comparable, only a minority of the population (30%) is covered by the public financing system, mainly through Medicare and Medicaid. The majority of the population (54%) are covered by private health insurance, and most of them obtaining coverage through their employers. While one in six Americans remains uninsured. However, even for those with coverage, high out-of-pocket (OOP) costs can be a barrier to receiving adequate care and medications.

Healthcare expenditure is much higher in the US than in any other country. In 2011, total spending exceeded $2.7 trillion. The US, in 2010, spend more than two times the OECD median per capita ($8233 as compared to $3309), which is 53% more than the second highest country, Norway ($5388).

1.2.1.2.2 Physical and Human Resources

The US uses relatively more medical technologies such as MRIs and CT scanners than comparable countries. Relative to comparable countries, the US is around the median in physician supply, but towards the top in nurse supply. The US benefits from net inward migration of health-care professionals from other countries, but suffers from internal maldistribution: by practice and setting (disproportionate number of specialist physicians compared to primary care physicians); by geographical location (variations in physician to population ratios of more than 50%); and by racial and ethnic representation in the workforce (African Americans, Latinos and American Indians underrepresented).

1.2.1.2.3 Provision of Services

Insured individuals generally access the health-care system through their primary care provider. However, some kinds of insurance (e.g. Preferred Provider Organizations - PPOs) allow individuals to go directly to a specialist. Those without insurance use community health centers (which is a primary care provider for low-income, uninsured and minority population) and hospital emergency rooms for their health care, which hinders continuity of care as they usually do not have a regular primary care provider. For receiving payment from Medicare, Emergency
departments in nearly all hospitals in the US, are required by law to provide care to anyone requiring emergency treatment until they are stable.

1.2.1.2.4 Principal Health Reforms

Though highly controversial, the Patient Protection and Affordable Care Act (ACA) of 2010 was the most significant health reform in the US since Medicare. The contents seem to reflect the general American preference for minimal government intervention. The main aim is to improve coverage through both the public and private sectors, through (i) subsidies targeting the lower-income individuals and families to purchase coverage; (ii) a mandate that most Americans obtain insurance or face a penalty; (iii) a requirement that firms with over 50 employees offer coverage or pay penalty; (iv) a major expansion of Medicaid; (v) regulating health insurers by requiring that they provide and maintain coverage to all applicants and not charge more for those with a history of illness, as well as requiring community rating, guaranteed issue, non-discrimination for pre-existing conditions, and conforming to a specified benefits package. There was increased funding for public health programs and for primary care to improve access. Although the ACA did not achieve universal health-care coverage, it represented, along with Medicare and Medicaid, a major effort towards that goal. However, under the current political scenario, the future directions of health care reforms remain uncertain.

1.2.1.2.5 Assessment of the Health System

The US health system has considerable strengths and some weaknesses. It has a well-trained workforce, high-quality medical specialists, secondary and tertiary health institutions, and a strong health sector research program. In some areas, they provide some of the best outcomes in the world (e.g., certain cancers). But it also offers incomplete coverage and inadequate care for the uninsured. Although expenditure far exceeds all other countries, poor results on objective and subjective measures of quality (e.g., asthma) as well as an unequal distribution of resources and outcomes among different population groups can be encountered. Compared to other high-income countries, life expectancy is lower, mortality and potential years of life lost is higher. However, there is disagreement over whether this relatively poor performance on mortality is due to structural problems within the health-care system. How much of the deficiencies are
health-system related is difficult to determine because multiple genetic, environmental, socioeconomic, and cultural factors affect health status. It seems, however, that at least some of the problems are related to poor access to care.

1.3 São Paulo, Brazil

The State of São Paulo covers an area of 248,808.8 square kilometers. It is the most populous State in Brazil, with 43 million inhabitants and is considered the “economic motor of the country”\(^ {20}\). Its GDP represents 28.7% of the country’s GDP.

In 2004, the Brazilian government represented by the Ministries of Health (Ministério da Saúde), Education (Ministério da Educação) as well as that of Science, Technology and Innovation (Ministério da Ciência, Tecnologia e Inovação), along with the Association of University and Teaching Hospitals (Associação Brasileira de Hospitais Universitários e de Ensino – ABRAHUE) and the Medical (Conselho Federal de Medicina - CFM) and Nursing Councils (Conselho Federal de Enfermagem – COFEN) initiated an effort to certify University Hospitals across the country. Following this work, the Health Secretariat of the State of São Paulo (Secretaria de Saúde do Estado de São Paulo – SES/SP), created a working group to monitor the University and Teaching Hospitals within the State, using a web-based instrument to collect information regarding their structures, processes, financing, and quality. In an attempt to compare the results with those in the USA, they recently published unadjusted mortality rates for eight surgical or invasive procedures (cardiac revascularization, coronary angioplasty, surgical correction of aneurisms of the abdominal aorta, carotid endarterectomy, pancreatic resection, esophageal resection, craniotomy and hip replacement)\(^ {11}\). This study reported higher surgical mortality in SP for each of the procedures evaluated, ranging from 1.3 times to 7.9 times those in the USA. Results of liver transplantation have not been compared previously.

An aspect of Brazil’s public health system, which has been praised, is its provision of universal access to AIDS treatment and its campaigns on prevention\(^ {21}\). Despite the mixed state and privately funded health system in Brazil, and consequently in São Paulo as well, transplant procedures are almost exclusively publicly funded, i.e., greater than 95% of the procedures\(^ {22}\). Therefore, universal public access to transplant procedures is provided by the public healthcare system. However, recently in an editorial in the Journal of the Brazilian College of Surgeons, a
former president of the Brazilian Association of Organ and Tissue Transplantation highlighted that in spite of the advances achieved nationally in liver transplantation, comprehensive evaluations of the outcomes are still lacking\textsuperscript{23}. Therefore, considering that Brazil has the second largest liver transplant volume in the world, that the transplant enterprise is almost exclusively state-funded with universal access to the procedure, and that the results of liver transplantation have not been compared at an international level, the aim of this study was to compare graft survival after primary liver transplantation (at 30 days, 3 months, 6 months, 1 year, 3 years and 5 years) between the State of SP and the USA (i.e., the pioneer in liver transplantation, who has set the standards for the procedure). The State of SP performs the largest number of liver transplants procedures in the country (36.7\%)\textsuperscript{24}. Furthermore, the availability of data from Brazil was restricted to the State of SP, hence the decision to compare SP to the USA. Based on publicly available data from Scientific Registry of Transplant Recipients in the USA (Figure 1) and the data from SES/SP (Figure 2), we hypothesized that the relative hazard for graft failure or patient mortality is greater in SP for the period up to one year, but for long-term follow-up, at 5 years, the HR is similar between the two jurisdictions.

**Figure 1. Graft survival among the United States adult liver transplant recipients transplanted in 2007: deceased donors.**

Source: OPTN/SRTR 2012 Annual Data Report: Liver
Figure 2. Unadjusted graft survival rates for São Paulo, Brazil, adult liver transplant recipients between 17/07/2006 and 31/06/2012.

Source: State Transplant System, Health Secretariat for the State of São Paulo (Sistema Estadual de Transplante, Secretaria de Estado da Saúde do Estado de São Paulo)
Chapter 2

2 Methods

2.1 Data Sources

Data on US patients was obtained from the Scientific Registry of Transplant Recipients (SRTR). SRTR is a mandatory, national, population-based registry that records all solid-organ transplants and their associated outcomes. Data in the SRTR database are from multiple sources, mostly collected by the Organ Procurement and Transplantation Network – OPTN (from transplant centers, Organ Procurement Organizations – OPO’s, histocompatibility laboratories), but also from the Centers for Medicare & Medicaid Services (CMS) and the Social Security Administration Death Master File (SSADMF).

Once a month the SRTR receives a snapshot of the OPTN database, providing all the new information as well as any historical revisions. This information is electronically evaluated and compiled with other data into the SRTR registry. SRTR also receives monthly updates from the SSADMF, which is used to crosscheck data received from the OPTN regarding the vital status of transplant candidates, living donors and transplant recipients.

The SRTR is required to publish an annual data report, which provides information on patient outcomes from all transplant centers in the USA as well as a semi-annual program-specific transplant survival rates (Program-Specific Reports – PSR’s) for all solid organ transplants in the USA. The PSR’s are published on the SRTR’s website every 6 months.

Data on patients in São Paulo (SP) was obtained from the State Transplant System, Health Secretariat for the State of São Paulo (Sistema Estadual de Transplante, Secretaria de Estado da Saúde do Estado de São Paulo). Transplant centers in SP are required to follow all liver transplant candidates and recipients and provide their information to the State registry. Non-complying centers are excluded from the graft allocation system until the required data are provided. Therefore, it is a state-wide, mandatory, population-based registry that tracks all liver transplant candidates and recipients and the respective graft and patient survival. The transplant
centers are the sole source of the data to this registry. The dataset is monitored using computerized range and consistency checks.

Although it has been used for research, the SP transplant registry has been primarily used for administrative purposes, allocation of grafts, and evaluation of outcomes. Individual centers have access to their respective unadjusted graft and patient survival rates as well as that of the State, but not of other transplant centers. This information is provided by the Health Secretariat to individual transplant centers, but not made publicly available.

2.2 Study Population

The study population included all adult patients (≥18 years of age at the time of transplant), who received a primary liver transplant, between July 17, 2006, and June 30, 2012, in the US and in SP. The accrual period was chosen to begin specifically on the 17th of July 2006 because the MELD (Model for End-Stage Liver Disease) criteria was adopted state-wide on this date for the allocation of liver grafts in SP. Exclusion criteria included: (i) pediatric recipients (<18 years of age), (ii) patients receiving multiple organ transplants (including liver-kidney transplant), (iii) prior non-liver transplant recipients and (iv) repeat liver transplants.

2.3 Study Exposures

The primary exposure of interest was the jurisdiction from which an end-stage liver disease patient received his/her liver transplant (SP vs. US). Patients receiving a liver transplant at a center based in SP (as per the SP registry) or the US (as per the SRTR) were classified as “SP” and “US” liver transplants, respectively.

2.4 Study Outcomes

The primary outcome is graft failure, which is defined as re-listing after current transplant, or patient death. Patient mortality includes all causes of death following liver transplantation.
Patients may or may not have functioning liver allografts at the time of death. As mentioned earlier, the SRTR captures death from the OPTN registry and this is crosschecked with data received from SSADMF. Mortality data on recipients in the SP registry is solely provided by the transplant centers themselves. Therefore, in order to harmonize the two datasets, the date of death used for survival analysis was the date reported in both registries as provided by the transplant centers. Transplant recipients who were alive at the end of the study follow-up were censored.

### 2.5 Potential Confounders

Recipient, donor, and transplant attributes, that may confound the relation between the region where the procedure is undertaken and the outcomes of interest, were selected on the basis of background clinical knowledge and prior studies in the literature \(^{27, 28, 29}\). This process also took into consideration the risk factors that were recorded to a comparable degree in both registries. Patient-level covariates were categorized into three groups: (i) recipient factors; (ii) donor factors; and (iii) transplant factors. Recipient factors included age at transplant, sex, MELD score, diagnosis of Acute Hepatic Necrosis, ever having been approved for hepatocellular carcinoma (HCC) exception, and time on the waiting list. Donor factors included donor age, sex, and weight. Transplant factors included cold ischemia time (in hours).

As the criteria for affording extra MELD points vary across regions, in order to harmonize this variable from the two datasets, the MELD score that was used for the analysis was calculated for each patient based on the last measured international normalized ratio (INR), bilirubin and creatinine values before transplantation (calculated MELD). No upper or lower limits were applied to the score and no extra points were awarded to patients with hepatocellular carcinoma or other special cases.

### 2.6 Missing Data

A total of 906 observations in the SRTR dataset had missing or implausible values (e.g., cold ischemia time < 12 minutes). Similarly, one patient in the SP cohort had missing survival data.
Therefore, as missing or implausible values constituted less 3% of the study cohort, these observations were deleted.

### 2.7 Subcohort Analysis

The cause of end-stage liver disease (primary diagnosis) is not reliably captured in the São Paulo cohort. Furthermore, although MELD provides some idea of the severity of liver disease, it does not do so in all cases\(^{30}\). Therefore, certain groups of patients are afforded extra points on the MELD scale (for example, MELD exception score for patients with hepatocellular carcinoma, portopulmonary hypertension among other conditions). Therefore, in an attempt to comprehend the influence of severity of liver disease on graft survival in the two jurisdictions, two subcohort analysis were performed. The association of country and mortality were assessed in \textit{a priori} subcohort analyses of two cohorts of patients: (i) patients with acute hepatic necrosis (AHN) and (ii) those with hepatocellular carcinoma (HCC). As mentioned above, although the variable ‘diagnosis’ is not well captured in the SP registry, these two conditions are well documented, as they are always audited by a group of transplant physicians before listing for transplantation and once again after the procedure (based on the histologic review of the explant). Any deviations from accepted protocols require justifications from the SP transplant centers. However, although the definition and indications for liver transplant for patients with AHN and HCC is standardized worldwide, there are variations both within and between the jurisdictions. For the purpose of this study, the AHN subcohort was defined as those patients in the US who were attributed the diagnosis Acute hepatic necrosis. This diagnosis is generally attributed to patients who fulfill the King’s College criteria or Clichy criteria for acute liver failure. They represent a cohort of severely ill patients (severely compromised liver function), with worse prognosis especially in the early post-transplant period. On the other hand, patients who received exception score due to hepatocellular carcinoma, represent the other end of the spectrum of liver disease severity, i.e., those with the least compromised liver function. Taken together in this study, in the absence the primary diagnosis, these two subcohorts attempt to capture the influence of the extremes of liver disease severity on graft survival. In order to harmonize the datasets from both jurisdictions, both subcohorts were established based on the diagnosis attributed to the patients preoperatively.
2.8 Sensitivity Analysis

To evaluate whether these differences in definition could influence the results obtained in this study and again estimate the influence of patient severity, we further performed a sensitivity analysis considering two subcohorts of patients, (i) those with high MELD scores (≥ 35, representing the most severely ill patients), and (ii) those with low MELD score (≤ 15, representing the least severely ill patients).

2.9 Statistical Analysis

The distributions of recipient, donor and transplant characteristics were evaluated for each jurisdiction, during the study period. For initial exploratory analysis, continuous variables were compared using non-parametric (Wilcoxon rank sum test) methods. Categorical variables were compared using the chi-square test for proportions. All numerical data were used as continuous variables in multivariable analyses.

Survival analysis was used to evaluate the outcome. Patients lost to follow-up were censored at the date of last follow-up and those requiring a second graft were considered to have the outcome at the date of re-listing for transplant. The probability of graft failure and patient death was estimated using the Kaplan-Meier product limit method. The log-rank statistic was used to test for differences in survival functions across the groups. Cox proportional hazards model was used to evaluate the impact of covariates on the outcome of interest. The analysis was censored at 31st of December 2012. A multivariable Cox proportional hazards regression model was constructed by initially entering the exposure and confounder variables, followed by the inclusion of the available covariates in the subsequent model (adjusted).

The risk-adjustment process can only account for the differences among the groups that are measured and reported completely and accurately for the entire cohort. The SRTR suggests that a broad range of factors could be used for risk-adjusted analyses (recipient related factors such as age, sex, race, primary liver disease, physiological reserve, pretransplant treatments, and blood type compatibility; donor related factors such as age, sex, race, cause of death, donor size and expanded criteria for donation/donation after cardiac death; transplant related factors such as cold-ischemia time). However, for the year 2012, the SRTR annual report presented the graft
survival estimates for adult, deceased donor, liver transplant recipients computed with Cox proportional hazards models adjusted only for age, sex and race\textsuperscript{32}. Therefore, the model used in this study is different from the one used by SRTR as all the variables, that were comparable between the two registries (presented in Table 2), were used for risk-adjustment.

As there was a violation of proportionality assumption, the model was stratified according to different follow-up periods (30 days, 3 months, 6 months, 1 year, 3 years and 5 years), based on the probability of patient death or graft failure reported in previous studies \textsuperscript{14}. This allowed for the assessment of risk during each period conditional on having survived the previous one, as depicted in Figure 5 \textsuperscript{33}.

The primary analysis used a conventional Cox proportional hazards model to assess the relation between the jurisdiction of transplant and mortality. In order to improve comparability at liver transplantation between the exposure groups, a secondary analysis was performed using propensity score matching described below \textsuperscript{34; 35}.

All analyses were performed using SAS 9.3 statistical software package. A two-sided $p$-value of \textless 0.05 was considered statistically significant. The study was approved by the University of Toronto Ethics Committee.

\textbf{2.10 A note on Survival Analysis and Time-dependent Effects}

Usually, in Kaplan-Meier and Cox regression analysis, the risk factors are measured at baseline and then related to mortality thereafter. However, many factors may change during follow-up. Some fixed baseline risk factors may have effects that vary over time, i.e time-dependent effects. The risk factors may themselves changes over time, representing time-varying risk factors. For example, patients’ blood pressure may vary over time. This effect of time should, therefore, be taken into consideration during the analysis.

In this study, all covariates were measured at baseline and then related to patient mortality. A clear way of showing the influence of the length of follow-up is by reporting mortality rates separately for each period of follow-up \textsuperscript{33}. For this analysis, we fit a Cox regression model to the entire sample, allowing the hazard ratio to vary over time (time windows defined a priori).
Figure 5 depicts the time-stratified hazards ratio obtained by this approach. As the risk factor is measured only once, at baseline, it is considered a fixed risk factor, and a separate hazards ratio is estimated for the distinct time windows. The time windows defined in this study were (i) the first 30 days, (ii) 2 to 3 months, (iii) 4 to 6 months, (iv) 7 months to 1 year, (v) 1 to 3 years and (vi) 3 to 5 years.

2.11 Propensity Score Matching (PS)

Ideally, for estimating treatment effects (or establishing a causal relationship), an important aspect of the study design is the random assignment of study subjects to the treatment (exposure) group or the control group, as in randomized controlled trials (RCT). However, that is not always feasible for ethical or practical reasons. In this retrospective cohort (observational) study, to estimate the effect of the jurisdiction on the outcome, beyond survival analysis using Cox regression, we also used the propensity score method as a secondary analysis.
The objective of this method is to reduce confounding by mimicking the characteristic of a RCT, where the probability of being assigned to the treatment or the control group is already known due to the study design as 0.5 (i.e a 50% chance of being assigned to one group or the other). This provides the greatest possibility for avoiding selection bias by comparing the outcomes between subjects with a similar distribution of baseline characteristics. With the propensity score method, the propensity score is the probability of being assigned to the treatment group or control group (for example, in this study the probability of receiving or being exposed to, the transplant procedure in SP) conditional on the measured baseline covariates. The propensity score is a balancing score. The distribution of the measured covariates will be similar between the control (unexposed) and treatment (exposed) subjects with the same value of the propensity score.\textsuperscript{36, 37}

### 2.11.1 Steps in PS analysis

The PS is frequently estimated using a logistic regression model in which the treatment assignment is regressed on the observed baseline characteristics. Although the true propensity score model is not known, it can be estimated based on the observed data. The variables to include in the model could be (i) all the variables that affect treatment selection, (ii) all variables that affect the outcome, (iii) all variables that affect the treatment and the outcome (confounding variables) or (iv) all measured variables. It has been recommended that we use prognostic variables, or if we intend to create a propensity score matched sample with only one outcome in mind, include only the potential or true confounders in the propensity score model.\textsuperscript{38} For this study, we were limited to the variables comparable between the jurisdictions. The inability to include all the confounders in the propensity score model could result in an imbalance between the jurisdictions and potentially a biased estimate of the effect of exposure.

The propensity score can be used in four ways: (i) propensity score matching, (ii) stratification on the propensity score, (iii) inverse probability of treatment weighting using the propensity score and (iv) covariate adjustment using the propensity score. In comparative studies, matching on the propensity score and weighting using the inverse probability of treatment have been reported to reduce the systematic difference between the treated and untreated subjects to a
greater degree, with PS matching tending to be similar or have a marginally superior performance among the two\textsuperscript{39}. In this study, we used the propensity-score matching method.

The method for matching on the PS include the (i) nearest-neighbor matching on the propensity score and (ii) nearest-neighbor matching within a specified caliper width. In this study, the nearest-neighbor matching within a specified caliper width was used to create the matched sample. For this, the exposed subjects were ranked according to the propensity score. The exposed subject with the highest propensity score was then matched with an unexposed subject with the closest propensity score. This process was repeated until all the exposed subjects were matched (1:1 matching). Matching was performed without replacement, i.e the unexposed subject was matched to at most one exposed subject. For most settings, when using the propensity score matching, the use of one or two untreated subjects for each treated subject has been recommended\textsuperscript{40}. In this study, we performed 1:1 matching between the exposed and unexposed subjects.

Once the matched sample has been obtained, the distribution of the baseline covariates between the treated and untreated subjects in the matched sample must then be compared. This balance assessment is crucial in propensity score analysis\textsuperscript{41}. It can be evaluated using (i) standardized differences, (ii) quantile-quantile plots of baseline covariates, (iii) density plots of baseline covariates and (iv) comparison of interactions. The process of matching may require repeated iterations to modify the specification of the PS model until adequate balance is achieved.

After adequate balance between the exposed and unexposed subjects has been demonstrated in the matched sample, the outcomes can be compared directly between them. The analysis should, however, take into account the matched nature of the sample\textsuperscript{42}.

It is important to keep in mind that although the propensity score method does mimic a RCT by providing a balance between the treatment groups for the measured baseline covariates, it does not balance the unmeasured covariates, and therefore does not necessarily avoid bias due to unmeasured confounding.

Therefore, in this study, the propensity score matching procedure involved the following steps. First, propensity scores were developed using the same covariates chosen for the Cox proportional hazards model, which were available from both jurisdictions and could potentially
influence the outcome (graft survival and patient mortality), with the jurisdiction where the transplant was undertaken as the dependent variable in a logistic regression model. All the covariates (recipient related: age, gender, MELD score, diagnosis of acute hepatic necrosis and hepatocellular carcinoma, time on the waitlist; donor related: age, gender, and weight; transplant-related: cold ischemia time) were forced into the model. This procedure created a dataset, containing the predicted probabilities of each subject being transplanted in SP vs. the USA. Second, recipients transplanted in SP were then matched to those transplanted in the U.S. using a greedy matching procedure with caliper set at 0.2 standard deviations of the logit of the propensity score, without replacement. Further restrictions were imposed on the matching process: patient age (within a 10-year difference), MELD score (within a 3-point difference), donor age (within a 10-year difference), donor weight (within a 15-kg difference), cold ischemia time (within a one-hour difference), and time on wait-list (within a 6-month difference). For the binary variables, a perfect match was requested. Third, the balance of means and variances of the matching continuous variables across the two exposure groups was verified using standardized differences 43.
Chapter 3

3 Results

3.1 Results for the Study Population

Among the 37,872 liver transplants procedures, undertaken in the USA from the 17th of July, 2006, to 30th of June, 2012, a total of 27,902 recipients satisfied the inclusion and exclusion criteria for entry into the study cohort (Figure 6). The following patients were excluded: (i) patients receiving multi-organ transplants (3,028 recipients); (ii) patients submitted to previous transplant procedures (1,952 recipients); (iii) patients below 18 years of age (2,965 recipients); (iv) living-donor transplant recipients (1,119 patients); and (v) missing data (906 recipients).

In SP, among the 2574 liver transplant recipients during the same time period, 2256 recipients satisfied the inclusion and exclusion criteria for entry into the study cohort (Figure 4). The following patients were excluded: (i) patients receiving multi-organ transplants (95 recipients), (ii) patients below 18 years of age (80 recipients), (iii) living-donor transplant recipients (141 recipients), (iv) split-liver transplant (1) and (v) missing survival data (1).

Figure 4. Study Flow Diagram
The distributions of recipient, donor, and transplant characteristics are presented in Table 2. There were statistically significant differences between the US and SP cohorts, in all the measured variables except recipient gender distribution and age of the donors. Larger differences in baseline characteristics were present in the proportion of cases of acute liver failure and hepatocellular carcinoma, as well as recipient time on waiting list and weight of the donors. In SP, there was a greater proportion of patients with acute liver failure (7.1% versus 4.9%) but a lesser proportion with hepatocellular carcinoma (24.7% versus 29.9%). The time on the waiting list for recipients in SP was almost twice that for those in the US (median of 155 days versus 80 days, respectively). While the donors in the US were heavier than those in SP (median 78.6 Kg versus 70 Kg, respectively).

Table 2. Characteristics of the Study Population

<table>
<thead>
<tr>
<th>Study Variables</th>
<th>USA (N = 27,902)</th>
<th>SP (N = 2,256)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Recipient Factors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age [median (Q1, Q3)*]</td>
<td>56 (50, 61)</td>
<td>53 (44, 59)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Sex [n (%)]</td>
<td></td>
<td></td>
<td>0.05</td>
</tr>
<tr>
<td>Male</td>
<td>18,833 (67.5)</td>
<td>1,568 (69.5)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>9,069 (32.5)</td>
<td>688 (30.5)</td>
<td></td>
</tr>
<tr>
<td>MELD** [median (Q1, Q3)]</td>
<td>19 (13, 28)</td>
<td>22 (13, 30)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Acute Hepatic Necrosis [n (%)]</td>
<td>1354 (4.9)</td>
<td>160 (7.1)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>HCC*** [n (%)]</td>
<td>8,328 (29.9)</td>
<td>557 (24.7)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Time on waitlist in days [median (Q1, Q3)]</td>
<td>80 (70, 268)</td>
<td>155 (31, 435)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td><strong>Donor Factors</strong></td>
<td></td>
<td></td>
<td>0.2412</td>
</tr>
<tr>
<td>Age [median (Q1, Q3)]</td>
<td>43 (27, 55)</td>
<td>43 (29, 53)</td>
<td></td>
</tr>
<tr>
<td>Sex [n (%)]</td>
<td></td>
<td></td>
<td>0.0001</td>
</tr>
<tr>
<td>Male</td>
<td>16,656 (59.7)</td>
<td>1,254 (55.6)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>11,246 (40.3)</td>
<td>1002 (44.4)</td>
<td></td>
</tr>
<tr>
<td>Weight in Kg [median (Q1, Q3)]</td>
<td>78.6 (67, 91.5)</td>
<td>70 (65, 80)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td><strong>Transplant Factors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cold ischemia time in hours [median (Q1, Q3)]</td>
<td>6.47 (5, 8.17)</td>
<td>7.91 (6.25, 9.57)</td>
<td>&lt; 0.0001</td>
</tr>
</tbody>
</table>

* Q1 – 25th percentile; Q3 – 75th percentile
**MELD – Model for End-Stage Liver Disease
***HCC – Hepatocellular Carcinoma
Overall, the patients in SP were slightly younger (median 53 years versus 56 years), with a similar gender distribution (69.5% versus 67.5% males) and slightly higher median MELD score (22 versus 19). Donor age was similar in the two cohorts (median 43 years), with a slightly lower male predominance of donors in SP (55.6% versus 59.7%). Median cold ischemia time was higher in SP (7.91 hours versus 6.47 hours). During the study period, the number of transplant procedures remained stable in the US, while it increased gradually in SP before decreasing in the last two years of the study period (2011 and 2012).

Figure 5 shows the 5-year Kaplan-Meier estimate for graft and patient survival. Overall, unadjusted five-year graft survival is significantly lower in SP (56.4%) compared to the USA (68%). The striking difference is the loss of graft and patient mortality in the first-year post-transplant among SP patients. In fact, much of the graft losses and mortality occur in the first 30-days (Figure 6). Beyond this period, there seems to be little loss in SP. Whereas in the USA, the loss is gradual, with a slightly higher graft loss and patient mortality in the early postoperative period relative to later periods.

**Figure 5. Kaplan-Meier 5-year Survival Estimate for the Study Population**
Table 3 presents the results of the time-stratified unadjusted Cox proportional hazards models. This model shows a significantly greater, though decreasing, relative hazard for graft failure or patient death in SP, for the first 6 months with the HR decreasing from 4.78 (95% CI: 4.33, 5.28; \( p < 0.0001 \)) to 2.40 (95% CI: 1.96, 2.93; \( p < 0.0001 \)) and 1.52 (95% CI: 1.19, 1.94; \( p = 0.0007 \)) for the time periods between zero to 30 days, 2 to 3 months, and 4 to 6 months respectively. For the period between 7 months and 1-year, there is no significant difference in HR between the two jurisdictions. Beyond 1-year, for the period to three years and between three and five years, the HRs are significantly lower in SP, with the values of 0.68 (95% CI: 0.55, 0.85; \( p = 0.0006 \)) and 0.55 (95% CI: 0.36, 0.84; \( p = 0.0052 \)) respectively.
Table 3. Time-stratified unadjusted hazard ratios for graft failure or patient mortality for patients receiving liver transplants in São Paulo (SP) vs. United States (US) liver transplant recipients

<table>
<thead>
<tr>
<th>Time period</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 to 30 days</td>
<td>4.78</td>
<td>4.33-5.28</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>2 to 3 mths</td>
<td>2.40</td>
<td>1.96-2.93</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>4 to 6 mths</td>
<td>1.52</td>
<td>1.19-1.94</td>
<td>0.0007</td>
</tr>
<tr>
<td>7 mths to 1 year</td>
<td>1.10</td>
<td>0.87-1.40</td>
<td>0.4405</td>
</tr>
<tr>
<td>13 mths to 3 years</td>
<td>0.68</td>
<td>0.55-0.85</td>
<td>0.0006</td>
</tr>
<tr>
<td>37 mths to 5 years</td>
<td>0.55</td>
<td>0.36-0.84</td>
<td>0.0052</td>
</tr>
</tbody>
</table>

Table 4 presents the adjusted Cox proportional hazards ratio, stratified on time: zero to 30 days, 2 to 3 months, 4 to 6 months, 7 months to 1 year, 13 months to 3 years and 37 months to 5 years. Stratified on time, the relative hazard for graft failure or patient mortality was significantly higher in SP compared to the USA in the early period post-transplant, especially in the first 30 days. HR at 30 days, 3 months and 6 months are 4.65 (95% CI: 4.21, 5.14; p < 0.0001), 2.34 (95% CI: 1.91, 2.87; p < 0.0001) and 1.49 (95% CI: 1.17, 1.90; p = 0.0014) respectively.

Table 4. Time-stratified adjusted hazard ratios for graft failure or patient mortality for patients receiving liver transplants in SP vs. US liver transplant recipients

<table>
<thead>
<tr>
<th>Time period</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 to 30 days</td>
<td>4.65</td>
<td>4.21-5.14</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>2 to 3 mths</td>
<td>2.34</td>
<td>1.91-2.87</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>4 to 6 mths</td>
<td>1.49</td>
<td>1.17-1.90</td>
<td>0.0014</td>
</tr>
<tr>
<td>7 mths to 1 year</td>
<td>1.10</td>
<td>0.84-1.37</td>
<td>0.5627</td>
</tr>
<tr>
<td>13 mths to 3 years</td>
<td>0.67</td>
<td>0.54-0.83</td>
<td>0.0002</td>
</tr>
<tr>
<td>37 mths to 5 years</td>
<td>0.53</td>
<td>0.35-0.80</td>
<td>0.0024</td>
</tr>
</tbody>
</table>
At 1-year, there was no significant difference in the HR between SP and the USA, 1.10 (95% CI: 0.84, 1.37; \( p = 0.5627 \)). Beyond this period, from 1 to 3 years and 3 to 5 years, the relative hazard for graft failure and patient death was significantly lower in SP, 0.67 (95% CI: 0.54, 0.83; \( p = 0.0002 \)) and 0.53 (95% CI: 0.35, 0.80; \( p = 0.0024 \)) respectively.

### 3.2 Results for the Subcohort with Acute Hepatic Necrosis

The subcohort of patients with Acute Hepatic Necrosis (1361 subjects) included 159 patients from São Paulo and 1202 patients from the USA. The recipient, donor and transplant characteristics of these patients are presented in table 5. The only variables which were similar between the two groups were the age and sex of the donors. Otherwise, the SP patients were younger (median 38 years compared to 45 years, \( p<0.0001 \)) and presented a greater proportion of women (81.1% compared to 60.5%, \( p<0.0001 \)). The MELD scores were significantly higher in SP (median 37 compared to 32, \( p<0.0001 \)). As in the overall cohort, the donors for this group of patients were predominantly male and weighed significantly less in SP (median 70 Kg compared to 74.9, \( p<0.0001 \)). Cold ischemia time was greater in SP (median 7.58 hours compared to 6.41 hours, \( p=0.0001 \)), but time on wait list was slightly lower in SP (median 2 days compared to 3 days, \( p<0.0001 \)).
Table 5. Characteristics of the subcohort of patients with Acute Hepatic Necrosis (AHN)

<table>
<thead>
<tr>
<th>Study Variables</th>
<th>USA</th>
<th>SP</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>1202</td>
<td>159</td>
<td></td>
</tr>
</tbody>
</table>

Recipient Factors

<table>
<thead>
<tr>
<th>Study Variables</th>
<th>USA</th>
<th>SP</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age [median (Q1, Q3)*]</td>
<td>45 (32, 55)</td>
<td>38 (27, 49)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Sex [n (%)]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>475 (39.5)</td>
<td>30 (18.9)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Female</td>
<td>727 (60.5)</td>
<td>129 (81.1)</td>
<td></td>
</tr>
<tr>
<td>MELD [median (Q1, Q3)]</td>
<td>32 (25, 38)</td>
<td>37 (33, 42)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Time on waitlist in days [median (Q1, Q3)]</td>
<td>3 (2, 10)</td>
<td>2 (1, 3)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Donor Factors

<table>
<thead>
<tr>
<th>Study Variables</th>
<th>USA</th>
<th>SP</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age [median (Q1, Q3)]</td>
<td>39 (23, 52)</td>
<td>41 (25, 52)</td>
<td>0.4049</td>
</tr>
<tr>
<td>Sex [n (%)]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>685 (57.0)</td>
<td>88 (55.4)</td>
<td>0.6944</td>
</tr>
<tr>
<td>Female</td>
<td>517 (43.0)</td>
<td>71 (44.7)</td>
<td></td>
</tr>
<tr>
<td>Weight in Kg [median (Q1, Q3)]</td>
<td>74.9 (65, 87.3)</td>
<td>70 (62, 80)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Transplant Factors

<table>
<thead>
<tr>
<th>Study Variables</th>
<th>USA</th>
<th>SP</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cold ischemia time in hours [median (Q1, Q3)]</td>
<td>6.41 (5, 8)</td>
<td>7.58 (6, 9)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

* Q1 – 25th percentile; Q3 – 75th percentile
**MELD – Model for End-Stage Liver Disease

Figure 7 shows the 5-year Kaplan-Meier survival estimate for graft and patient survival in the AHN subcohort. This graph depicts a similar trend of greater graft loss and patient mortality in SP as in the complete cohort, but with a more pronounced loss within the first 30 days. The overall unadjusted 5-year survival, for this subcohort also, is significantly lower in SP (42.4%) compared to the USA (69.9%).
Figure 7. Kaplan-Meier 5-year survival estimate for the subcohort of patients with Acute Hepatic Necrosis

Table 6 presents the time-stratified unadjusted Cox proportional hazards ratios for this subcohort of patients with AHN. Here we see a significantly higher HR for the patients in SP (HR 7.04; 95% CI: 5.29, 9.37; \( p < 0.0001 \)) during the first 30 post-operative days. Beyond this period, there was no significant difference between the two jurisdictions. Between 4 and 6 months, there were too few events in SP to present meaningful results.
Table 6. Time-stratified unadjusted hazard ratios for the subcohort of patients with Acute Hepatic Necrosis

<table>
<thead>
<tr>
<th>Time period</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>P value</th>
<th>USA At Risk</th>
<th>USA Number of Events</th>
<th>USA At Risk</th>
<th>USA Number of Events</th>
<th>SP At Risk</th>
<th>SP Number of Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 to 30 days</td>
<td>7.04</td>
<td>5.29</td>
<td>9.37</td>
<td>&lt;0.0001</td>
<td>1202</td>
<td>114</td>
<td>159</td>
<td>81</td>
<td></td>
</tr>
<tr>
<td>2 to 3 mths</td>
<td>0.45</td>
<td>0.06</td>
<td>3.30</td>
<td>0.4329</td>
<td>1067</td>
<td>30</td>
<td>78</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>4 to 6 mths</td>
<td>Not applicable (zero events in SP)</td>
<td></td>
<td></td>
<td></td>
<td>1024</td>
<td>20</td>
<td>76</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>7 mths to 1 year</td>
<td>0.70</td>
<td>0.17</td>
<td>2.89</td>
<td>0.6184</td>
<td>962</td>
<td>36</td>
<td>76</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>13 mths to 3 years</td>
<td>0.23</td>
<td>0.03</td>
<td>1.66</td>
<td>0.1449</td>
<td>774</td>
<td>52</td>
<td>65</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>37 mths to 5 years</td>
<td>0.73</td>
<td>0.18</td>
<td>3.31</td>
<td>0.7285</td>
<td>391</td>
<td>20</td>
<td>42</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

*AHN – Acute Hepatic Necrosis

Table 7 presents the time-stratified adjusted Cox proportional hazards ratios with covariates (excluding the HCC variable), for this subcohort (AHN). Recipients in SP present a significantly higher HR during the first 30 days (HR 6.76; 95% CI: 5.00, 9.14; p < 0.0001), but no difference beyond this time period. And again, between 4 and 6 months, there were too few events in SP to present meaningful results.

Table 7. Time-stratified adjusted hazard ratios for the subcohort of patients with Acute Hepatic Necrosis

<table>
<thead>
<tr>
<th>Time period</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>P value</th>
<th>USA At Risk</th>
<th>USA Number of Events</th>
<th>USA At Risk</th>
<th>USA Number of Events</th>
<th>SP At Risk</th>
<th>SP Number of Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 to 30 days</td>
<td>6.76</td>
<td>5.00</td>
<td>9.14</td>
<td>&lt;0.0001</td>
<td>1202</td>
<td>114</td>
<td>159</td>
<td>81</td>
<td></td>
</tr>
<tr>
<td>2 to 3 mths</td>
<td>0.44</td>
<td>0.06</td>
<td>3.21</td>
<td>0.4148</td>
<td>1067</td>
<td>30</td>
<td>78</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>4 to 6 mths</td>
<td>Not applicable (zero events in SP)</td>
<td></td>
<td></td>
<td></td>
<td>1024</td>
<td>20</td>
<td>76</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>7 mths to 1 year</td>
<td>0.66</td>
<td>0.16</td>
<td>2.76</td>
<td>0.572</td>
<td>962</td>
<td>36</td>
<td>76</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>13 mths to 3 years</td>
<td>0.22</td>
<td>0.03</td>
<td>1.59</td>
<td>0.133</td>
<td>774</td>
<td>52</td>
<td>65</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>37 mths to 5 years</td>
<td>0.74</td>
<td>0.17</td>
<td>3.20</td>
<td>0.6906</td>
<td>391</td>
<td>20</td>
<td>42</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

*AHN – Acute Hepatic Necrosis
3.3 Results for the Subcohort with Hepatocellular Carcinoma

The subcohort of patients with Hepatocellular Carcinoma (8885 subjects) included 557 patients from SP and 8328 patients from the USA. Their baseline characteristics are presented in Table 8. In this subcohort, the two jurisdictions were similar with regard to recipient gender distribution, MELD score, and donor age. Recipient age was slightly lower in SP (median 57 years compared to 58 years; \( p = 0.0011 \)). Wait-list time was significantly greater in SP (median 224 days compared to 142 days; \( p < 0.0001 \)). Gender distribution of donors showed a slightly lower proportion of male donors in SP (55.3% compared to 59.6%; \( p = 0.0451 \)). The weight of the donors was significantly lower in SP (median 70 Kg compared to 79 Kg; \( p < 0.0001 \)), while cold ischemia time was significantly greater in SP (median 7.92 hours compared to 6.38 hours; \( p < 0.0001 \)).

Table 8. Characteristics of the subcohort of patients with Hepatocellular Carcinoma

<table>
<thead>
<tr>
<th>Study Variables</th>
<th>USA</th>
<th>SP</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>8328</td>
<td>557</td>
<td></td>
</tr>
<tr>
<td><strong>Recipient Factors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age [median (Q1, Q3)*]</td>
<td>58 (54, 62)</td>
<td>57 (51, 63)</td>
<td>0.0011</td>
</tr>
<tr>
<td>Sex [n (%)]</td>
<td></td>
<td></td>
<td>0.1224</td>
</tr>
<tr>
<td>Male</td>
<td>6405 (76.9)</td>
<td>445 (79.9)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>1923 (23.1)</td>
<td>112 (20.1)</td>
<td></td>
</tr>
<tr>
<td>MELD** [median (Q1, Q3)]</td>
<td>12 (9, 15)</td>
<td>12 (9, 15)</td>
<td>0.5227</td>
</tr>
<tr>
<td>Time on waitlist in days [median (Q1, Q3)]</td>
<td>142 (52, 323)</td>
<td>224 (122, 439)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Donor Factors</strong></td>
<td></td>
<td></td>
<td>0.6751</td>
</tr>
<tr>
<td>Age [median (Q1, Q3)]</td>
<td>44 (27.5, 55)</td>
<td>43 (30, 53)</td>
<td>0.0451</td>
</tr>
<tr>
<td>Sex [n (%)]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>4961 (59.6)</td>
<td>308 (55.3)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>3367 (40.4)</td>
<td>249 (44.7)</td>
<td></td>
</tr>
<tr>
<td>Weight in Kg [median (Q1, Q3)]</td>
<td>79 (67, 92)</td>
<td>70 (63, 80)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td><strong>Transplant Factors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cold ischemia time in hours [median (Q1, Q3)]</td>
<td>6.38 (5, 8)</td>
<td>7.92 (6.27, 9.55)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

* Q1 – 25\textsuperscript{th} percentile; Q3 – 75\textsuperscript{th} percentile
**MELD – Model for End-Stage Liver Disease
Figure 8 shows the 5-year Kaplan-Meier estimate for graft and patient survival in the HCC subcohort. This graph indicates non-proportional hazards between the two jurisdictions, with lower graft and patient survival in SP, but with a lesser difference between SP and the USA when compared to the overall liver transplant population in this study. On long-term follow-up, close to 5 years, the survival curves cross each other presenting a slightly higher survival estimate in SP (67.5% compared to 66.2%). Table 9, presenting the time-stratified unadjusted Cox proportional hazards ratios for this subcohort of patients with HCC, illustrates this change in risk well. It portrays a trend similar to that of the general population of liver transplant recipients in both regions, with a higher HR for graft failure and patient mortality during the period of the first 6 months - (i) first 30 days: HR 2.26; 95% CI: 1.71, 2.98; \( p = 0.0001 \); (ii) two to three months: HR 1.80; 95% CI: 1.09, 2.98; \( p = 0.0214 \); and (iii) 4 months to 6 months: HR 2.00; 95% CI: 1.34, 2.99; \( p = 0.0007 \). For the period from 7 months to 1 year, no difference is detected in the HR. Beyond this period, between one and 3 years (HR 0.69; 95% CI: 0.49, 0.98; \( p = 0.0373 \)) and between 3 and 5 years (HR 0.43; 95% CI: 0.19, 0.97; \( p = 0.0429 \)) recipients in SP present a lower HR.

**Figure 8. Kaplan-Meier 5-year survival estimate for the subcohort of patients with Hepatocellular Carcinoma**
Table 9. Time-stratified unadjusted hazard ratios for the subcohort of patients with Hepatocellular Carcinoma

<table>
<thead>
<tr>
<th>Time period</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 to 30 days</td>
<td>2.26</td>
<td>1.71</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>2 to 3 mths</td>
<td>1.80</td>
<td>1.09</td>
<td>0.0214</td>
</tr>
<tr>
<td>4 to 6 mths</td>
<td>2.00</td>
<td>1.34</td>
<td>0.0007</td>
</tr>
<tr>
<td>7 mths to 1 year</td>
<td>0.99</td>
<td>0.64</td>
<td>0.9564</td>
</tr>
<tr>
<td>13 mths to 3 years</td>
<td>0.69</td>
<td>0.49</td>
<td>0.0373</td>
</tr>
<tr>
<td>37 mths to 5 years</td>
<td>0.43</td>
<td>0.19</td>
<td>0.0429</td>
</tr>
</tbody>
</table>

Table 10 presents the time-stratified adjusted Cox proportional hazards model (excluding the dichotomous AHN variable), for this subcohort (HCC). Similar to the overall liver transplant population in this study, recipients in SP had a higher hazard during the first 30 days (HR 2.26; 95% CI: 1.71, 3.0; p < 0.0001), from two to 3 months (HR 1.82; 95% CI: 1.09, 3.01; p = 0.0199) as well as between 4 and 6 months (HR 2.02; 95% CI: 1.35, 3.02; p = 0.0006). For the period between 7 months and 1 year, no difference is detected in the hazard of the outcome. Beyond these time periods, between one and 3 years (HR 0.69; 95% CI: 0.49, 0.98; p = 0.036) and between 3 and 5 years (HR 0.43; 95% CI: 0.19, 0.96; p = 0.0398) recipients in SP present a lower hazard.
Table 10. Time-stratified adjusted hazard ratios for the subcohort of patients with Hepatocellular Carcinoma

<table>
<thead>
<tr>
<th>Time period</th>
<th>Hazard Ratio</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 to 30 days</td>
<td>2.26</td>
<td>1.71</td>
<td>3.0</td>
</tr>
<tr>
<td>2 to 3 mths</td>
<td>1.82</td>
<td>1.09</td>
<td>3.01</td>
</tr>
<tr>
<td>4 to 6 mths</td>
<td>2.02</td>
<td>1.35</td>
<td>3.02</td>
</tr>
<tr>
<td>7 mths to 1 year</td>
<td>0.99</td>
<td>0.64</td>
<td>1.55</td>
</tr>
<tr>
<td>13 mths to 3 years</td>
<td>0.69</td>
<td>0.49</td>
<td>0.98</td>
</tr>
<tr>
<td>37 mths to 5 years</td>
<td>0.43</td>
<td>0.19</td>
<td>0.96</td>
</tr>
</tbody>
</table>

3.4 Results for the Propensity Score-Matched Cohort

The propensity score matched cohort included (3436 subjects) 1718 patients from SP and 1718 patients from the USA. Their baseline characteristics are presented in Table 11 and show an adequate match of these covariates between the two jurisdictions. Figure 9, depicts the 5-year Kaplan-Meier estimate for graft and patient survival in this matched cohort. This graph shows a significantly lower graft and patient 5-year survival among the patients in SP (57.3% compared to 67.9% in the USA).
**Table 11. Characteristics of the Propensity Score-Matched Cohort**

<table>
<thead>
<tr>
<th>Study Variables</th>
<th>USA</th>
<th>SP</th>
<th>Standardized Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>1718</td>
<td>1718</td>
<td></td>
</tr>
</tbody>
</table>

**Recipient Factors**

<table>
<thead>
<tr>
<th>Study Variables</th>
<th>USA</th>
<th>SP</th>
<th>Standardized Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age [median (Q1, Q3)*]</td>
<td>54 (49, 59)</td>
<td>54 (47, 60)</td>
<td>-0.0378</td>
</tr>
<tr>
<td>Sex [n (%)]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1263 (73.5)</td>
<td>1263 (73.5)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>455 (26.5)</td>
<td>455 (26.5)</td>
<td></td>
</tr>
<tr>
<td>MELD** [median (Q1, Q3)]</td>
<td>22 (14, 30)</td>
<td>22 (13, 30)</td>
<td>0.0107</td>
</tr>
<tr>
<td>AHN*** [n (%)]</td>
<td>100 (5.8)</td>
<td>100 (5.8)</td>
<td>0.0087</td>
</tr>
<tr>
<td>HCC**** [n (%)]</td>
<td>471 (27.4)</td>
<td>471 (27.4)</td>
<td>0.0087</td>
</tr>
<tr>
<td>Time on waitlist in days [median (Q1, Q3)*]</td>
<td>83 (15, 254)</td>
<td>120 (25, 274)</td>
<td>0.0525</td>
</tr>
</tbody>
</table>

**Donor Factors**

<table>
<thead>
<tr>
<th>Study Variables</th>
<th>USA</th>
<th>SP</th>
<th>Standardized Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age [median (Q1, Q3)]</td>
<td>44 (28, 53)</td>
<td>43 (30, 53)</td>
<td>0.0179</td>
</tr>
<tr>
<td>Sex [n (%)]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>968 (56.3)</td>
<td>968 (56.3)</td>
<td>0.0087</td>
</tr>
<tr>
<td>Female</td>
<td>750 (43.7)</td>
<td>750 (43.7)</td>
<td></td>
</tr>
<tr>
<td>Weight in Kg [median (Q1, Q3)]</td>
<td>73 (65, 81.6)</td>
<td>70 (65, 80)</td>
<td>-0.0984</td>
</tr>
</tbody>
</table>

**Transplant Factors**

<table>
<thead>
<tr>
<th>Study Variables</th>
<th>USA</th>
<th>SP</th>
<th>Standardized Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cold ischemia time in hours [median (Q1, Q3)]</td>
<td>7.68 (6.08, 9.1)</td>
<td>7.7 (6.16, 9.16)</td>
<td>0.0087</td>
</tr>
</tbody>
</table>

* Q1 – 25th percentile; Q3 – 75th percentile
**MELD – Model for End-Stage Liver Disease
***AHN – Acute Hepatic Necrosis
****HCC – Hepatocellular Carcinoma
The time-stratified HR for the propensity score-matched cohort presented in Table 12 shows a significantly greater hazard for graft failure and patient mortality in SP compared to the US for the post-operative periods up to 30 days (HR 4.20; 95% CI: 3.36, 5.26; \( p < 0.0001 \)), two to 3 months (HR 2.45; 95% CI: 1.68, 3.58; \( p < 0.0001 \)) and 4 to 6 months (HR 1.55; 95% CI: 1.04, 2.32; \( p = 0.0328 \)). No difference in HR is detected between the jurisdictions from 7 months to 3 years of follow-up. However, for the period beyond 3 years, recipients in SP face a significantly lower hazard for graft failure and mortality (HR 0.47; 95% CI: 0.26, 0.85; \( p = 0.0127 \)).
Table 12. Time-stratified hazard ratios for the Propensity Score-Matched cohort

<table>
<thead>
<tr>
<th>Time period</th>
<th>Hazard Ratio</th>
<th>95% CL</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 to 30 days</td>
<td>4.20</td>
<td>3.36</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>2 to 3 mths</td>
<td>2.45</td>
<td>1.68</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>4 to 6 mths</td>
<td>1.55</td>
<td>1.04</td>
<td>0.0328</td>
</tr>
<tr>
<td>7 mths to 1 year</td>
<td>1.06</td>
<td>0.73</td>
<td>0.7719</td>
</tr>
<tr>
<td>13 mths to 3 years</td>
<td>0.83</td>
<td>0.61</td>
<td>0.247</td>
</tr>
<tr>
<td>37 mths to 5 years</td>
<td>0.47</td>
<td>0.26</td>
<td>0.0127</td>
</tr>
</tbody>
</table>

3.5 Sensitivity Analysis

Sensitivity analysis performed to evaluate the influence of disease definition (AHN and HCC) and disease severity on the results obtained in this study, detected a similar tendency as those patients with AHN and HCC respectively, i.e greater hazard for graft failure and mortality in the early postoperative period.

The subcohort of patients in SP with high MELD scores (> 35), faced significantly higher hazard for graft failure and mortality in the early postoperative period, i.e the first 30 days (HR 5.38; 95% CI:4.30, 6.73; p < 0.0001) and between the first and third postoperative month (HR 2.39; 95% CI: 1.49, 3.85; p = 0.0003). Beyond this period, between the first and third postoperative year, these patients in SP face a significantly lower hazard (HR 0.29; 95% CI: 0.11, 0.81; p = 0.017) (Table 13).

The subcohort of patients in SP with low MELD scores (<15), also faced significantly higher hazard for graft failure and mortality in the early postoperative period, i.e in the first 30 days (HR 3.89; 95% CI: 3.18, 4.77; p <0.0001) and between the first and third postoperative month (HR 1.65; (95% CI: 1.03, 2.65; p = 0.0388). Beyond this period, between the third and fifth-year post-transplant, recipients in SP face a significantly lower hazard (HR 0.47; 95% CI: 0.23, 0.94; p = 0.0338).
Table 13. Sensitivity analysis

<table>
<thead>
<tr>
<th></th>
<th>30 days</th>
<th>3 mths</th>
<th>6 mths</th>
<th>1 year</th>
<th>3 years</th>
<th>5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Complete cohort</strong></td>
<td>4.65</td>
<td>2.34</td>
<td>1.49</td>
<td>1.1</td>
<td>0.67</td>
<td>0.53</td>
</tr>
<tr>
<td></td>
<td>4.21, 5.14</td>
<td>1.91, 2.87</td>
<td>1.17, 1.90</td>
<td>0.84, 1.37</td>
<td>0.54, 0.83</td>
<td>0.35, 0.80</td>
</tr>
<tr>
<td></td>
<td>0 &lt; 0.0001</td>
<td>0 &lt; 0.0001</td>
<td>0 = 0.0014</td>
<td>0 = 0.5627</td>
<td>0 = 0.0002</td>
<td>0 = 0.0024</td>
</tr>
<tr>
<td><strong>AHN</strong>*</td>
<td>6.76</td>
<td>0.44</td>
<td>Not applicable, see table 7.</td>
<td>0.66</td>
<td>0.22</td>
<td>0.74</td>
</tr>
<tr>
<td></td>
<td>5.0, 9.14</td>
<td>0.06, 3.21</td>
<td>0.16, 2.76</td>
<td>0.572</td>
<td>0.133</td>
<td>0.6906</td>
</tr>
<tr>
<td></td>
<td>0 &lt; 0.0001</td>
<td>0 = 0.4148</td>
<td>0 = 0.572</td>
<td>0 = 0.133</td>
<td>0 = 0.6906</td>
<td></td>
</tr>
<tr>
<td><strong>HCC</strong>*</td>
<td>2.26</td>
<td>1.82</td>
<td>2.02</td>
<td>0.99</td>
<td>0.69</td>
<td>0.43</td>
</tr>
<tr>
<td></td>
<td>1.71, 3.0</td>
<td>1.09, 3.01</td>
<td>1.35, 3.02</td>
<td>0.64, 1.55</td>
<td>0.49, 0.98</td>
<td>0.19, 0.96</td>
</tr>
<tr>
<td></td>
<td>0 &lt; 0.0001</td>
<td>0 = 0.0199</td>
<td>0 = 0.0006</td>
<td>0 = 0.9871</td>
<td>0 = 0.0036</td>
<td>0 = 0.00398</td>
</tr>
<tr>
<td><strong>PS</strong>* matched</td>
<td>4.2</td>
<td>2.45</td>
<td>1.55</td>
<td>1.06</td>
<td>0.83</td>
<td>0.47</td>
</tr>
<tr>
<td></td>
<td>3.36, 5.26</td>
<td>1.68, 3.58</td>
<td>1.04, 2.32</td>
<td>0.73, 1.52</td>
<td>0.61, 1.13</td>
<td>0.26, 0.85</td>
</tr>
<tr>
<td></td>
<td>0 &lt; 0.0001</td>
<td>0 &lt; 0.0001</td>
<td>0 = 0.0328</td>
<td>0 = 0.7719</td>
<td>0 = 0.0247</td>
<td>0 = 0.0127</td>
</tr>
<tr>
<td><strong>High MELD</strong>**</td>
<td>5.38</td>
<td>2.39</td>
<td>1.28</td>
<td>0.82</td>
<td>0.29</td>
<td>0.31</td>
</tr>
<tr>
<td></td>
<td>4.30, 6.73</td>
<td>1.49, 3.85</td>
<td>0.62, 2.65</td>
<td>0.38, 1.77</td>
<td>0.11, 0.81</td>
<td>0.08, 1.29</td>
</tr>
<tr>
<td></td>
<td>0 &lt; 0.0001</td>
<td>0 = 0.0003</td>
<td>0.5006</td>
<td>0.6154</td>
<td>0 = 0.017</td>
<td>0 = 0.1079</td>
</tr>
<tr>
<td><strong>Low MELD</strong>**</td>
<td>3.89</td>
<td>1.65</td>
<td>1.32</td>
<td>1.09</td>
<td>0.82</td>
<td>0.47</td>
</tr>
<tr>
<td></td>
<td>3.18, 4.77</td>
<td>1.03, 2.65</td>
<td>0.83, 2.12</td>
<td>0.72, 1.65</td>
<td>0.59, 1.14</td>
<td>0.23, 0.94</td>
</tr>
<tr>
<td></td>
<td>0 &lt; 0.0001</td>
<td>0 = 0.0388</td>
<td>0 = 0.2411</td>
<td>0 = 0.6831</td>
<td>0 = 0.2363</td>
<td>0 = 0.0338</td>
</tr>
</tbody>
</table>

*AHN – Acute Hepatic Necrosis  
** HCC – Hepatocellular Carcinoma  
*** PS – Propensity score  
**** MELD – Model for End-Stage Liver Disease
Chapter 4

4 Discussion

4.1 Interpretation of the Findings

For the present study, to evaluate the outcomes of routine liver transplants for acute and chronic end-stage liver disease in the State of SP, cases of re-transplants, pediatric transplants and multi-organ transplants were excluded, and the results compared to similar primary liver transplants in the USA (the pioneer for such procedures and a country that provides benchmarks for comparisons). The State of SP performed the first liver transplant in Brazil and still performs the largest number of liver transplants procedures in the country (36.7%). It is worthy of mention that the first report of living donor liver transplant in the world was also from SP.

Certainly, many more variables than those evaluated in this study influence the outcomes after liver transplantation, such as patient comorbidity, the presence of portal vein thrombosis, previous abdominal surgery, cancer-related risk factors, post-operative immunosuppressive regimens, access to medication, characteristics of the hepatocellular carcinoma (such as the size, number, serum alpha-fetoprotein levels etc.) to name just a few. A considerable number of these variables are available in the SRTR dataset. However, to harmonize the datasets from SP and the US, only those available in the SP dataset were included in this study.

In this study, despite the statistically significant difference detected, between the jurisdictions, in all variables (except recipient gender distribution and age of the donors), clinically meaningful differences were present for relatively few variables, namely in the proportion of cases of acute liver failure (AHN) and hepatocellular carcinoma (HCC), the time on waitlist and weight of the donors. This is probably due to the large sample sizes of the cohorts. SP had a greater proportion of patients with AHN (7.1% versus 4.9%). Despite the worry among transplant physicians in SP, that a high proportion of the scarce grafts are being used by patients with HCC, a lesser proportion of transplants in SP was for these patients when compared to the USA (24.7% versus 29.9%). A notable difference between the cohorts is the time on the waitlist. Patients in SP waited almost twice the amount of time compared to their counterparts in the US (median of 155 days versus 80 days). This likely reflects lower rates of organ donation and retrieval in SP. For
example, during the year 2011, according to the Brazilian Association of Organ Transplantation, SP recovered organs from less than half the number of donors per million inhabitants compared to the USA (10.1 compared to 26.0)\textsuperscript{45}. Another important difference was that donors in SP weighed on average 9 kg less than in the US. This could possibly reflect a more conservative approach of transplant surgeons in SP towards the use of steatotic livers as well as the convention of not using donors after cardiac death.

The present study detected a significantly lower overall graft survival after liver transplant in SP compared to in the USA. The striking difference occurs mainly in the early post-operative period (particularly in the first 30 days), where the greatest number of graft failures and patient deaths occurred in SP. This can be seen well in the Kaplan-Meier survival estimate for one year (Figure 6), where practically all the loss occurs within the first 30 days. Curiously, on long-term follow-up, beyond 3 years, the hazard for graft failure or patient mortality is similar between the two jurisdictions. However, overall unadjusted 5-year survival is significantly lower in SP (56.4\%) compared to (68\%), as depicted by the Kaplan-Meier survival estimate in figure 5.

To deal with the non-proportionality between the survival curves demonstrated in the Kaplan-Meier survival estimate, we used the Cox proportional hazards model stratified on time. The time frames used for stratification were based on clinically significant periods of post-operative follow-up. The unadjusted Cox proportional hazards model (Table 3), reveals a significantly higher and gradually decreasing HR for graft failure or patient death in SP during the first 6 postoperative months (from 4.78 at 30 days to 2.40 at 3 months and finally 1.52 at 6 months). For the period between 6 months and one year, no difference was detected between the two jurisdictions. But for the periods from one to 3 years and 3 to 5 years, SP seemed to have significantly lower HRs, 0.68 and 0.55 respectively.

When the Cox proportional hazards model was adjusted for the recipient, donor, and transplant-related covariates, a similar trend remained with similar HRs, i.e a significantly higher but gradually reducing HR during the first 6 months, no difference at one year, followed by a lower HR for the periods from one to 3 years and 3 to 5 years.

Despite being unable to capture the diagnosis accurately for the SP cohort, two categories of diagnosis are regularly audited by a State-level Technical Committee attached to the State Transplant System: acute hepatic necrosis and hepatocellular carcinoma. Each category
represents a distinct group of patients requiring liver transplantation, on opposite extremes of the spectrum of liver disease severity. Patients with acute hepatic necrosis are typically extremely ill, with higher MELD scores and consequently higher pre-transplant and early post-transplant mortality. On the other hand, patients with hepatocellular carcinoma are afforded extra points on the waitlist and so are typically transplanted before serious deterioration of their liver function. Therefore, hepatocellular carcinoma patients tend to represent a relatively healthier cohort with consequently lower pre and immediate post-transplant mortality, though with a slightly higher mortality between the 6 months to one-year post-operative period, when compared to the general cohort. This is probably due to the presence of the carcinoma. So, analyzing each category as a subcohort gives an idea of the extremes of the spectrum of outcomes in each jurisdiction.

For patients who were attributed the diagnosis of AHN, the Kaplan-Meier survival curves demonstrate a similar shape as the general cohort, but with a significant and much higher cumulative probability of graft loss and patient death in SP when compared to the USA. In both the unadjusted and adjusted time-stratified Cox proportional hazards models, the patients in SP had a higher HR than the general cohort when compared to the USA, but only during the first 30 days (unadjusted HR 7.04; adjusted HR 6.76). Beyond the 30-day post-operative period, no statistically significant difference was detected between the jurisdictions. However, although the diagnostic criteria for AHN are fairly standardized worldwide, there may be some differences both within and between jurisdictions. This subcohort is not as homogenous as expected in the study plan prepared a priori. The SP subcohort is younger, with a greater number of women and a higher MELD score. Adjusting for these variables may not have been sufficient as further underlying differences probably persist. There seems to be a systematic difference between the subcohort, with a bias towards the inclusion of more severely ill patients in SP. Therefore, the results suggest that the direction of the outcome is true, as it is in keeping with the rest of the results. The magnitude of the outcome, however, is probably less marked, as can be seen by the trend towards a decreasing HR on adjusting for the available variables.

On the other extreme of the liver disease severity, the Kaplan-Meier survival curve for patients with HCC displays a distinctly non-proportional hazard but with curves much closer to each other than in the total cohort, although still with lower survival in SP than in the USA. Interestingly, the survival curves cross each other close to 5 years of follow-up, suggesting higher long-term survival in SP for this subcohort of patients. Both the unadjusted and adjusted
time-stratified Cox proportional hazards model for this subgroup reveals a significantly higher HR for patients in SP, though lower than the general cohort (unadjusted HR varying from 2.26 to 1.80 and adjusted HR varying from 2.26 to 1.82) for the initial 6 months. Similar to the overall cohort, between 6 months and one year, both unadjusted and adjusted time-stratified HR are not significantly different between the jurisdictions. In a similar trend as the overall cohort, between one and three years, and between 3 and 5 years of follow-up, SP patients present a lower hazard (unadjusted and adjusted HR 0.69 and 0.43 respectively).

To compare a more homogeneous population, propensity score-matched cohorts were constructed and analyzed. This analysis essentially showed a similar trend as the total cohort, with significantly lower survival for the SP cohort for the period up to 6 months (ranging from HR of 4.2 for the first month to 1.55 between 3 to 6 months). However, different from the total cohort, beyond 6 months, patients in SP presented a lower hazard for graft failure and death only for the period between 3 and 5 years.

Sensitivity analysis using patients with high MELD and low MELD scores verified the similar results, i.e significantly higher graft failure and patient mortality among the patients in SP during the postoperative period up to 3 months. For the late postoperative periods, low MELD patients in SP present a significantly lower HR for the period between 3 and 5 years, while the High MELD patients present a lower HR for the period between one and three years.

Overall, patients in SP present greater graft loss and mortality compared to their counterparts in the USA. The significantly higher hazard essentially reflects the loss of graft or patient mortality seen early in the postoperative period with an attenuation of the effect later on. It gradually decreases over the first 6 months, becoming comparable at one year and beyond, with a tendency to be lower beyond 3 years. The difference in survival seems more pronounced in the severely ill patients, as the hazard is even greater in the subcohort of patients with acute hepatic necrosis and those with high MELD scores, but less so in the patients with low MELD scores and those with hepatocellular carcinoma, who represent patients with less severe liver disease.

Differences in the economic and social backgrounds between SP and the USA, make comparisons difficult as they reflect disparate realities. These differences must be kept in mind while performing comparisons, as health system related factors not measured in the study, such as the type of healthcare system, access to care and medication, potentially affect the outcomes.
Equally important, factors beyond the healthcare system also influence outcomes \(^1\). However, such differences haven’t discouraged other routine comparisons between countries, using criteria such as gross domestic product (GDP), GDP per capita, Programme for International Student Assessment (PISA) scores, to name a few. And indeed, they permit benchmarking, providing goals for jurisdictions and nations to strive towards.

Reports of outcomes, including surgical, from low-middle income countries, have gradually started to appear \(^1\); \(^4\) and evaluation of outcomes are believed to be a necessary first step towards improvement \(^4\); \(^8\). Though some recent publications seem to question this assumption \(^4\); \(^5\) as they did not detect any difference between institutions that participate in the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) and those that do not. Possibly, in these studies, not participating in the ACS-NSQIP program did not necessarily mean that these institutions are not implementing quality improvement programs. In these large studies, the average effects of the institutions may not reflect the improvements achieved by those institutions pursuing quality improvement programs. Furthermore, for the centers participating in the program, just measuring outcomes is not sufficient, improvement requires actions beyond measurement and detection, which are not easy to implement and may not be uniform across all centers \(^5\).

Some countries and registries regularly present their liver transplant outcomes to the public, such as the Annual Data Report presented by OPTN/SRTR in the USA\(^3\), the Annual Report on Liver Transplantation presented from the UK Transplant registry in collaboration with the National Health Service in England\(^4\), the Annual Reports from the Australia and New Zealand Liver Transplant Registry and the Annual Report presented by the Canadian Organ Replacement Registry (CORR)\(^5\). Some of these reports present center-specific results, while others provide aggregate results for the region. These registries are generally maintained by high-income countries.

The few transnational comparisons of solid organ transplant conducted have all compared the outcomes among high-income countries \(^1\); \(^4\); \(^2\); \(^5\). No study so far has reported outcomes of liver transplant comparing countries of middle and high-income.

Among the studies reported, Stell \textit{et al.}\(^1\) evaluated the results for primary adult liver transplants for chronic liver disease, during the year 2000, from the US, UK, and Canada. Data were
obtained from the United Network for Organ Sharing (UNOS), the United Kingdom Transplant Registry and Canadian Organ Replacement Registry (CORR) respectively. For this study, the MELD score was used as a measure of disease severity, even though it wasn’t yet in use for graft allocation purposes at that point in time. Patients in North America were seen to have higher MELD scores. The authors reported similar 1-year survival rates between the countries, despite the differences in disease severity.

Similarly, Dawwas et al. compared the outcomes after liver transplant in the UK and Ireland to those in the US. They used data from high-quality national databases. The outcome measures were post-transplant mortality during the first 90 days, between 90 days and one year, and beyond one year. According to this study, patients in the UK and Ireland, had higher risk-adjusted mortality during the first 90 days (HR 1.17), no difference between 90 days and one year, and a lower overall risk-adjusted mortality beyond that (HR 0.88). In this study, they were unable to use MELD score for risk-adjustment because this variable was not available for the entire study period.

### 4.2 Methodological Strengths and Limitations

This is a population-based study including all the liver transplant recipients in SP and the US during the study period who met the inclusion and exclusion criteria. A study of this nature, comparing the outcomes of this procedure between a middle income and a high-income country, has not been previously reported. Due to the differences in the backgrounds of the two jurisdictions, attempts to account for the case-mix used Cox regression to adjust for the variables included in the study. A secondary analysis, taking into consideration the two extremes of disease severity (represented by patients with hepatocellular carcinoma and with acute hepatic necrosis) provided the spectrum within which lies the relative hazard of graft failure or patient mortality for the liver transplant recipients in SP compared to those in the US. A propensity score matched cohort was also analyzed to provide a balance in the variables available. Sensitivity analysis further evaluated the potential influence of primary liver disease and patient severity on the results.
A few important methodological limitations must be taken into consideration when evaluating the findings of this study. First, the etiology of the liver disease is related to long-term outcomes, but unfortunately, except for AHN and HCC, we could not ascertain the primary diagnosis for the patients in SP. Studies on the etiology of liver disease in Brazil are scarce, and the primary diagnosis is not well captured. One such study investigating this issue, analyzed death certificates between the years 2000 and 2010, in the State of Espírito Santo, Brazil, but the etiology of liver cirrhosis was identified in only 49% of the documents. Among the causes registered for these 262 cases, were alcoholism (40.5%), hepatitis B or C (26.7%), other causes (3.8%) and cryptogenic (10.6%). The authors themselves recognized that alcoholism was probably overestimated, and hepatitis B and C, underestimated.

However, for the purpose of this study, as AHN and HCC represent two extremes of disease severity, the inability to capture primary liver diagnoses reliably is unlikely to change the message of this study, i.e., there are opportunities to improve the early post-liver transplant outcomes for SP patients. Sensitivity analysis performed further strengthens this interpretation. As mentioned above, the AHN subcohort is not as homogenous as was expected in the study plan, indicating there could be a bias towards the inclusion of more severely ill patients in SP. However, this shouldn’t change the message of the study, although the true difference in outcome between the jurisdictions for the AHN subcohort is probably more attenuated.

Second, comorbid disease burden is an important predictor of outcomes but could not be evaluated in this study. Improved ascertainment of comorbid conditions could possibly explain an important component of differences in outcomes. However, considering the magnitude of the difference in outcome detected, improved ascertainment and adjustment for comorbidity will likely diminish the observed difference but not remove it entirely.

Third, many more risk factors, than those measured in the present study, may influence long-term transplant outcomes, including postoperative variables such as immunosuppressive regimens, renal function, episodes of acute rejection to name a few. Although perioperative care in liver transplant is fairly standardized worldwide, center-specific variations do exist for aspects such as the immunosuppressive protocols. Unfortunately, these variables are not audited in the SP registry, and therefore could not be reliably incorporated in the analysis. Future studies
should be able to account for these risk factors as well as reliably record the cause of death (whether they are related to surgical complications, infection, episodes of rejection, etc.).

Fourth, rigor in the ascertainment of outcomes in the long-term may differ across the two registries.

### 4.3 Explanation for the Observed Differences

In SP, in spite of restricting access to the waitlist to those with MELD scores above 15, patients still have a waiting time that is almost twice that in the US. This is likely a reflection of the lower rates of organ harvesting and not an earlier inclusion to the waitlist.

Compared to the US, the median MELD score at transplantation was greater in SP, and though it could contribute to the difference in outcome, a median 3-point higher MELD score is unlikely to cause a clinically significant impact on the differences seen in this study\(^{30; 58}\), especially as the difference persists in the propensity score-matched cohorts. Additionally, though a greater proportion of patients in the SP cohort were transplanted for AHN and a lesser proportion with HCC, which might suggest that some of the patients in SP were more critically ill, risk-adjusted analysis maintained the significantly greater perioperative graft loss and patient mortality among SP patients in these subcohorts.

Longer cold ischemia time is known to be related to poor outcomes\(^{59}\), and although transplants in SP presented greater cold ischemia times, the median difference of 1.2 hours is unlikely to be responsible for the magnitude of difference in perioperative outcomes encountered in this study as the differences persist after adjusting for this variable.

Considering the reports from previous studies\(^{13; 14}\), the general trend displayed in the results does indicate plausibility with excellent results in the early post-operative period among the US patients but comparable long-term risk for graft failure and patient mortality beyond three years.

The remaining explanation for the difference is a genuine difference in the quality of care and differences in the healthcare systems. The US is known to have very good acute care, therefore seriously ill patients in SP may have had a better survival had they been transplanted in the
USA. The observed high postoperative mortality in SP is consistent with another report of non-transplant procedures, with mortality ranging from 1.3 times to 7.9 times those in the USA.11

Similarly, the slightly lower long-term mortality in SP may be due to survival bias, caused by the early death of sicker patients in SP, who would have survived the early phase, had they been transplanted in the US, but would subsequently present a higher risk of dying later. However, regarding long-term survival, a study comparing kidney transplant recipients between the US and Canada, detected similar risk for death, between the two countries, during the first post-transplant year but greater risk for the US patients beyond one year (HR 1.49 – 1.53)25. This seems to indicate that there is room for improvement in long-term survival in the USA.

Taken together, the results of this study detect a higher hazard for graft failure and patient mortality for liver transplant recipients in SP. This is consistent with the other studies available in the literature showing very good early postoperative survival after liver in the USA. SP definitely needs to improve its short-term outcomes for liver transplant patients. Furthermore, as reported by Bittar et al.11, the improvement needed is not restricted to liver transplant procedure, but also for other surgical and clinical conditions11. If these are the results obtained in SP, other regions in Brazil can probably expect similar results. This is an important message for policymakers in the country.

On the other hand, a lack of improvement in long-term survival among US transplant recipients, in spite of optimal short-term survival, has been reported60. As pointed out in that study, tailoring immunosuppressive regimes to individual needs maybe an answer, but considering the fairly standardized nature of these regimes worldwide and the better long-term results reported in other countries when compared to the US, indicates the need to search for other explanations such as the need for better funding for long-term immunosuppression. Factors relating to the health system itself may be at play, as pointed out by previous studies suggesting that patients in the US may forgo or fail to comply with treatment recommendations because of costs61. Health insurance status has been seen to be a predictor of long-term mortality in US liver transplant recipients62. Furthermore, improvement in patient and graft survival has been reported with the extension of insurance coverage of immunosuppressive medication for kidney transplant recipients beyond one year63;64, and accordingly the importance of providing these patients life-long insurance coverage for post-transplant immunosuppressive medication has
been pointed out. In SP, on the other hand, access to medication is provided by the State with no time restrictions. The structures and processes of care have to be taken into consideration in order to understand the differences in outcome, especially if we are seeking quality improvement measures. Consequently, considering the results of this study along with other available international comparisons, there does seem to be an opportunity for improving long-term outcomes for US liver transplant recipients.

Ultimately, we seek to improve our quality of life and measurements are compared so that we can learn from others with better performance. But as most of what people value is a matter of judgement, no measurement can be perfect. Even the use of GDP as a measure of material well-being and prosperity is considered insufficient. There is a suggestion that a modified metric, which could be called the GDP-plus, should incorporate other factors, including intangible capital (skills, brands, design, scientific ideas and online networks) as well as the quality of services (for example increased longevity as an estimate of health care output). On that note, multiple factors contribute to transplant outcomes and can be broadly related to the recipients themselves, to the donors, to the transplant procedure, to the healthcare system (organization, access, financing etc.) and to the general development of the region (education level, transport etc.), offering a summary of the regions status. Therefore, studies such as this, providing transnational comparisons of highly standardized procedures, such as transplantation, could contribute to evaluations of the regions development and be included in the construction of such metrics as GDP-plus.

### 4.4 Conclusions

In summary, although patients with end-stage liver disease in SP are probably benefiting from the procedure, as the alternative to the procedure is death due to disease, acute care in SP needs urgent improvement. The situation in SP seems to favor the long-term survival of patients who recover from the procedure, which could reflect the positive contribution of universal access to care including medication.

The information from this study, therefore, provides a message for SP: the economic engine for Brazil urgently needs to improve the acute care results of its health system. This may also be the
case in other regions within Brazil. The policy to provide universal health care to Brazilians was an important decision, but just these decisions are not enough. Monitoring health outcomes and benchmarking against international standards are essential to improve healthcare quality and its results.
References


AUSTIN, P. C. The relative ability of different propensity score methods to balance measured covariates between treated and untreated subjects in observational studies.


54  Canadian Organ Replacement Register 2016. Canadian Institute for Health Information. 2016


Appendices

Appendix 1: University of Toronto Ethics Approval Letter

PROTOCOL REFERENCE # 28607

January 24, 2017

Dr. David Urbach                Dr. Ajith Kumar Sankaranckutty
DEPT OF SURGERY                  DEPT OF SURGERY
FACULTY OF MEDICINE              FACULTY OF MEDICINE

Dear Dr. Urbach and Dr. Ajith Kumar Sankaranckutty,

Re: Your research protocol entitled, "A comparison of mortality after liver transplantation between the state of Sao Paulo (Brazil) and the USA"

ETHICS APPROVAL

| Original Approval Date: February 11, 2013 |
| Expiry Date: February 10, 2018 |
| Continuing Review Level: 1 |
| Renewal: Data Analysis Only |

We are writing to advise you that you have been granted annual renewal of ethics approval to the above-referenced research protocol through the Research Ethics Board (REB) delegated process. Please note that all protocols involving ongoing data collection or interaction with human participants are subject to re-evaluation after 5 years. Ongoing research under this protocol must be renewed prior to the expiry date.

Any changes to the approved protocol or consent materials must be reviewed and approved through the amendment process prior to its implementation. Any adverse or unanticipated events should be reported to the Research Oversight and Compliance - Human Research Ethics Program as soon as possible. If your research is funded by a third party, please contact the assigned Research Funding Officer in Research Services to ensure that your funds are released.

Please ensure that you submit an Ethics Renewal Form or a Study Completion/Closure Report 15 to 30 days prior to the expiry date of your protocol. Note that ethics renewals for studies cannot be accepted more than 30 days prior to the date of expiry as per our guidelines.

Please note, all approved research studies are eligible for a routine Post-Approval Review (PAR) site visit. If chosen, you will receive a notification letter from our office. For information on PAR, please see [http://www.research.utoronto.ca/wp-content/uploads/documents/2014/06/PAR-Program-Description.pdf](http://www.research.utoronto.ca/wp-content/uploads/documents/2014/06/PAR-Program-Description.pdf).

Best wishes for the successful completion of your research.

Yours sincerely,