IMPACT OF THE OPIOID CRISIS ON TRANSPLANTATION IN BRITISH COLUMBIA, CANADA; EVALUATING ORGAN UTILIZATION AND TRANSPLANT OUTCOMES FOR RECIPIENTS OF DECEASED DONOR ORGANS FROM INDIVIDUALS WHO DIED FROM OVERDOSE

by

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Abstract

Background

Opioid overdoses, particularly from fentanyl are a growing public health crisis throughout North America. Canada recorded a staggering 21,056 opioid-related overdose deaths between 2016-2020. In the same period, compared to other provinces, British Columbia (BC) has constantly had the highest annual opioid overdose death rate. Individuals that experience fatal overdose are eligible to become organ donors. This study characterizes overdosed deceased donors (ODDs) and examines safety of outcomes for recipients of ODD compared to non-ODD organ transplantation in BC.

Methods

Data on deceased donors and their recipients were extracted from the Patient Records and Outcome Management Information System database from 2013-2019. Chart review was undertaken for each donor to determine whether drug overdose was the cause of death. We analyzed recipient outcomes for double-lung, heart, liver, and kidney transplantations. The Kaplan-Meier method was used to estimate unadjusted 5-year recipient outcomes. Donor, recipient, and transplant characteristics were balanced using inverse probability of treatment weighting. Weighted multivariable Cox proportional hazards regression models were used to estimate 3-year recipient outcomes comparing recipients of ODD and non-ODD transplantation.

Results

Between 2013-2019, 605 local deceased donors (457 non-ODDs and 148 ODDs) donated a solid organ to 1,795 transplant recipients resulting in 1,857 transplantations in BC. Compared to non-ODDs, ODDs were more likely to be young white males with fewer comorbidities such as hypertension and diabetes but have higher terminal creatinine and a greater prevalence of HCV.

The probability of remaining event free at 5-year post-transplant for ODD double-lung (80%), heart (87%), liver (84%), and kidney (97%) recipients were high. ODD status did not affect recipient transplant survival in double-lung (hazard ratio (HR): 1.06, 95% confidence interval (CI): 0.41 – 2.70, p = 0.908) and liver (HR: 0.96, 95% CI: 0.42 – 2.20, p = 0.930) analyses but was inconclusive for hearts. Recipients of an ODD kidney saw significantly reduced risk of all cause graft loss (HR: 0.30, 95% CI: 0.12 – 0.77, p = 0.012).

Conclusion

In BC, overdose deaths and ODDs are increasing. ODD double-lung, liver, and kidneys have been shown to be safe for transplantation due to ODDs currently being mostly younger with fewer comorbidities.

Lay Summary

Opioid overdose has been an ongoing public health crisis across North America for the last two decades. In the last decade, a sharp increase has been seen in overdose deaths due to the increased circulation of synthetic opioids such as fentanyl. Drug overdose deaths have become the leading unnatural cause of death in British Columbia. Donors who die of drug overdose and meet certain criteria for organ donation may become overdosed deceased donors (ODDs). This study examined trends in deceased organ donation between 2013-2019 and compared transplant recipient outcomes between recipients of organs from ODDs and non-ODDs.

We found that ODD representation in the donor pool increased during the study period. We concluded that double-lung, liver, and kidney transplantations from ODDs were safe. Analysis for the heart organ group remains inconclusive and requires more data.

Preface

The reviewing of literature, data analyses, interpretation of results, and drafting of the manuscript was done by Max Xie. Dr. Caren Rose was the supervisory author on this project and was responsible for formation of concept, grant, and ethics applications. Dr. Caren Rose was also involved throughout the project in analytical methodology, interpretation of results, and revisions of the thesis. Members of the thesis committee (Dr. Joel Singer and Dr. Sean Keenan) assisted with reviewing of analytical methodology and interpretation of results. The data used in this study came from the BC Transplant; Patient Records and Outcome Management Information System database. Key identification of donor overdose status was conducted by Dr. Sean Keenan.

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List of Abbreviations

ACGL	All cause graft loss
BC	British Columbia
BMI	Body mass index
CIT	Cold ischemia time
DAA	Direct acting antiviral
DCD	Donation after circulatory death
DCGL	Death censored graft loss
ECD	Expanded criteria donor
ESRD	End-stage renal disease
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
IPTW	Inverse probability of treatment weight
IRD	Increased risk donor
KDPI	Kidney donor profile index
KDRI	Kidney donor risk index
MDD	Medical-death donor
NAT	Nucleic acid testing
NDD	Neurological determination of death
ODD	Overdosed deceased donor
PRA	Panel reactive antibody

PROMIS	Patient Records and Outcome Management Information System
SMD	Standardized mean difference
SRTR	Scientific Registry of Transplant Recipients
TDD	Trauma-death donor
UNOS	United Network for Organ Sharing
US	United States

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Dedication

To my family.

Chapter 1: Introduction

1.1 Organ transplantation

Organ transplantation is used to treat individuals who experience end-stage organ failure. For individuals with end-stage renal disease (ESRD), transplantation is the preferred treatment compared to dialysis because it improves survival, quality of life, and is cost saving (1–3). For individuals with end-stage liver failure, transplantation is the only treatment. Heart transplantation is the optimal treatment for end-stage heart failure. Temporary treatment options for end-stage heart failure vary depending on the underlying condition and include use of ventricular assist devices, heart bypass surgery, heart valve repair or replacement surgery, and ventricular aneurysm repair surgery. For patients experiencing respiratory failure, lung transplantation is also the preferred treatment option. Lung volume reduction surgery is a temporary treatment option; however, it is done on very few patients, usually patients with symptomatic emphysema or severe lung hyperinflation. Pancreas transplantations or pancreas-islet transplantations are primarily done for individuals diagnosed with type 1 diabetes. Transplantation allows patients to recover their insulin production capabilities. Pancreas transplants may often be performed in conjunction with a kidney transplant for patients who have diabetes and are also at risk of kidney failure. Organ transplantation monitored globally include kidney, liver, heart, lung, pancreas, and small intestine. The majority of transplantations performed are for kidney and liver. In 2019, kidney and liver transplantation represented 65% and 23% of the estimated 153,863 transplants performed globally (4).

Transplantation is only possible due to organ donation. Organ donors can be living or deceased individuals. In 2019, of all organ donors in Canada, 57% were deceased donors and 43% were

living donors. In the last decade the annual number of deceased donors has increased 76% from 466 in 2010 to 820 in 2019 while the annual number of living donors has remained relatively constant (5). Living donors are usually family members, close friends, or altruistic individuals. The most common living donation is kidney donation however, partial liver, partial lung, and partial pancreas donation is also possible. Living donation is encouraged as living donation can reduce or eliminate patient wait list times. Living donors are generally younger and healthier which contribute to better outcomes (6,7). Deceased donors are those who have died in hospital on mechanical ventilation who do not have medical contraindications to donation defined by the Canadian Standards Association (8,9). Deceased individuals are not restricted in the organs they are able to donate. Similar to global statistics, in Canada, the most common deceased donation is for kidney and liver; in 2019 these organ groups represented 49% and 21% of national transplantations respectively (10).

1.2 Organ supply not meeting demand

In the last decade, global transplantation has increased between 2% to 7% annually resulting in an approximate 46% increase in global transplantations from 100,900 in 2008 to 146,840 in 2018 (11). Despite the year over year increase in transplantations, there are still not enough organs available to treat all individuals who would benefit from transplantation, and many individuals die while awaiting transplantation. For example, among more than 100,000 individuals on the organ transplant waiting list in the United States (US) in 2020, 5,539 (5%) individuals died while awaiting transplantation (12). Eurotransplant, an international non-profit organization that mediates organ matching between donor hospitals and transplant centers across a number of European countries (Austria, Belgium, Croatia, Germany, Hungary, Luxembourg, the

Netherlands, and Slovenia) recorded 1,138 (8%) deaths among 13,985 individuals on the 2020 wait list (13). In Australia 37 (3%) out of the 1,358 individuals on the 2018 wait list died (14). These annual death counts do not accurately represent the magnitude of mortality on the wait list; not included are many patients who withdrew or were not registered onto the waiting list due to declining health conditions.

The discrepancy between organ supply and the demand for transplantation can lead to the exploitation of individuals in less developed countries. Unequal international economic and health systems enable transplant tourism and the commercialization of organ transplantation whereby rich patient-tourists travel to countries to acquire transplantation from impoverished and vulnerable donors who are exploited for their organs. This issue noted in the Declaration of Istanbul and further emphasized by the World Health Organization and its partners at the Third Global Consultation on Organ Donation and Transplantation culminated to a new paradigm of national self-sufficiency which calls on governments to take action in realizing the organ donation needs of patients within their own borders. The World Health Organization outlines that national self-sufficiency can be achieved by increasing support for living kidney donation, increasing utilization of potential deceased donors, investing in preventative interventions targeting risk factors for end-stage organ failure, investing in better medical professional education, and improving public education on the responsibilities of organ donation as a societal rather than a donor and recipient level responsibility (15,16).

In 2019 there were 4,419 patients across Canada waitlisted for transplantation, 3,299 (75%) of these individuals were waiting for a kidney transplant, 526 (12%) individuals were waiting for a

liver transplant, 234 (5%) individuals were waiting for a lung transplant, and 142 (3%) individuals were waiting for a heart transplant. In that year, 250 (6%) individuals died on the waiting list. In British Columbia (BC), in 2019, 23 of the 787 individuals on the waiting list died (10). To move towards national self-sufficiency and eliminate the organ wait list, maximizing deceased donation from eligible donors is imperative. A Canadian study of administrative data conducted between 2005-2009 comparing chart audits of in hospital deaths with potential deceased donors identified a conservative estimate of 400 potential deceased donors annually not utilized in Canada (17). As the number of potential deceased donors as well as their cause of death are ever changing, ensuring processes and resources are in place to evaluate all potential donors are needed.

1.3 Deceased donation in Canada & British Columbia

In Canada, individuals who die in hospital, free of health contraindications, and on mechanical ventilation are eligible to become deceased organ donors. In 2019, Canada ranked 15th internationally in its "actual deceased organ donor" rate at 21.9 per million population. Canada lags behind countries leading in "actual deceased organ donor" rates such as Spain, the US, and Croatia at 49.61, 36.88, and 34.63 donors per million population respectively (18). However, Canada reports deceased donor rates based on total utilized donors, counting donors who have had their organs successfully transplanted; this is opposed to other countries counting "actual deceased organ donors" which only includes donors that have had their organs retrieved successfully, but not necessarily successfully transplanted (18,19).

Deceased donors can be described by the mechanism of donor death. For example, donors who experienced complete and irreversible loss of brain function determined by a series of neurological tests are referred to as neurological determination of death (NDD) donors. Donors who experience a permanent stop in heartbeat have experienced circulatory death and are referred to as donation after circulatory death (DCD) donors. In Canada, the number of deceased donors increased significantly in the past decade, absolute counts increased 76% from 466 in 2010 to 820 in 2019, and the deceased donor rate increased 59% from 13.7 per million population in 2010 to 21.9 per million population in 2019. Comparatively Canada is similar to Australia at 21.6 donors per million population but lower than the United Kingdom at 24.9 donors per million population (20). Increased deceased donation in the past decade was due to a 37% increase in NDD donors and a 471% increase in DCD donors (5). The percentage of organs used from deceased donors increased for lungs in 2018 compared to 2009 but, stayed the same for kidneys and decreased for liver, heart, and pancreas. The greater proportional increase in DCD donors may be the reason for reduced proportion of donors utilized in some organ groups as fewer or no liver, heart, and pancreas are used from DCD donors (21).

In parallel with the increased use of DCD donors, efforts have also been made to expand the donor pool by using more expanded criteria donor (ECD) kidneys. ECD is defined by the United Network for Organ Sharing (UNOS) as any brain-dead donor over the age of 60 or any donor over the age of 50 with two of the following conditions: a history of hypertension, recent serum creatinine greater than or equal to 1.5 mg/dL, or death resulting from stroke (22). In short, ECDs are individuals who are older or slightly more comorbid. The characteristics of donors in Canada differ from the US and this definition is approximately used, often primarily using the 60 years

of age and over criteria with regional program flexibility when considering local factors that further define an ECD (23).

The province of BC (similar to most of Canada excluding Nova Scotia) follows an opt-in donor system for organ donation. In the opt-in system, in order to donate an organ after death an individual needs to have indicated their decision for organ donation on BC Transplant's Organ Donation Registry or, in the absence of donor registration, a close family member may advocate on their behalf. BC has seen a 2-fold increase in deceased donation from 10.9 to 22.9 donors per million population between 2010-2019, placing BC as the province with the second highest deceased donor rate behind Ontario at 26.1 donors per million population in 2019 (24).

Recent increases in deceased donation in BC have in part resulted from the opioid crisis. Increases in fatal opioid overdoses in the province since 2015 have manifested in a larger number of individuals donating after overdose death.

1.4 The opioid crisis

1.4.1 History

Opioid addiction is the abuse of prescription, non-prescription, and illegal pain relievers that are derived from the opium poppy plant or are synthetically manufactured. Opioids include oxycodone, hydrocodone, codeine, fentanyl, tramadol, morphine, and heroin. Death rates from overdoses have dramatically increased since 2013 in the US and 2015 in Canada, attributable to an increase in the supply of illicit street drugs laced with synthetically manufactured fentanyl

(25,26). The increase in overdose deaths accelerated an already existing issue of prescription opioid abuse which started in the late 1990's (27,28).

Canada recorded 21,056 opioid-related overdose deaths between January 2016 to December 2020. The crude death rate increased more than 2-fold from 7.8 to 16.5 deaths per 100,000 population between 2016-2020. In the year 2020, the COVID-19 (SARS-CoV-2) pandemic resulted in national lockdowns and disruptions to healthcare, exacerbating the opioid crisis with Canada recording 16.5 deaths per 100,000 population, a 1.7-fold increase from 9.7 deaths per 100,000 population in 2019 (29).

BC data shows that the increase in overdose deaths started as early as 2015 (Figure A - 1). Compared to other Canadian provinces, BC has recorded the highest annual crude opioid related overdose death rate since 2017 and the highest annual age-adjusted opioid related overdose death rate since 2016. Of note, unlike other provinces, BC death counts include deaths related to all illicit drugs including, but not limited to opioids. However, fentanyl has been detected in over 80% of illicit drug overdose deaths since 2017 and detected in over 65% of illicit drug overdose deaths since 2016 (30,31).

The US has similarly been going through an opioid epidemic. The US recorded 70,630 illicit drug overdose deaths in 2019 of which 49,860 (70.6%) involved opioids and 36,359 (51%) involved synthetic opioids other than methadone (fentanyl, fentanyl analogs, and tramadol). The percentage of drug overdose deaths that involved synthetic opioids was concentrated in the northeastern states and less concentrated in the western states. US states with the highest age

adjusted illicit drug overdose death rates in 2019 were West Virginia (56.6 deaths per 100,000 population), Delaware (48.7 deaths per 100,000 population), and Ohio (39.9 deaths per 100,000 population) (32,33). For reference, BC's 2019 age adjusted illicit drug overdose death rate of 31.4 deaths per 100,000 population (29) was less severe but is approaching the high rates of illicit drug overdose death in some US states.

1.4.2 Fatal overdose characteristics in British Columbia

In 2020, a record 6,265 opioid related deaths were recorded in Canada; of those deaths, 1,746 (27.9%) occurred in BC. Among drugs involved in illicit drug overdose deaths, fentanyl has increased 17-fold from 5% in 2012 to 85% in 2020. In 2020, the proportion of illicit drug overdose deaths for which illicit fentanyl was detected alone or in combination with other drugs was approximately 86% followed by cocaine at 46%. Since 2016, illicit drug use has become the leading unnatural cause of death in BC far surpassing motor vehicle incidents and suicide (31). In April of 2016 the BC Provincial Health Officer declared a public health emergency due to the significant rise in opioid related overdose deaths (34). Between 2016 to 2020 illicit drug overdose deaths were overwhelmingly male (80.01%) and more likely to be between ages 19 – 59 (89.7%) with the 30 – 39 years age group recording the highest overdose death rates annually. In the same period over 60% of overdose deaths have come from the two most populous Health Authorities in the province: Vancouver Coastal Health (28.6%) and Fraser Health (33.3%). The demographics of those who died of overdose in BC are similar to national overdose death statistics, on average mostly males between the age of 19 – 59 who had fentanyl and at least one other illicit substance detected in their system (29,35).

1.4.3 Overdosed Deceased Donors (ODD)

Most individuals who die of drug overdose do not die in the hospital setting (31). However, a small proportion of individuals do make it to the hospital but die in the intensive care unit after being resuscitated; the majority of these individuals have suffered severe anoxic brain injury and may be eligible to become organ donors (36). Donors who die as a result of drug overdose are more likely to be flagged as "exceptional distribution" donors (see Chapter 2) that have contraindications (i.e. primarily, concerns of infectious disease transmission such as human immunodeficiency viruses (HIV), hepatitis C virus (HCV), and hepatitis B virus (HBV)) to transplantation set by the Canadian Standards Association (9), regulated by Health Canada's Safety of Human Cells, Tissues and Organs for Transplantation Regulations (8,37). These donor organs are considered for transplantation when the benefit of receiving the transplant exceeds the risk of recipient illness from possible donor disease transmission. Patient education on perceived risks of exceptional distribution donors is important as patients must consent prior to transplantation of organs from exceptional distribution donors. In 2009, focus groups comprised of Johns Hopkins deceased donor waiting list patients found that "increased risk" donor (IRD) (US equivalent to exceptional distribution) kidneys were more acceptable in scenarios of imminent death or if patients viewed time on dialysis as degrading their quality of life. However, after education regarding details of IRD classification and options for serological testing prior to transplantation, 79% of patients reported increased willingness to consider IRD kidneys (38), highlighting the importance of patient education.

Of note, not all drug overdose death donors are labeled as exceptional distribution or carry increased risk of disease transmission as many of these deaths in BC are accidental and not due

to high-risk lifestyles associated with possible infectious disease transmission. Moving forward in this study we define donors who have died of drug overdose as overdosed deceased donors (ODDs).

1.5 Literature on overdose transplantation

In the United Kingdom drug overdose deaths have been on the rise with a large proportion of deaths having involved some form of opioids. In 2018, parts of the United Kingdom such as Scotland recorded 29.5 deaths per 100,000 population, similar to BC rates. However regions such as England, Wales, and Northern Ireland recorded relatively low rates of overdose deaths (less than 10 deaths per 100,000 population) (39–41). In the rest of Europe most countries have seen overdose deaths steadily increase but, national rates are low compared to the US and Canada, with the exception of Estonia having relatively high overdose death rates in 2012 (approximately 19 deaths per 100,000 population) which steadily decreased moving towards 2018. Moderate overdose deaths rates (between 4 - 10 deaths per 100,000 population) are concentrated in Northern and Eastern European countries such Austria, Denmark, Finland, Ireland, Luxembourg, Norway, Sweden, Bulgaria, Croatia, and Romania (42). Since 1997 Australia has observed between 47% to 72% of annual drug overdose deaths having involved some form of opioids. Drug overdose death rates have steadily increased in Australia since 2006 but, overdose death rates have not surpassed 1999 highs of 9.1 deaths per 100,000 population (43). According to Eurotransplant, there was no significant change over time of overdose donor representation in the donor pool between 2000-2016 (44). This is similarly echoed in institutions such as the Australia and New Zealand Organ Donation Registry, and the United Kingdom

National Health Service Blood and Transplant body; whereby despite increasing overdose death rates, little to no change of ODDs has occurred in the national donor pool (45).

Literature analyzing transplantation outcomes for recipients of ODD organs are limited to the US. To date the largest retrospective observational study of transplant outcomes for overdosed donors has been conducted by Durand et al. who analyzed the Scientific Registry of Transplant Recipients (SRTR) database (includes data on all donors, wait-listed candidates, and transplant recipients in the US) involving 337,934 adult patients from 297 transplant centers who received a deceased donor transplantation between January 1st, 2000 and September 1st, 2017. Durand et al. compared survival for recipients of ODD organs to recipients of trauma-death donors (TDD) (donors with cause of death categorized as blunt injury, drowning, gunshot, stab wound, asphyxiation, seizure, electric shock, or sudden infant death syndrome) organs and recipients of medical-death donor (MDD) (donors with cause of death categorized as intracranial hemorrhage, stroke, myocardial infarction, or other natural causes) organs. Durand et al. found that standardized 5 year survival for recipients of ODD organs were similar compared to recipients of both TDD and MDD organs across lung, heart, liver, and kidney transplant groups (46). Similar studies were conducted by Phillips et al. which focused on lung and heart transplantations, and Wanis et al. which focused on kidney and liver transplantations, both studied the SRTR at differing time periods. Warraich et al. focused on heart transplant outcomes using the Standard Transplant Analysis and Research database provided by UNOS and Whited et al. studied lung transplantation outcomes using the UNOS thoracic transplant database. All these studies arrived at the same conclusion that survival was similar when comparing ODD organ recipient to non-ODD organ recipients (47–51).

1.6 Research objectives

With the increase in illicit drug overdose deaths and the increase in ODD transplantation in BC (31,36), this study aims to understand the trend of ODD donation and evaluate the safety of ODD organs in BC. These objectives will be fulfilled by 1) exploring deceased donor characteristics by donor cause of death (overdosed versus non-overdosed), and 2) by comparing survival after transplantation of ODD and non-ODD organs by organ type.

Chapter 2: Methods

This chapter provides an overview of the common methods throughout the thesis. Methodological details that are unique to each chapter are provided in the individual chapters.

2.1 Data

2.1.1 Data source

Donor data was obtained from the BC Transplant; Patient Records and Outcome Management Information System (PROMIS) database. PROMIS collects data from transplant programs across the province to facilitate patient management, organ donation and transplantation, and transplant research (52). The PROMIS database contains information for donors and recipients of lung, heart, liver, kidney, pancreas, pancreas islet, and multi-organ transplantations. This study was approved by the Research Ethics Board at the University of British Columbia (H18-01784).

2.1.2 Study population and restrictions

Data on solid organ donation and transplantations that occurred between January 2013 and December 2019 were extracted to capture a period spanning the rapid increase in illicit drug toxicity deaths. Information for donations and transplantations was restricted to those from donors aged 12-70 years to mirror the common age of individuals dying after overdose (35). Only donors with identifiable overdose death status were included into the analytical sample (N = 605). Donors with a missing donor overdose death status (N = 38) or out of province donors (N = 165) were excluded from the analytical sample (Table 1). Organ groups identified as having less than 50 transplants were excluded from outcome analyses due to small sample size. This leaves four organ groups (double-lung, heart, liver, and kidney) for which outcome analyses

were conducted. For each organ group, we analyzed single organ transplants, this means that combination transplants such as heart and kidney, kidney and pancreas, and kidney and liver transplants were excluded from the analytical sample. For organ groups where recipients do not often undergo re-transplantation (double-lung and heart), first time transplant recipients in the study period were selected. For organ groups where recipients more often undergo re-transplantation (liver and kidney), the first transplant in the study period was selected and adjustments were made for prior transplants.

Table 1. Deceased donor categories between 2013-2019.

Donor Type	2013	2014	2015	2016	2017	2018	2019	Total
Donor Overdose Status								
Overdosed Deceased Donor	6	6	11	19	40	39	27	**148**
Non-Overdosed Deceased Donor	50	46	70	71	71	72	77	**457**
Out of province	15	16	26	29	31	27	21	**165**
Missing	5	7	5	1	7	10	3	**38**
Total	**76**	**75**	**112**	**120**	**149**	**148**	**128**	**808**

2.1.3 Donor overdose status identification

Chart review of donors were conducted by BC Transplant's Medical Director of Organ Donation Services to identify cause of donor death resulting from drug overdose. Specifically, toxicology, ambulance services, emergency room, ICU admission, and consult history notes were reviewed and donors were designated to be dead due to drug overdose if it was the clinical impression of the admitting team. Of note, due to incomplete toxicology for patients admitted to hospital (often not tested for fentanyl) a positive toxicology was absent in some cases. Conversely, patients with a positive toxicology were not included if the clinical history did not support a clear case of drug overdose.

2.1.4 Study variables and definitions

Variables in this study are categorized into donor, recipient, and transplant specific variables. The explanatory variable is overdose as a primary or contributing cause of donor death. The primary outcome is recipient death (without censoring for graft failure but, censored at re-transplantation or end of follow up: August 23, 2020). The failure of non-renal transplant graft almost always leads to death, as the likelihood of re-transplantation is very small. For kidney transplant recipients, the failure of the graft does not lead directly to death as there is an alternative treatment for end-stage kidney failure (i.e., dialysis). Therefore, for kidney transplantation, we examined all cause graft loss (ACGL) (defined as graft loss due to any cause including death, censored at end of follow up) as the primary outcome. Secondary outcomes for all organ groups except for heart transplants was the first episode of acute rejection (defined as experiencing an immune rejection of the transplanted organ, censored at death, re-transplantation, or end of follow up). Additional secondary outcomes only for kidney transplants were death with function (defined as experiencing death with a functioning graft, censored at re-transplant, return to dialysis, or end of follow up) and death censored graft loss (DCGL) (defined as graft loss due to graft failure characterized by re-transplantation or return to dialysis, censored at death or end of follow up).

Donor variables include sex, age, race, body mass index (BMI), last measured creatinine, history of diabetes, history of hypertension, cause of death, HCV, HBV, and HIV status. Donors are flagged as “exceptional distribution” if they have an increased risk for infectious disease transmission. Exceptional distribution donors require patient consent for transplantation and are acceptable due to a combination of organ shortage factors that fall under the exceptional

distribution regulation indicated in the Canadian Cells, Tissues, and Organ Regulations (53). The designation of exceptional distribution is equivalent to the US. Public Health Services "increased risk" donor (IRD) designation which flags behavioral risk factors such as injection or non-injection drug use, men who had sex with men, engagement in prostitution, or incarceration to list a few (54).

There are three derived kidney-specific donor variables: expanded criteria donor (ECD) status, the kidney donor risk index (KDRI) and the kidney donor profile index (KDPI). In BC, ECDs are defined as donors older than 60 years of age or between 50 to 59 years of age with two of the following four conditions: history of hypertension, history of diabetes, last measured creatinine greater than or equal to 133 μmol/L (equivalent to 1.5 mg/dL), and or death resulting from stroke. Donors can also be flagged as ECDs solely due to acute kidney injury, renal biopsy, history of hypertension, or history of diabetes. KDRI, developed by Rao et al. through national analyses of deceased donor kidney transplants in the US; is a derived continuous measure of donor quality. The "full" version of KDRI is calculated based on a combination of ten donor factors and four transplant factors (55). In 2014 a ten-variable version of the KDRI restricted to donor factors was adopted as part of the Kidney Allocation System in the US (56,57). Lower KDRI values are associated with increased donor quality and higher KDRI values are associated with decreased donor quality. KDPI is a transformed version of KDRI, such that donors are ranked based on KDRI, and their corresponding percentile is the KDPI. For example, a KDPI of 50% recognizes a donor whose quality is in the middle by rank (median kidney donor quality recovered in a recent year as reference) and not by actual risk. Both values are calculated according to methodology provided by the Organ Procurement and Transplantation Network.

Missing donor hypertension and donor diabetes statuses required for KDRI and KDPI calculations were handled by substituting multiplying factors by the proportion of hypertensive and diabetic donors between 2013 – 2019 (58).

Recipient variables include sex, age, race, BMI, HCV status, recipient peak panel reactive antibody (PRA) percentage (defined as the proportion of reactions against a sample of donor pool lymphocytes, a higher percentage indicates greater probability that a recipient will experience acute rejection from a donor in the donor pool), and duration of dialysis prior to transplantation (applicable only to kidney transplant recipients).

Transplant variables are defined as variables unique to the transplant operation and includes organ(s) transplanted, the order number of the transplantation (i.e., some patients have received previous/repeat transplantation), and cold ischemia time (CIT) defined as the amount of time the organ spends in cold preservation between recovery from the donor and transplantation into the recipient. We also have recipient human leukocyte antigen (HLA) mismatch defined as the number of non-matching HLA between the specific recipient and donor organ, a higher number of mismatches leads to a greater probability of acute rejection and the need for greater immunosuppression whereas a fewer number of mismatches indicates the donor organ is a better fit for the recipient. For kidney transplantations we also examined delayed graft function, defined as dialysis within the first week after transplantation.

All variable types, units, and categorizations are listed in Table 2. Some variable categories used different thresholds based on relevance to the type of organ transplanted. For example, cold

ischemia time is shorter for hearts compared to kidneys. Categorizations that vary by organ group are expanded upon in the organ specific chapters.

Missing data assumptions for all organ groups include missing or indeterminate donor and recipient HCV status assigned as no HCV, missing donor history of hypertension assigned as no hypertension, and missing donor history of diabetes assigned as no diabetes. Any other variables with missing data were not altered.

Table 2. Description and availability of explanatory, outcomes, donor, recipient, and transplant variables by organ group.

Variables	Categorical/ Continuous	Categories	Double Lung	Heart	Liver	Kidney
Main Explanatory Variable						
Donor overdose status	categorical	ODD, non-ODD	✓	✓	✓	✓
Patient Outcomes						
Death	categorical	Yes, No	✓	✓	✓	-
All cause graft loss (ACGL)	categorical	Yes, No	-	-	-	✓
Death with function	categorical	Yes, No	-	-	-	✓
Death censored graft loss (DCGL)	categorical	Yes, No	-	-	-	✓
First episode of acute rejection	categorical	Yes, No	✓	-	✓	✓
Donor Variables						
Sex	categorical	Male, Female	✓	✓	✓	✓
Age, years	both	varies by organ group	✓	✓	✓	✓
Race	categorical	varies by organ group	✓	✓	✓	✓
BMI, kg/m2	categorical	varies by organ group	✓	✓	✓	✓
Creatinine, mg/dL	categorical	< 1.5, ≥1.5	✓	✓	✓	✓
History of diabetes	categorical	Yes, No	✓	✓	✓	✓
History of hypertension	categorical	Yes, No	✓	✓	✓	✓
Cause of death	categorical	Hypoxia, CVA, Trauma, Other	✓	✓	✓	✓
Donor death Health Authority	categorical	Provincial, Vancouver Coastal, Fraser, Interior, Northern, Vancouver Island	✓	✓	✓	✓
HBV	categorical	Yes, No	✓	✓	✓	✓
HCV	categorical	Yes, No	✓	✓	✓	✓
HIV	categorical	Yes, No	✓	✓	✓	✓
Deceased donor type	categorical	DCD, NDD	✓	✓	✓	✓
Exceptional distribution donor	categorical	Yes, No	✓	✓	✓	✓
Expanded criteria donor	categorical	SCD, ECD	-	-	-	✓
Kidney donor risk index (KDRI)	both	-	-	-	-	✓
Kidney donor profile index (KDPI)	both	-	-	-	-	✓
Recipient Variables						
Sex	categorical	Male, Female	✓	✓	✓	✓
Age	both	varies by organ group	✓	✓	✓	✓
Race	categorical	varies by organ group	✓	✓	✓	✓
BMI, kg/m2	categorical	varies by organ group	✓	✓	✓	✓
HCV	categorical	Yes, No	✓	✓	✓	✓
Recipient peak PRA %	categorical	<30, 30 - 79, ≥80	✓	✓	✓	✓
Transplant Variables						
Dialysis duration prior to transplant, years	categorical	<1, 1 – 3, >3	-	-	-	✓
Organ CIT, hours	categorical	varies by organ group	✓	✓	✓	✓
HLA mismatch	categorical	0 - 2 Mismatch, 3-5 Mismatch, 6 Mismatch	✓	✓	✓	✓
Transplant number	categorical	First transplant, Not first transplant	-	-	✓	✓
Delayed graft function	categorical	Yes, No	-	-	-	✓

ODD, overdosed deceased donor; ACGL, all cause graft loss; DCGL, death censored graft loss; BMI, body mass index; CVA, cerebrovascular accident; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; HLA, human leukocyte antigen; PRA, panel reactive antibody; NDD, neurological determination of death; DCD, donation after circulatory death; SCD, standard criteria donor; ECD, expanded criteria donor; KDRI, kidney donor risk index; KDPI, kidney donor profile index; PRA, panel reactive antibody; CIT, cold ischemic time; HLA, human leukocyte antigen.

The identification of potential confounders was selected through literature and in consult with organ specialists. Each organ group analysis included a different set of variables at each modeling stage depending on the theoretical confounding of the variable and missing data considerations (**section 2.3**). Common biological traits such as donor and recipient sex, age, race and BMI were considered for adjustment. Donor and recipient HCV status has been shown to not affect recipient survival in studies involving lung, liver, and kidney transplants (59–61), but some studies have also found that donor and recipient HCV status negatively affects kidney transplant recipient survival (62,63). Given donor and recipient HCV status are highly debated conditions in literature, donor and recipient HCV status were included in modeling depending on HCV prevalence when stratified by donor overdose status. Depending on the organ group, donor history of hypertension, history of diabetes, and elevated creatinine are often cited as being associated with poorer recipient transplant survival (64–66). ECD kidney transplant recipients also experience increased risk of graft loss and death compared to recipients of standard criteria donor kidneys (67,68). Understanding that donor hypertension, diabetes, and elevated serum creatinine are factors that identify an expanded criteria kidney donor, these variables were included in organ group analyses depending on prevalence of conditions in strata of donor overdose status. Deceased donor type is not of concern for heart transplant analyses as in BC donor hearts are only transplanted from NDD donors. However, deceased donor type is important to consider in lung, liver, and kidney analyses as recipients of DCD donor organs have been shown to have an increased risk of death compared to recipients of NDD donor organs (69–72). Lastly transplant variables such as organ CIT and HLA mismatch were considered for adjustment across organ groups as prolonged cold storage of an organ prior to transplantation (72,73) and increased HLA mismatch (74–76) have also been associated with poorer transplant

recipient outcomes, but HLA mismatch was not considered for liver analyses as increased HLA mismatch has been shown to not be an independent risk factor for liver recipient graft loss (77,78). Duration of dialysis prior to transplantation was adjusted for in kidney specific analyses as prolonged duration of dialysis is associated with poorer kidney transplant recipient outcomes (79–81).

2.2 Methods for descriptive analyses

2.2.1 Deceased donor and transplant trends in British Columbia

We described donors with an identifiable overdose death status in this study period by comparing trends in ODD and non-ODD donation stratified by several donor variables. These methods are expanded on in the donor specific **section 3.1.2**.

2.2.2 Donor, recipient, and transplant characteristics

Donor, recipient, and transplant characteristics were compared between ODDs and non-ODDs using frequencies and proportions for categorical variables and medians and quartiles for continuous variables. Categorical variables were compared using the chi-square test or Fisher's exact test as appropriate. Continuous variables were compared using the Wilcoxon rank-sum test.

2.3 Methods for outcome analyses of transplant recipients

2.3.1 Time to event analyses

Depending on the organ type several outcomes of interest were studied. As previously mentioned, outcomes of interest include death, ACGL, death with function, DCGL, and first episode of acute rejection. For primary outcomes (death and ACGL) and kidney specific

secondary outcomes such as death with function and DCGL; the Kaplan-Meier method was used to look at the 1-, 3-, and 5-year cumulative probability of being event-free post-transplant. For the secondary outcome first episode of acute rejection, the reverse Kaplan-Meier method was used to observe the cumulative probability of experiencing the outcome at 1-, 3-, and 5-year post-transplant. Univariate and multivariable Cox proportional hazards models were used to determine the hazard ratio of outcome between ODD and non-ODD transplant recipients at 3-year post-transplant.

For the double-lung, heart, and liver analyses donor and recipient age were modeled as continuous variables. Categorization of donor and recipient age can potentially bias hazard ratio estimates of donor overdose status as age was highly imbalanced between levels of donor overdose status in small samples. To check the functional form of donor and recipient age, we fit a smooth curve through martingale residuals of the final adjusted model against donor and recipient age. If the fitted smooth curve did not center around zero across age, then age was modeled with a restricted cubic spline. For kidney analysis due to sufficient sample size, donor and recipient age were modeled as categorical variables. As kidney transplantation follows specific donor and recipient age matching criteria (expanded on in **section 7.1.1**), categorical age cut offs allow us to better follow these age allocation criteria.

The proportional hazards assumption for each variable was checked by looking at the log negative log (log -log) survival curves between strata of confounding variables. Parallel log -log survival curves between levels of a variable indicate that the proportional hazards assumption has not been violated. When a variable was observed to violate the proportional hazards

assumption due to crossing of the log -log survival curves, consideration was given as to whether the violation needed to be addressed given the sample size and event size of the specific organ group as well as the degree of crossing. If the violation of the proportional hazards needed to be addressed for a specific variable, it was treated as a time dependent coefficient and incorporated in the model as a step function. Based on the log -log survival plot, follow up time was split at intervals where the proportional hazards assumption failed and an interaction term of the variable and intervals of time was included into the model (82).

2.3.2 Propensity score analyses and inverse probability of treatment weights (IPTW)

The propensity score is defined as the conditional probability of assignment to a particular treatment given a vector of observed covariates (83). For this study, the probability of being assigned an ODD organ based on a vector of donor and recipient characteristics was estimated using multivariable logistic regression.

The propensity score is a balancing score that allows for adjustment of covariates through techniques such as adjustment on the propensity score, stratification or subclassification on the propensity score, matching on the propensity score, and inverse probability of treatment weight (IPTW) assignment based on the propensity score. These methods all aim to simulate randomization in observational data, specifically simulating the conditional independence between treatment assignment and outcome to obtain a more accurate estimate of treatment effect (84). In our analyses, we chose to use IPTW assignment in combination with weighted Cox proportional hazard regression models to simulate the randomization of donor overdose status and account for residual confounding.

IPT weights derived from the propensity score are defined as the inverse of the probability of receiving the treatment that was received. Assuming Z is a dichotomous value representing the treatment received with 1 representing ODD and 0 representing non-ODD and *e* representing the propensity score, the IPT weights (w) can be derived via the equation:

$$w = \frac{Z}{e} + \frac{1 - Z}{1 - e}$$

These weights can then be utilized in a weighted Cox proportional hazards regression model which will have adjusted for a vector of donor and recipient characteristics without the need to specifically define adjustments for these variables as model coefficients (85). We chose this analysis sequence to bypass the issue of not reaching the 10 events per variable threshold for multivariable Cox proportional hazards regression that has been suggested in other studies (86,87). Although it's been shown that these rules may be relaxed and that 5-9 events per variable models do not have greatly biased effect estimates or lack of confidence interval coverage (88), some organ groups such as heart and double-lung have fewer than one event per variable given the number of potential confounding factors. Therefore, given inadequate events per variable ratios, IPTW was selected as it was capable of providing a standardized approach of analysis for each organ group.

The core goal of IPTW is to simulate balance between exposure groups. To assess balance of weights derived from the IPTW method we used the standardized mean difference (SMD) of variable distributions between donor overdose status groups. Variables with a SMD > 0.1 after weight assignment were adjusted for in the weighted multivariable Cox proportional hazards

regression models (84). Regression coefficients were compared between univariate, univariate IPTW, and multivariable IPTW Cox proportional hazards regression models.

2.3.2.1 Dealing with missing data for inverse probability of treatment weights

We did not make assumptions about missing data that did not have an administrative explanation. Variables missing greater than 10% of data were excluded from modeling. For small sample size organ groups such as double-lung and heart, variables with missing data could not be included in the logistic regression models as missingness in small samples are more likely to result in inflated propensity scores. In these scenarios variables with missing values were excluded from the logistic regression models but were later adjusted for in the multivariable IPTW Cox proportional hazards models. For larger sample size organ groups such as liver and kidney, including variables with less than 10% missing data in the logistic regression models did not inflate estimated propensity scores due to sufficient sample size. Variables with missingness were included in the logistic regression models with a dummy level coded for missing values.

Chapter 3: Descriptive Analyses of Donors and Transplantations

3.1 Methods

3.1.1 Data

Descriptions of data source, study population, and study variables are found in **section 2.1**. Donor race is categorized as white and other, donor BMI is categorized as <25, 25-29, and ≥30 kg/m^2, and donor age is categorized into 12-19, 20-39, 40-59, and 60-70 years of age.

3.1.2 Deceased donor and transplant trends in British Columbia

Baseline characteristics of donors by overdose death status were compared as outlined in **section 2.2.2**. Count and proportions of donors stratified by donor overdose status were tabulated and graphed annually over the study period to look at variation in donor pool representation over time. To understand organ utilization per donor, mean, standard deviation, median, and first and third quartile values were tabulated annually. Stacked bar charts were used to show the distribution of donor age and organs donated by donor overdose death status. HCV prevalence as count and percentages were also graphed over time. A flowchart was made to illustrate the breakdown of all transplants between 2013 – 2019 by transplant type.

3.2 Results

3.2.1 Donor population

There were 605 local deceased donors between the ages of 12 to 70 years from 2013 to 2019. Of these, 148 (24.5%) were ODDs and 457 (75.5%) were non-ODDs. There was a 1.75-fold increase in the number of local deceased donations from 2013-2019 (Table 1); the increase occurred in both ODDs (350% increase) and non-ODDs (54% increase) during the study period.

The proportion of ODDs increased more than 2.3-fold from 11% in 2013 to 26% in 2019 with a high of 36% in 2017. Subsequently, this resulted in the proportional decrease of non-ODD representation dropping from 89% in 2013 to 74% in 2019 despite non-ODDs representing the largest numerical increase (Figure 1).

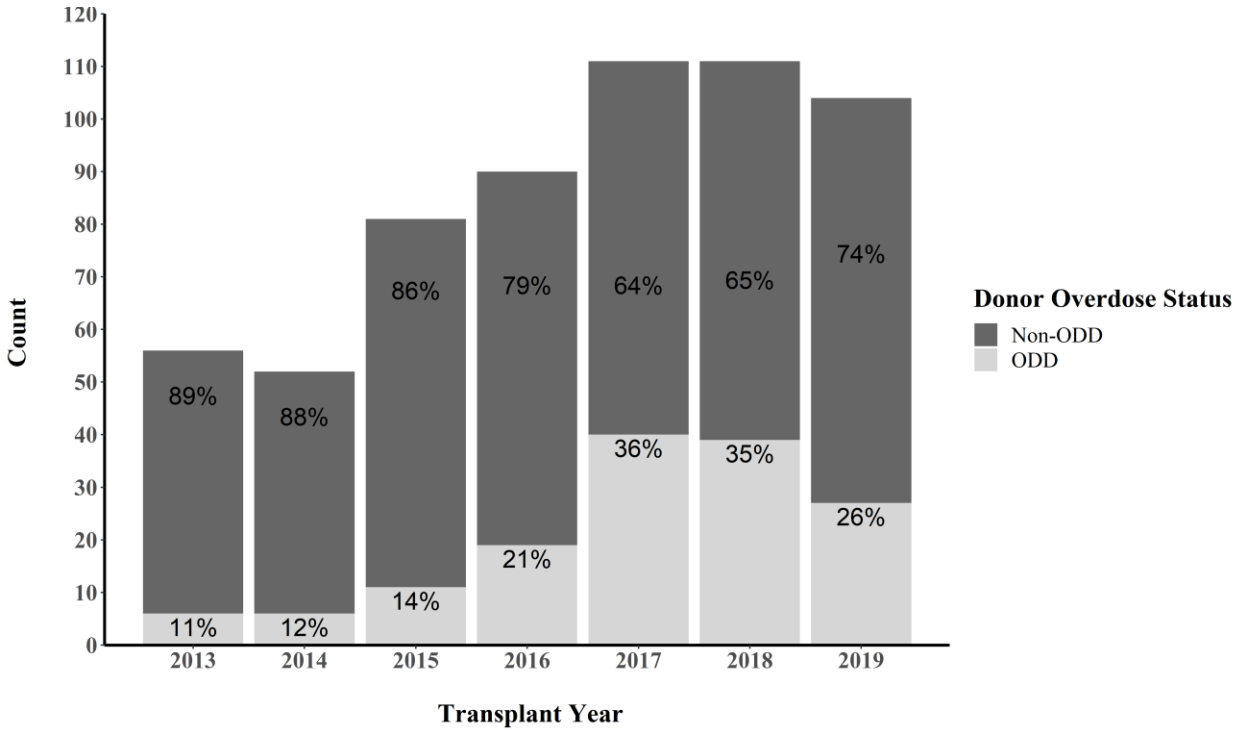

Figure 1. ODD and non-ODD count and proportional comparison between 2013-2019.

3.2.2 Donor characteristics

ODDs were younger (median [Q1; first quartile], [Q3; third quartile]): (35.0 [26.8, 42.0] years vs. 49.0 [33.0, 59.0] years, $p < 0.001$) and more likely to be white (84.5% vs. 77.9%, $p = 0.109$) and male (75.7% vs. 60.0%, $p = 0.001$), with fewer comorbidities such as hypertension (7.2% vs. 25.1%, $p < 0.001$) and diabetes (1.4% vs 9.0%, $p = 0.004$). ODDs were also more likely to have a last creatinine measurement before transplantation ≥ 1.5 mg/dL (23.6% vs 14.5%, $p = 0.013$).

Out of all donors, 22 were HCV positive (10 non-ODDs and 12 ODDs) and ODDs were more likely to be HCV positive (8.2% vs 2.2%, $p = 0.002$). Only two non-ODDs were HBV positive and none of the ODDs or non-ODDs were HIV positive. Most ODDs had a cause of death due to hypoxia (98.6% vs 32.6%, $p < 0.001$). ODDs were more likely to be flagged as an exceptional distribution donor (88.3% vs 54.5%, $p <0.001$). Donation after circulatory death and neurological determination of death donor distribution was similar between ODDs and non-ODDs. ODDs donated more hearts (27.7% vs 16.2%, $p = 0.003$) and fewer pancreas/pancreas islets (5.4% vs 11.4%, $p = 0.051$) but, showed similar donation distributions of all other solid organs (Table 3).

Table 3. Donor characteristics for donors with an identifiable donor overdose death status between 2013-2019.

Characteristics	Level	Non-ODD (N = 457)	ODD (N = 148)	p
Sex (%)	Male	274 (60.0)	112 (75.7)	0.001
	Female	183 (40.0)	36 (24.3)	
Median age (Q1, Q3)		49.0 (33.0, 59.0)	35.0 (26.8, 42.0)	<0.001
Age (%)	12-19 (min = 12)	31 (6.8)	7 (4.7)	<0.001
	20-39	117 (25.6)	95 (64.2)	
	40-59	205 (44.9)	43 (29.1)	
	60-70 (max = 70)	104 (22.8)	3 (2.0)	
Race (%)	White	356 (77.9)	125 (84.5)	0.109
	Other	101 (22.1)	23 (15.5)	
BMI[1], kg/m2 (%)	<25	182 (39.9)	62 (41.9)	0.690
	25-29	153 (33.6)	52 (35.1)	
	≥30	121 (26.5)	34 (23.0)	
History of diabetes (%)	Yes	40 (9.0)	2 (1.4)	0.004
History of hypertension (%)	Yes	111 (25.1)	10 (7.2)	<0.001
Cause of death (%)	Hypoxia	149 (32.6)	146 (98.6)	<0.001
	CVA	148 (32.4)	0 (0.0)	
	Trauma	116 (25.4)	0 (0.0)	
	Other	44 (9.6)	2 (1.4)	
Creatinine[1], mg/dL (%)	<1.5	390 (85.5)	113 (76.4)	0.013
	≥1.5	66 (14.5)	35 (23.6)	
HCV (%)	Yes	10 (2.2)	12 (8.2)	0.002
HBV[1] (%)	Yes	2 (0.4)	0 (0.0)	1.000
HIV[1] (%)	Yes	0 (0.0)	0 (0.0)	1.000
Deceased donor type (%)	DCD	121 (26.5)	33 (22.3)	0.365
	NDD	336 (73.5)	115 (77.7)	
Exceptional distribution donor	Yes	170 (54.5)	121 (88.3)	<0.001
Death in Health Authority (%)	Provincial Health Services Authority	9 (2.0)	2 (1.4)	0.722
	Vancouver Coastal Health Authority	137 (30.0)	36 (24.3)	
	Fraser Health Authority	150 (32.8)	51 (34.5)	
	Interior Health Authority	81 (17.7)	33 (22.3)	
	Northern Health Authority	11 (2.4)	4 (2.7)	
	Vancouver Island Health Authority	69 (15.1)	22 (14.9)	
Kidney (%)	One transplanted	63 (13.8)	18 (12.2)	0.740
	Two transplanted	357 (78.1)	120 (81.1)	
Heart (%)	Transplanted	74 (16.2)	41 (27.7)	0.003
Lung (%)	One transplanted	6 (1.3)	1 (0.7)	0.775
	Two transplanted	171 (37.4)	58 (39.2)	
Liver (%)	Transplanted	307 (67.2)	103 (69.6)	0.656
Pancreas/pancreas islet (%)	Transplanted	52 (11.4)	8 (5.4)	0.051

ODD, overdosed deceased donors; BMI, body mass index; CVA, cerebrovascular accident; HCV, hepatitis C virus; HBV, hepatitis B virus; HIV, human immunodeficiency virus; NDD, neurologically determination of death; DCD, donation after circulatory death; Variable level frequencies between ODD and non-ODD were compared using the chi-square test, Fisher's exact test, or the Wilcoxon rank sum test as appropriate.

[1]Missing: Donor BMI (0.17%); Creatinine (0.17%); HBV (0.33%); HIV (0.17%).

The mean number of organs donated by non-ODDs did not greatly change over time, from 3.6 to 3.3 organs per donor between 2013-2019. The mean number of organs donated by ODDs increased from 3 to 3.8 organs per donor between 2013-2019 with a high of 4.2 organs per donor in 2016. This is also reflected in the median number of organs donated per donor as ODD donation increased from 3 to 4 organs per donor between 2013-2019 while median organs donated per donor for non-ODDs did not change (Table 4).

Table 4. Organ utilized per donor statistics by donor overdose status between 2013-2019.

Donor Overdose Status	Statistic	2013	2014	2015	2016	2017	2018	2019
Non-ODD	**Mean (Standard Deviation)**	3.6 (1.5)	3.4 (1.6)	3.5 (1.4)	3.5 (1.4)	3.2 (1.6)	3.5 (1.5)	3.3 (1.5)
ODD	**Mean (Standard Deviation)**	3.0 (1.3)	3.0 (2.1)	3.0 (1.4)	4.2 (1.7)	3.4 (1.1)	3.6 (1.4)	3.8 (1.4)
Non-ODD	**Median (Q1, Q3)**	3.0 (3.0, 4.8)	3.0 (2.0, 5.0)	3.0 (2.0, 5.0)	3.0 (2.0, 5.0)	3.0 (2.0, 4.5)	3.0 (2.0, 4.3)	3.0 (2.0, 5.0)
ODD	**Median (Q1, Q3)**	3.0 (3.0, 3.0)	2.5 (1.3, 4.5)	3.0 (2.0, 4.0)	4.0 (3.0, 5.5)	3.0 (2.8, 4.0)	3.0 (2.0, 5.0)	4.0 (3.0, 5.0)

The greater number of hearts donated from ODDs was primarily driven by the 20–39 years of age donor group. Compared to non-ODDs, the 20-39 years of age donor group represented a greater proportion of donors across all organ groups (Figure 2).

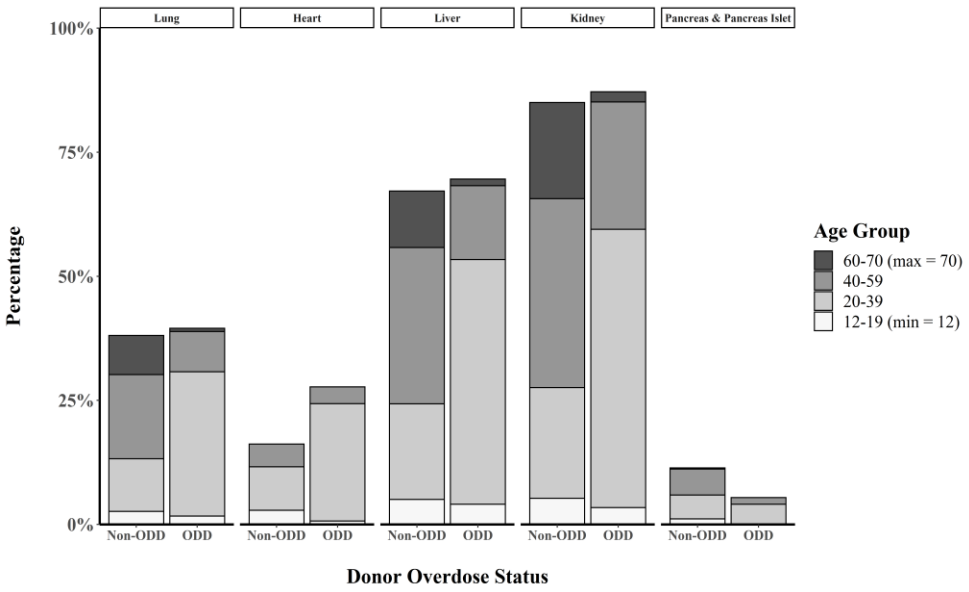

Figure 2. Solid organ utilization distribution by organ type and donor age compared by donor overdose status.

HCV prevalence stayed relatively constant for ODDs from 16.7% to 11.1% in 2019. The number of HCV positive ODDs increased from 1 in 2013 to 3 in 2019. Non-ODD HCV prevalence shifted from 6% in 2013 to 3.9% in 2019 and often had years with 0 HCV positive donors (Figure 3).

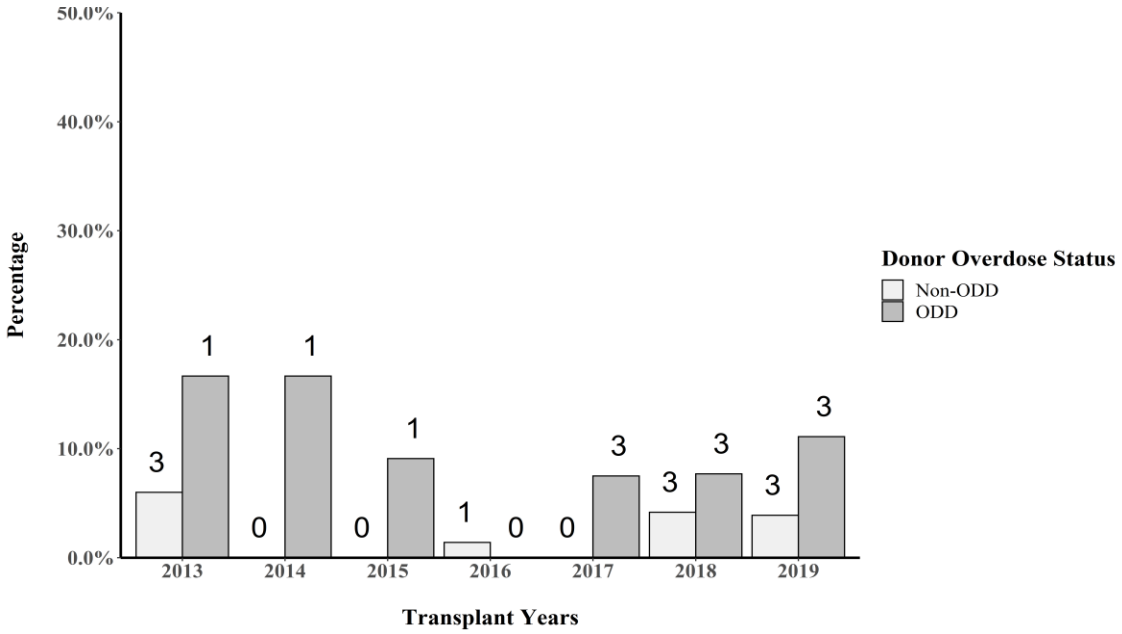

Figure 3. Donor HCV percentage prevalence by transplant year among donors with an identifiable overdose death status between 2013-2019.

3.2.3 Characteristics of ODD/non-ODD transplantation

From the 605 donors, 1,857 transplants resulted, of which 469 (25.3%) transplants included organs from ODDs and 1,388 (74.7%) transplants included organs from non-ODDs. Of these, 1,015 (54.7%) were kidney, 404 (21.8%) were liver, 228 (12.3%) were double-lung, 9 (0.5%) were single-lung, 113 (6.1%) were heart, 13 (0.7%) were pancreas, 35 (1.9%) were pancreas islet, 24 (1.3%) were pancreas & kidney, 4 (0.2%) were heart & kidney, and 12 (0.6%) were kidney & liver transplants (Figure 4).

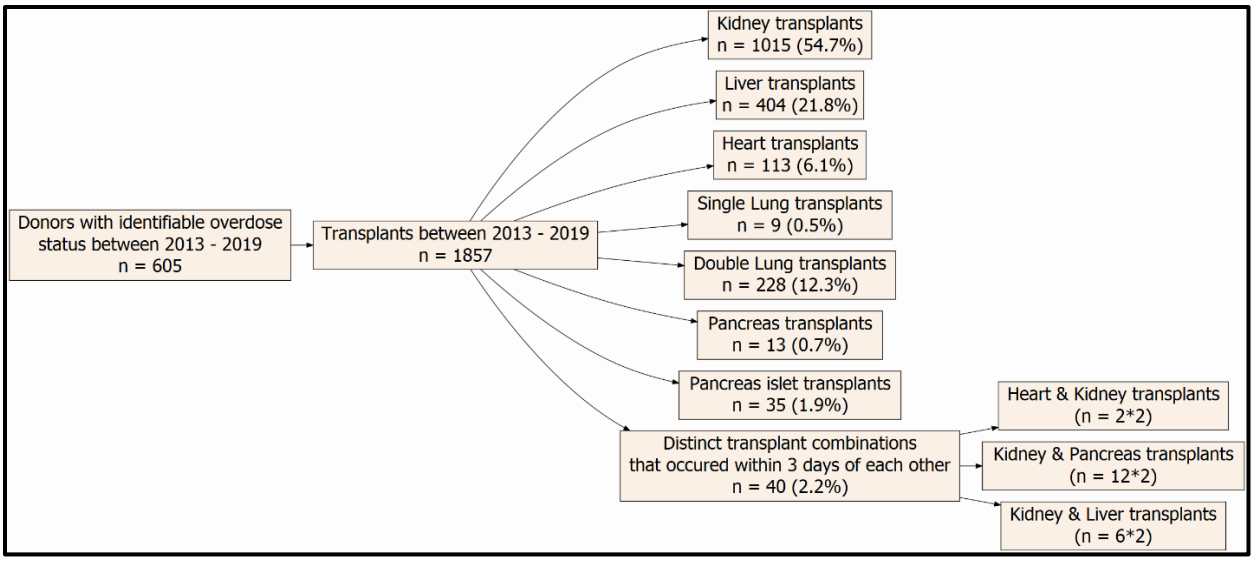

Figure 4. Flowchart of transplant types resultant from donors with identifiable overdose death status between 2013-2019. Combination transplants are multiplied by 2 implying the operation is made up of two organs types.

3.3 Discussion

The absolute count of both ODDs and non-ODDs increased during the study period. ODD proportional representation in the donor pool increased considerably during the study period. In contrast, non-ODD proportional representation in the donor pool decreased during the study period. ODDs noticeably increased in 2016 coinciding with the BC provincial health officer's declaration of a public health emergency in April 2016 (89). In 2017 ODD representation reached a high of 27% of all donors in the donor pool and 36% of all donors with an identifiable overdose death status.

Mean and median organs donated per donor by ODDs increased during the study period and were higher compared to mean and median values of organs donated per donor by non-ODDs. This was primarily driven by younger ODDs donating more hearts. This may be because heart donors are usually younger which is a criteria ODDs satisfy due to the young age of many

ODDs. Subsequently because ODDs are younger, they also come with less comorbidities such as diabetes and hypertension. The caveat is that ODDs are more likely to have higher last measured creatinine and are at least 3.5 times more likely to be HCV positive but, the absolute number of HCV positive ODDs was low (N = 12). In the largest American national registry study of ODDs by Durand et al. spanning from 2000-2017, it was found that ODDs were also likely to be younger, of white race, were less likely to have a history of diabetes or hypertension but, had an increased risk of HCV infection and a higher last measured creatinine. Comparatively, ODDs in BC share similar characteristics to those in the US except ODD HCV prevalence in the US has increased over time from 7.8% in 2000 to 24.2% in 2017 whereas HCV prevalence for ODDs in BC has not exceeded 17% for any year during the study period. Provincial to national comparisons are not ideal given sample size differences as well as the variation of ODD characteristics within individual states. However, understanding that ODDs in BC are similar to ODDs at the national level in the US may support transplant outcome comparisons.

Observing ODDs in the PROMIS database does not account for individuals who died of overdose but were never considered as suitable donors or individuals who were never able to die in hospital on mechanical ventilation to become organ donors. Therefore, ODDs should be compared with the population dying of illicit drug overdose to evaluate population representativeness. In BC between 2013-2019, 69% of illicit drug overdose deaths were between the ages of 19-49 and 79% of illicit drug overdose deaths were male (35). Fentanyl or its analogues were detected within 83.8% of overdose deaths between the ages of 20-49 and 80.32% of overdose deaths were among males (30). In our analytical sample, younger individuals who died because of overdose are overrepresented as donors (84% of ODDs were 20-49 years of age),

and the sex distribution of ODDs was similar to the population of overdose deaths (76% were male). Although ODDs are not a random sample of overdose deaths in the population, it is probable that the majority of deaths involved fentanyl as 70% of illicit drug overdose deaths involved fentanyl or its analogues between 2013-2019 (30,35).

Chapter 4: Double Lung Transplant Outcomes

4.1 Methods

4.1.1 Data

We studied recipients of first time double-lung transplantation between January 2013 – December 2019. Descriptions of data source, study population and definitions of study variables are presented in **section 2.1**. Of note, the following variable categorizations specific to double-lung transplantation analyses include: recipient age categorized as 21-29, 30-39, 40-49, 50-59, and 60-69 years; donor age categorized as 14-19, 20-29, 30-39, 40-49, 50-59, and 60-70 years; recipient and donor race categorized as white and other; and recipient and donor BMI categorized as < 25, 25-29, and ≥ 30 kg/m^2; cold ischemia time categorized as < 6 and ≥ 6 hours. Five double lung transplants (4 ODD and 1 non-ODD) were excluded because 2 (1 ODD and 1 non-ODD) transplants were not the recipient's first double-lung transplant and 3 other ODD transplants (1 missing lung cold ischemia time and 2 missing HLA mismatch) who did not experience death were removed from the analytical sample.

4.1.2 Descriptive analysis

The number of ODD and non-ODD double-lung transplantations were plotted annually over the study period. Donor and recipient characteristics were compared by donor overdose status using the methods described in **section 2.2.2**.

4.1.3 Analysis of post-transplant outcomes

Time to death was examined using the Kaplan-Meier method and the IPTW Cox proportional hazards model as described in **section 2.3.1** and **section 2.3.2**. Time to death was calculated as

time from transplantation to date of death, censored at re-transplantation or end of follow-up. The multivariable logistic regression model used to calculate the propensity score included recipient (sex, age, race, HCV), donor (sex, age, race, last measured creatinine, history of hypertension, and history of diabetes), and transplant (HLA mismatch, organ cold ischemia time) factors. Variable SMDs calculated for the weighted sample comparing donor overdose status groups that were greater than 0.1 were adjusted for in the multivariable IPTW Cox proportional hazards model. The proportional hazards assumption was assessed using log -log survival plots and the functional form of continuous donor and recipient age was assessed if needed using plots of martingale residuals against age.

The cumulative probability of experiencing the first episode of acute rejection at 1-, 3-, and 5-year post-transplant was analyzed using cumulative incidence curves as outlined in **section 2.3.1**.

4.2 Results

4.2.1 Descriptive analyses

From 2013-2019 the number of double-lung transplantations from donors with an identifiable overdose death status increased (Figure 5): in 2015, annual ODD transplantations quadrupled to four per year whereas non-ODD transplantations increased 79% from 2013 but, the largest absolute increase occurred for non-ODD transplantations. Then in 2016, there was more than a two-fold increase in ODD transplantations in parallel with the increased number of overdose deaths in BC. Proportionally, in 2013, 7% (1 out of 15) of donors were ODDs compared to in 2019; 33% (15 out of 45) of donors were ODDs. The yearly average number of ODD transplantations was 5-fold higher after 2016 compared to before 2016.

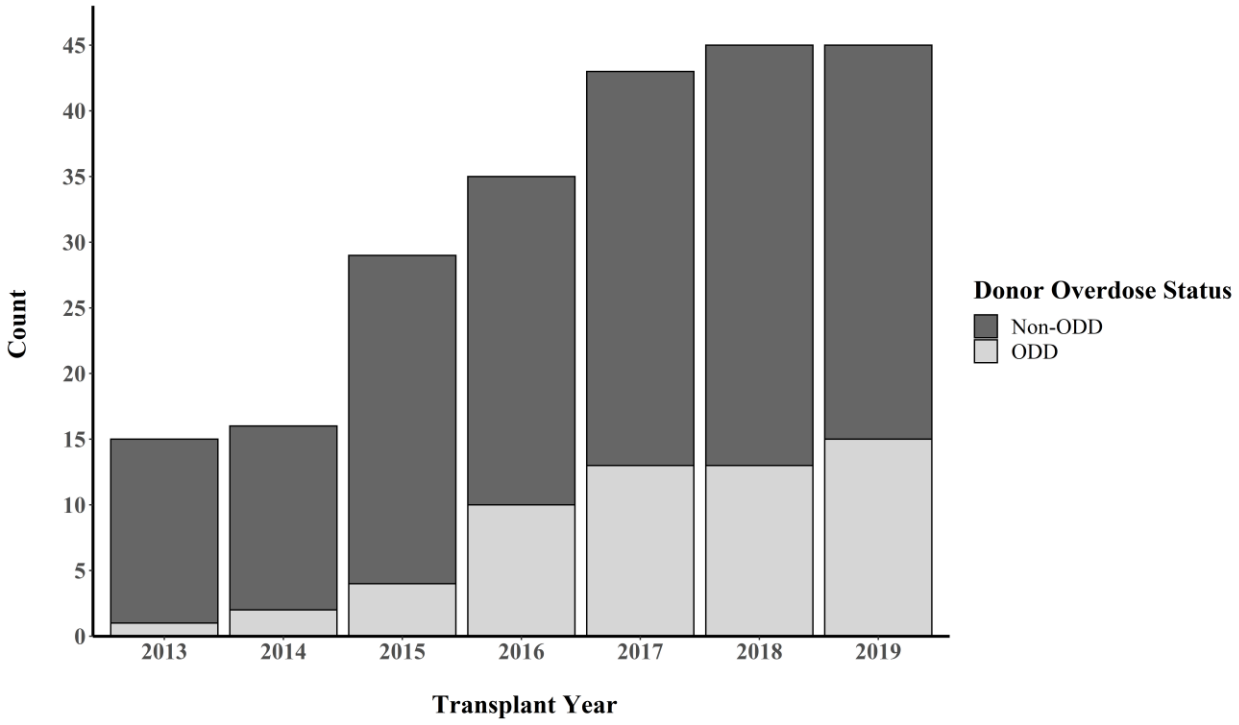

Figure 5. Bar graph showing the number of double-lung transplantations during the study period categorized by donor cause of death resulting from overdose (ODD) or not resulting from overdose (non-ODD).

The total number of double-lung transplants in this period was 228 transplants. After excluding 5 transplants due to non-first transplant and missing variable exclusion criteria, the analytical sample comprised of 223 transplants with lungs donated from 169 non-ODDs (76%) and 54 ODDs (24%). Recipients of ODD transplantation in the analytic sample were more likely to be male (70.4% vs 58.0%, p = 0.143) and white (90.7% vs 81.1%, p = 0.146). Of note, approximately half of all recipients of non-ODD transplantations were between 60-69 years of age (51.5% vs 37.0%). ODDs were more likely to be younger (median age [Q1; Q3]): 30 [25, 38] years vs. 47 [32, 58] years, p < 0.001), white (90.7% vs 71.6%, p = 0.007), males (74.1% vs 54.4%, p = 0.017), who were less likely to have a history of hypertension (3.7% vs 23.1%, p = 0.003) or diabetes (1.9% vs 9.5%, p = 0.079). ODDs were also more likely to have a terminal creatinine ≥ 1.5 mg/dL (24.1% vs 11.8%, p = 0.047), and were more likely to be flagged as an

exceptional distribution donor (79.6% vs 34.3%, p < 0.001). All ODDs had a cause of death due to hypoxia (Table 5).

Table 5. Lung Transplantation: Donor and recipient characteristics compared by overdose as the cause of donor death for first-time double lung transplants.

Characteristics	Level	Non-ODD (N = 169)	ODD (N = 54)	p
Recipient Variables				
Sex (%)	Male	98 (58.0)	38 (70.4)	0.143
	Female	71 (42.0)	16 (29.6)	
Age (%)	21-29 (min = 21)	9 (5.3)	2 (3.7)	0.341
	30-39	14 (8.3)	6 (11.1)	
	40-49	13 (7.7)	5 (9.3)	
	50-59	46 (27.2)	21 (38.9)	
	60-69 (max = 69)	87 (51.5)	20 (37.0)	
Median age (Q1, Q3)		60.0 (51.0, 64.0)	58.0 (51.2, 63.8)	0.435
Race (%)	White	137 (81.1)	49 (90.7)	0.146
	Other	32 (18.9)	5 (9.3)	
BMI[1], kg/m2 (%)	<25	75 (51.4)	21 (42.9)	0.570
	25-29	49 (33.6)	20 (40.8)	
	≥30	22 (15.1)	8 (16.3)	
HCV (%)	Yes	4 (2.4)	3 (5.6)	0.364
Peak PRA[1] % (%)	<30	75 (62.0)	25 (55.6)	0.467
	30-79	29 (24.0)	15 (33.3)	
	≥80	17 (14.0)	5 (11.1)	
Donor Variables				
Sex (%)	Male	92 (54.4)	40 (74.1)	0.017
	Female	77 (45.6)	14 (25.9)	
Age (%)	14-19 (min = 14)	11 (6.5)	2 (3.7)	<0.001
	20-29	25 (14.8)	20 (37.0)	
	30-39	22 (13.0)	19 (35.2)	
	40-49	41 (24.3)	10 (18.5)	
	50-59	36 (21.3)	2 (3.7)	
	60-70 (max = 70)	34 (20.1)	1 (1.9)	
Median age (Q1, Q3)		47.0 (32.0, 58.0)	30 (25.0, 38.0)	<0.001
Race (%)	White	121 (71.6)	49 (90.7)	0.007
	Other	48 (28.4)	5 (9.3)	
BMI, kg/m2 (%)	<25	75 (44.4)	22 (40.7)	0.895
	25-29	59 (34.9)	20 (37.0)	
	≥30	35 (20.7)	12 (22.2)	
History of hypertension (%)	Yes	39 (23.1)	2 (3.7)	0.003
History of diabetes (%)	Yes	16 (9.5)	1 (1.9)	0.079
HCV (%)	Yes	0 (0.0)	0 (0.0)	1.000
Creatinine, mg/dL (%)	≥1.5	20 (11.8)	13 (24.1)	0.047
Cause of death (%)	Hypoxia	53 (31.4)	54 (100.0)	<0.001
	CVA	59 (34.9)	0 (0.0)	
	Trauma	40 (23.7)	0 (0.0)	
	Other	17 (10.1)	0 (0.0)	
Deceased donor type (%)	NDD	132 (78.1)	46 (85.2)	0.351
	DCD	37 (21.9)	8 (14.8)	

Characteristics	Level	Non-ODD (N = 169)	ODD (N = 54)	p
Exceptional distribution donor (%)	Yes	58 (34.3)	43 (79.6)	<0.001
Transplant Variables				
Number of HLA mismatches (%)	0-2	10 (5.9)	5 (9.3)	0.680
	3-5	131 (77.5)	41 (75.9)	
	6	28 (16.6)	8 (14.8)	
CIT, hours (%)	<6	108 (63.9)	31 (57.4)	0.486
	≥6	61 (36.1)	23 (42.6)	

ODD, overdosed deceased donors; BMI, body mass index; CVA, cerebrovascular accident; HCV, hepatitis C virus; HLA, human leukocyte antigen; PRA, panel reactive antibody; NDD, neurologically determination of death; DCD, donation after circulatory death; HLA, human leukocyte antigen; CIT, cold ischemic time; Variable level frequencies between ODD and non-ODD organ recipients were compared using the chi-square test, Fisher's exact test, or the Wilcoxon rank sum test as appropriate.

[1]Missing: Recipient BMI (12.56%); Recipient peak PRA % (25.56%)

4.2.2 Outcomes analyses

4.2.2.1 Primary outcome

Survival after ODD transplantation was 93% at 1-year and, 80%, at 3- and 5-year post-transplant. Survival after non-ODD transplantation was 93%, 85%, and 76% at 1-, 3-, and 5-year post-transplant (Figure 6). There was no difference in death between overdose groups in the first 5-years of post-transplant follow-up (log-rank, p = 0.65).

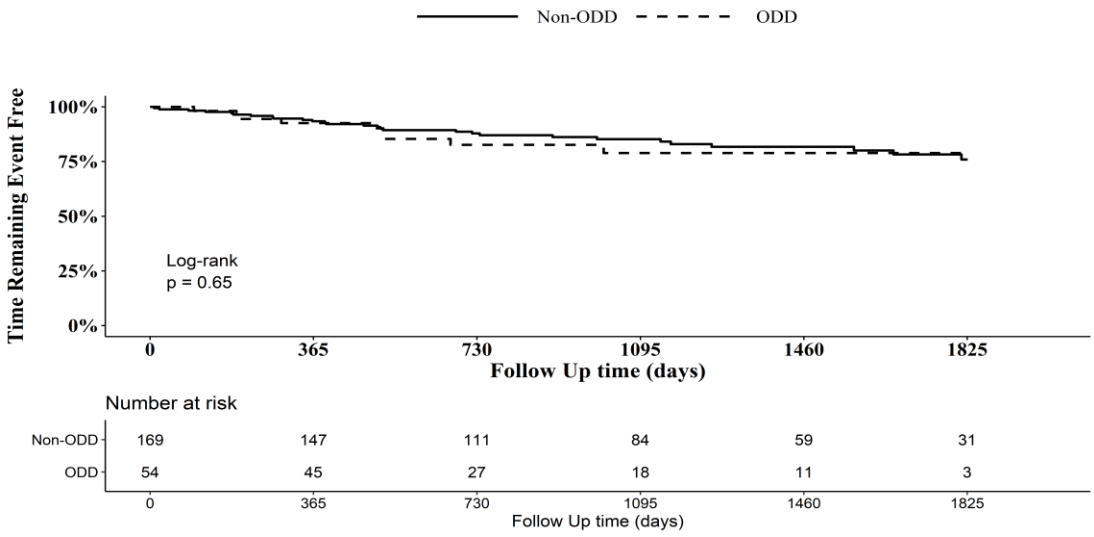

Figure 6. 5-year Kaplan Meier curves and corresponding risk tables for death among double-lung transplants compared between donor overdose cause of death.

After IPT weights were calculated from the propensity scores generated by the multivariable logistic regression model adjusted for variables mentioned in **section 4.1.3**; recipient race and donor sex, age, last measured creatinine, history of diabetes, and deceased donor type all had a SMD > 0.1 and were adjusted for in the multivariable IPTW Cox proportional hazards model (Table 6).

Table 6. Standardized mean difference table after inverse probability of treatment weight assignment for first time double-lung transplantation.

Characteristics	Level	Non-ODD (Weighted N = 230.6)	ODD (Weighted N = 178.8)	SMD
Recipient Variables				
Sex (%)	Male	140.4 (60.9)	105.9 (59.2)	0.034
	Female	90.2 (39.1)	72.9 (40.8)	
Median age (Q1, Q3)		60.0 (50.3, 64.0)	58.0 (49.5, 62.3)	0.014
Race (%)	White	194.0 (84.1)	161.0 (90.0)	0.177
	Other	36.6 (15.9)	17.8 (10.0)	
HCV (%)	Yes	8.5 (3.7)	5.6 (3.1)	0.029
Donor Variables				
Sex (%)	Male	141.2 (61.2)	123.6 (69.1)	0.167
	Female	89.4 (38.8)	55.2 (30.9)	
Median age (Q1, Q3)		42.0 (25.0, 54.0)	33.1 (27.5, 42.0)	0.377
Race (%)	White	177.5 (77.0)	141.5 (79.1)	0.052
	Other	53.1 (23.0)	37.3 (20.9)	
Creatinine, mg/dL (%)	≥1.5	42.1 (18.2)	44.0 (24.6)	0.156
History of hypertension (%)	Yes	41.1 (17.8)	28.1 (15.7)	0.056
History of diabetes (%)	Yes	16.9 (7.3)	5.3 (2.9)	0.200
Deceased donor type (%)	NDD	187.9 (81.5)	156.6 (87.6)	0.169
	DCD	42.7 (18.5)	22.2 (12.4)	
Transplant Variables				
Number of HLA mismatches (%)	0-2	13.9 (6.0)	8.5 (4.7)	0.096
	3-5	175.1 (75.9)	132.1 (73.9)	
	6	41.6 (18.1)	38.3 (21.4)	
CIT, hours (%)	<6	142.3 (61.7)	115.9 (64.8)	0.064
	≥6	88.2 (38.3)	62.9 (35.2)	

ODD, overdosed deceased donors; SMD, standardized mean difference; HCV, hepatitis C virus; HLA, human leukocyte antigen; NDD, neurologically determination of death; DCD, donation after circulatory death; CIT, cold ischemic time.

The univariate Cox model showed that recipients of ODD double-lungs did not have significantly differing risk of death (HR: 1.39, 95% CI: 0.64 – 3.03, p = 0.404) compared to recipients of non-ODD double-lungs. After IPT weighting, the risk of death for recipients of ODD double-lungs marginally decreased (HR: 1.16, 95% CI: 0.47 – 2.86, p = 0.752) and further decreased towards the null after multivariable adjustment in the IPTW Cox model (HR: 1.06, 95% CI: 0.41 – 2.70, p = 0.908) (Table 7).

Table 7. Three models examining the relationship between donor overdose as a cause of donor death and recipient death.

	Model 1: Univariate Cox model		Model 2: Univariate IPTW Cox model		Model 3: Multivariable IPTW Cox model	
Variable	**HR (95% CI)**	**p**	**HR (95% CI)**	**p**	**HR (95% CI)**	**p**
Donor overdose status						
ODD	1.39 (0.64, 3.03)	0.404	1.16 (0.47, 2.86)	0.752	1.06 (0.41, 2.70)	0.908

ODD, overdosed deceased donors; IPTW, inverse probability of treatment weight; HR, hazard ratio; CI, confidence interval.

Model 2 is weight adjusted for recipient sex, age, race, HCV status; donor overdose status, sex, age, race, last measured creatinine, history of hypertension, history of diabetes, deceased donor type; transplant number of HLA mismatches, and organ cold ischemia time.

Model 3 is weight adjusted for all variables mentioned in Model 2 as well as adjusted for as covariates in the IPTW Cox proportional hazards model for recipient race; donor overdose status, sex, age, last measured creatinine, history of diabetes, and deceased donor type.

The functional form of donor age was visually adequate. The log -log survival plot was visually inadequate for recipient race violating the proportional hazards assumption (Figure B - 1). An interaction term for recipient race and time was created with a split into two intervals at 300 days. However, because the hazard ratio of ODD status on recipient death did not greatly change (HR: 1.06, 95% CI: 0.42 – 2.77, p = 0.914) after adding a step function for recipient race, we retained coefficient estimates from the multivariable IPTW Cox proportional hazards model without a step function.

4.2.2.2 Secondary outcome

The probability of experiencing acute rejection for ODD double-lung transplantation was 31%, 43%, and 49% at 1-, 3-, and 5-year post-transplant. The probability of acute rejection for non-ODD double-lung transplantation was 46%, 53%, and 56% at 1-, 3-, and 5-year post-transplant. Although recipients of ODD transplantation were less likely to have experienced acute rejection, there was no significant difference (log-rank, p = 0.21) in the first 5 years of follow up (Figure 7).

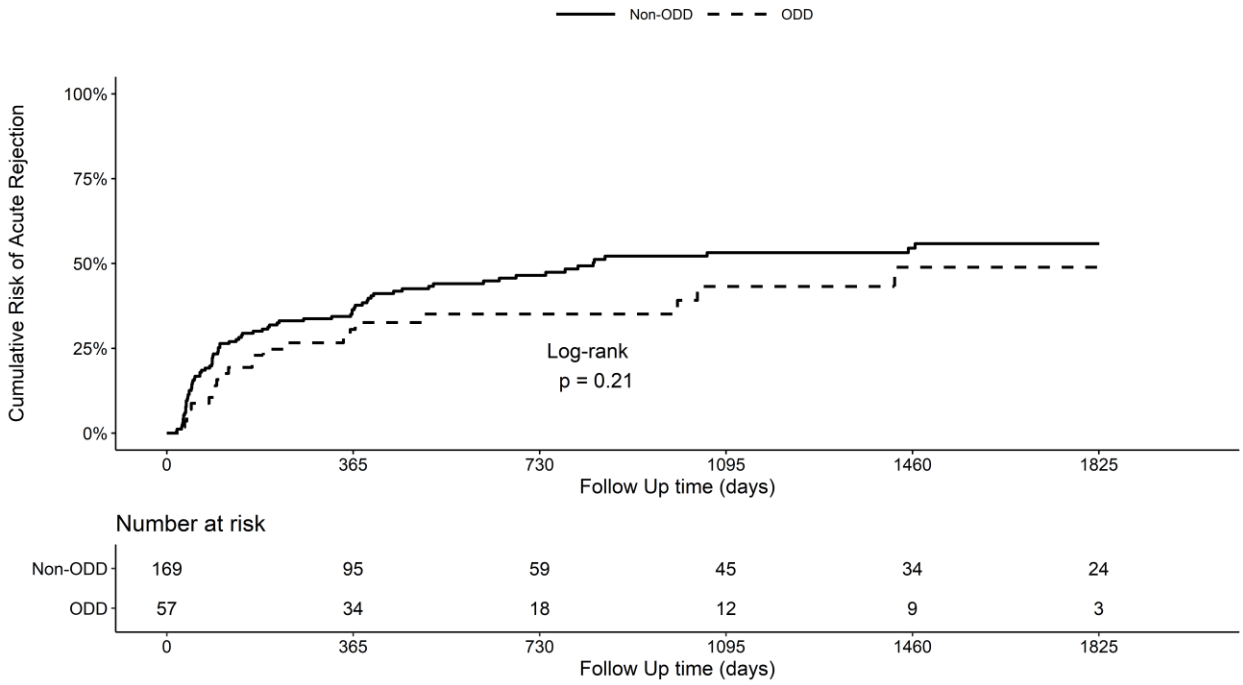

Figure 7. 5-year cumulative incidence curves and corresponding risk tables for the first episode of acute rejection among double-lung transplants compared by donor overdose death status.

4.3 Discussion

Double-lung transplantation from ODDs increased over the study period in parallel with increases in overdose deaths in BC. In 2019, ODDs represented 33% of all double-lung deceased donor transplants in the province. Compared to recipients of non-ODD double-lung transplants, recipients of ODD double-lung transplantation had similar survival probabilities and incidence of acute rejection within five years after transplantation. Adjusted for donor and recipient characteristics ODD status was not found to affect recipient survival at 3-years post-transplant.

Three studies in the US reported similar survival outcomes to our analyses. Durand et al. studied the national SRTR database between 2000-2017 utilizing similar IPTW methodology with standardized risk differences to examine 5-year survival rates for recipients of ODD lung

transplantation and found no increased risk of death for recipients of ODD lung transplants compared to trauma death donor (3.9% [95% CI, −5.3% to 8.5%]) and medical death donor (5.2% [95% CI, −4.5% to 9.8%]) lung transplant recipients with a unadjusted 5-year survival rate of 56.5% for recipients of ODD lungs (46). Phillips et al. also conducted a study using the SRTR database between January 2010 and June 2017, using a 5-year Kaplan-Meier comparison method and a 5-year Cox proportional hazards regression model (adjusted only for donor characteristics) on lung transplant recipients and found no difference in survival between recipients of ODD and non-ODD lungs with 5-year unadjusted ODD lung recipient survival below 70% (48). Whited et al. studied the UNOS thoracic transplant database for lung transplantations between January 2005 and March 2015, performing a propensity score matched (based on donor and recipient characteristics) Kaplan-Meier analysis of lung transplant recipients at 1-, 3-, and 5-year post-transplant and found no difference in survival between ODD and non-ODD lung recipients with recipients of ODD lungs recording 5-year unadjusted survival of 48% (51). These national studies at different time periods all reinforce that survival for recipients of ODD and non-ODD lung transplantation are very similar and at least prove non-inferiority of ODD lung transplantation. This is likely because overdosed donors in the US share similar characteristics to overdosed donors in BC; on average are more likely to be younger with fewer chronic conditions such as diabetes and hypertension. ODDs in the US did not show sex differentiation or at times were more likely to be female (48,51). Five-year unadjusted ODD lung transplantation survival in BC (80%) is higher compared to the American studies mentioned. This may be partly due to improvement in care over time. Phillips et al. recorded higher unadjusted 5-year survival for ODD lung transplant recipients compared to Durand et al. and Whited et al. Phillips et al.

conducted their study between 2010-2017 which matches more closely to our study period whereas Durand et al. and Whited et al. included transplant recipients prior to 2010.

A strength of our analysis is the exclusion of three first time ODD double-lung transplant recipients that did not experience death. These three recipients were excluded to create a complete case multivariable logistic regression model that incorporated HLA mismatch and organ cold ischemia time, generating more accurate propensity scores and eliminating the need to adjust for these variables in the IPTW Cox proportional hazards model. Exclusion of these three transplant recipients biases the effect of ODD status on recipient death away from the null as the ODD group is missing three non-event records. Another strength of this study was the restriction to double-lung only transplants. US studies did not specify what proportion of lung transplants studied were single- or double-lung transplants but, this may have been due to the sample size sufficiency of the studies.

Violation of the proportional hazards assumption for recipient race was addressed but the model without a step function was retained as the hazard ratio for ODD status did not greatly change after incorporating a step function for recipient race. Unfortunately, sample size was a limitation in our study given the number of variables we wanted to adjust for. Select double-lung ODDs had a combination of characteristics that were difficult to balance through IPT weighting as shown by high SMD values of the adjusted variables after weighting. A number of these variables needed to be adjusted for in the IPTW multivariable Cox proportional hazards model resulting in a final model with four events per adjusted variable. However, observing the comparable crude rates, as well as the steady hazard ratios of the Cox models through multiple

adjustments, we are more confident in supporting the hypothesis that donor overdose status is not a factor that affects recipient double-lung transplantation survival. Lastly, a limitation of this analysis was the lack of data for donor history of smoking. Durand et al., Phillips et al., and Whited et al. all explored donor history of smoking in their adjusted models which is a known risk factor for poor lung transplant recipient survival (90,91). If ODDs are more likely to smoke and this results in poorer quality lungs and thus poorer recipient survival, then adjusting for smoking status would bias the hazard ratio of donor overdose status away from the null towards increased risk of death. We do not want to make any assumptions as we do not have data for smoking status. This variable will be important to include for future iterations of this analysis.

ODD double lung transplantation leads to high survival rates in the first five years after transplantation. This analytical sample does not contain many ODDs who are older or more likely to have comorbidities such as diabetes or hypertension. Utilization of older ODDs with more comorbid conditions may not guarantee the same results. In the interest of reducing the waitlist, given current rates of survival, transplantation of ODD double-lungs is safe.

Chapter 5: Heart Transplant Outcomes

5.1 Methods

5.1.1 Data

We studied recipients of first-time heart transplantation between January 2013 – December 2019. Descriptions of data source, study population and definitions of study variables are presented in **section 2.1**. Of note, the following variable categorizations specific to heart analyses include: recipient age categorized as 13-19, 20-29, 30-39, 40-49, 50-59, and 60-70 years; donor age categorized as 12-19, 20-29, 30-39, and 40-59 years; recipient and donor race categorized as white and other; recipient and donor BMI categorized as < 30 and ≥ 30 kg/m^2; and cold ischemia time categorized as < 4 hours and ≥ 4 hours. Five heart transplants (4 non-ODD and 1 ODD) were excluded because 2 (1 ODD and 1 non-ODD) hearts went towards heart kidney combination transplants and 3 (non-ODD) hearts went to recipients for whom it was not their first heart transplant.

5.1.2 Descriptive analysis

The number of ODD and non-ODD heart transplantations were plotted annually over the study period. Donor and recipient characteristics were compared by donor overdose death status using the methods described in **section 2.2.2**.

5.1.3 Analysis of post-transplant outcomes

Time to death was examined using the Kaplan-Meier method and the IPTW Cox proportional hazards model as described in **section 2.3.1** and **section 2.3.2**. Time to death was calculated as time from transplantation to date of death, censored at re-transplantation or end of follow-up.

The multivariable logistic regression model used to calculate the propensity score included recipient (sex, age, race, BMI), donor (sex, age, race, BMI, last measured creatinine, history of hypertension), and transplant (HLA mismatch) factors. Organ cold ischemia time was missing for two recipients and the variable was not included in the logistic regression model. Instead, organ cold ischemia time was adjusted for in the IPTW multivariable Cox proportional hazards model with missing values coded as "missing". Variable SMDs calculated for the weighted sample comparing donor overdose status groups that were greater than 0.1 were adjusted for in the multivariable IPTW Cox proportional hazards model. The proportional hazards assumption was assessed using log -log survival plots and functional form of continuous donor and recipient age was assessed if needed using plots of martingale residual against age. First instance of acute rejection is common in heart transplant recipients therefore, this outcome was not analyzed.

5.2 Results

5.2.1 Descriptive analyses

From 2013-2019 the number of heart transplantations from donors with an identifiable overdose status increased 100% from 12 in 2013 to 24 in 2019; this increase was primarily driven by an increase in ODD utilization. ODD utilization started in 2014, a year after kidney, liver, and double-lung. However, this number increased rapidly jumping 400% from 2 to 10 ODD transplants between 2015-2016, coinciding with the increased number of overdose deaths in BC. After 2016, annual ODD transplantations stayed steady between 8-11 transplants per year. Annual non-ODD utilization increased slightly before and after 2016 ranging from 8-12 transplants per year prior to 2016, to 9-15 transplants per year after 2016 (Figure 8).

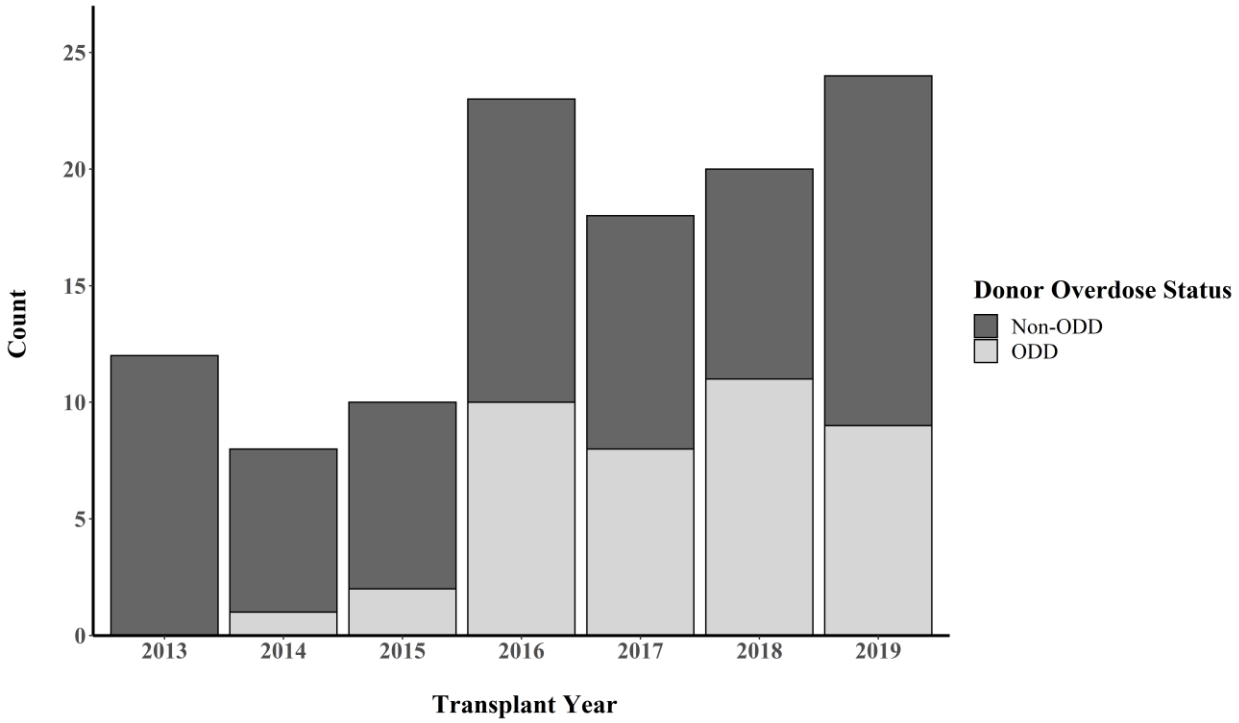

Figure 8. Bar graph showing the number of heart transplantations during the study period categorized by donor cause of death resulting from overdose (ODD) or not resulting from overdose (non-ODD).

The total number of heart transplants in this period from donors with an identifiable overdose death status was 115 transplants. After combination and non-first transplant exclusions, 110 transplants were included in the analytical sample. Of these, 70 (64%) hearts were from non-ODDs and 40 (36%) hearts were from ODDs. It should be noted for heart transplant characteristics, descriptions were based on percentages as large p values are present due to the small sample size. Recipients of ODD transplantations were more likely to be male (75.0% vs 65.7%, $p = 0.424$) and white (80.0% vs 70.0%, $p = 0.357$), notably almost half of all recipients of ODD hearts were between 60 – 70 years of age (47.5% vs 37.1%). ODDs were more likely to be between 20-39 years of age (85.0% vs 55.7%), white (85.0% vs 72.9%, $p = 0.220$), and flagged as an exceptional distribution donor (67.5% vs 35.7%, $p < 0.003$). Of note, all ODDs had hypoxia as the primary cause of death. All non-ODDs were HCV negative, but two ODDs were

HCV positive (serology tested negative), these two HCV positive ODDs donated hearts to two HCV negative recipients. These two recipients did not develop HCV in the study period (Table 8).

Table 8. Heart Transplantation: donor and recipient characteristics compared by overdose as the cause of donor death for first-time heart transplants.

Characteristics	Level	Non-ODD (N = 70)	ODD (N = 40)	p
Recipient Variables				
Sex (%)	Male	46 (65.7)	30 (75.0)	0.424
	Female	24 (34.3)	10 (25.0)	
Age (%)	13-19 (min = 13)	3 (4.3)	1 (2.5)	0.819
	20-29	4 (5.7)	2 (5.0)	
	30-39	4 (5.7)	1 (2.5)	
	40-49	11 (15.7)	8 (20.0)	
	50-59	22 (31.4)	9 (22.5)	
	60-70 (max = 70)	26 (37.1)	19 (47.5)	
Median age (Q1, Q3)		56.0 (46.2, 62.0)	58.5 (48.0, 65.0)	0.256
Race (%)	White	49 (70.0)	32 (80.0)	0.357
	Other	21 (30.0)	8 (20.0)	
BMI, kg/m2 (%)	<30	51 (72.9)	28 (70.0)	0.920
	≥30	19 (27.1)	12 (30.0)	
HCV (%)	Yes	1 (1.4)	0 (0.0)	1.000
Peak PRA[1] % (%)	<30	24 (49.0)	18 (56.2)	0.146
	30-79	14 (28.6)	12 (37.5)	
	≥80	11 (22.4)	2 (6.2)	
Donor Variables				
Sex (%)	Male	49 (70.0)	27 (67.5)	0.953
	Female	21 (30.0)	13 (32.5)	
Age (%)	12-19 (min = 12)	11 (15.7)	1 (2.5)	0.010
	20-29	23 (32.9)	16 (40.0)	
	30-39	16 (22.9)	18 (45.0)	
	40-59 (max = 59)	20 (28.6)	5 (12.5)	
Median age (Q1, Q3)		30.0 (23.0, 42.5)	32.0 (25.8, 38.0)	0.621
Race (%)	White	51 (72.9)	34 (85.0)	0.220
	Other	19 (27.1)	6 (15.0)	
BMI, kg/m2 (%)	<30	56 (80.0)	30 (75.0)	0.711
	≥30	14 (20.0)	10 (25.0)	
History of hypertension (%)	Yes	8 (11.4)	2 (5.0)	0.322
History of diabetes (%)	Yes	2 (2.9)	0 (0.0)	0.533
HCV (%)	Yes	0 (0.0)	2 (5.0)	0.130
Creatinine, mg/dL (%)	≥1.5	9 (12.9)	10 (25.0)	0.174
Cause of death (%)	Hypoxia	23 (32.9)	40 (100.0)	<0.001
	CVA	12 (17.1)	0 (0.0)	
	Trauma	26 (37.1)	0 (0.0)	
	Other	9 (12.9)	0 (0.0)	
Exceptional distribution donor (%)	Yes	25 (35.7)	27 (67.5)	0.003
Transplant Variables				

Characteristics	Level	Non-ODD (N = 70)	ODD (N = 40)	p
Number of HLA mismatches (%)	0-2	5 (7.1)	3 (7.5)	0.966
	3-5	54 (77.1)	30 (75.0)	
	6	11 (15.7)	7 (17.5)	
CIT[1], hours (%)	<4	48 (69.6)	28 (71.8)	0.981
	≥4	21 (30.4)	11 (28.2)	

ODD, overdosed deceased donor; BMI, body mass index; CVA, cerebrovascular accident; HCV, hepatitis C virus; HLA, human leukocyte antigen; PRA, panel reactive antibody; NDD, neurologically determination of death; DCD, donation after circulatory death; CIT, cold ischemic time; Variable level frequencies between ODD and non-ODD organ recipients were compared using the chi-square test, Fisher's exact test, or the Wilcoxon rank sum test as appropriate.

[1]Missing: Recipient peak PRA % (26.36%); CIT, hours (1.82%)

5.2.2 Outcomes analyses

5.2.2.1 Primary outcome

Survival after ODD transplantation was 95% at 1-year and, 87%, at 3- and 5-year post-transplant. Survival after non-ODD transplantation was 96%, 90%, and 86% at 1-, 3-, and 5-year post-transplant (Figure 9). There was no difference in death between overdose groups in the first 5-years of post-transplant follow-up (log-rank, p = 0.75).

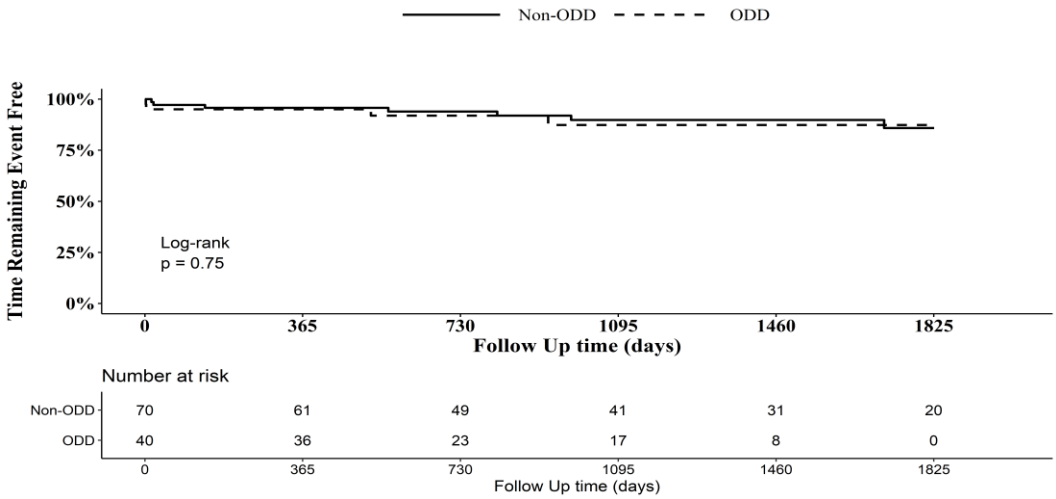

Figure 9. 5-year Kaplan Meier curves and corresponding risk tables for death among heart transplants compared between donor overdose cause of death.

After IPT weights were calculated from the propensity scores generated by the multivariable logistic regression model adjusted for select variables listed in **section 5.1.3**; recipient sex and cold ischemia time had a SMD > 0.1 and were adjusted for in the multivariable IPTW Cox proportional hazards model (Table 9).

Table 9. Standardized mean difference table after inverse probability of treatment weight assignment for heart.

Characteristics	Level	Non-ODD (Weighted N = 110.2)	ODD (Weighted N = 111.9)	SMD
Recipient Variables				
Sex (%)	Male	77.0 (69.9)	83.3 (74.4)	0.101
	Female	33.2 (30.1)	28.6 (25.6)	
Median age (Q1, Q3)		58.0 (47.5, 62.0)	54.9 (47.9, 65.0)	0.007
Race (%)	White	81.4 (73.9)	81.1 (72.4)	0.032
	Other	28.8 (26.1)	30.8 (27.6)	
Recipient BMI, kg/m2 (%)	<30	78.5 (71.2)	76.6 (68.4)	0.061
	≥30	31.7 (28.8)	35.3 (31.6)	
Donor Variables				
Sex (%)	Male	75.9 (68.8)	81.4 (72.8)	0.086
	Female	34.3 (31.2)	30.5 (27.2)	
Median age (Q1, Q3)		28.3 (22.0, 42.2)	31.8 (25.0, 38.0)	0.010
Race (%)	White	85.8 (77.8)	85.0 (76.0)	0.044
	Other	24.5 (22.2)	26.9 (24.0)	
Donor BMI, kg/m2 (%)	<30	85.6 (77.7)	90.9 (81.2)	0.086
	≥30	24.6 (22.3)	21.1 (18.8)	
Creatinine, mg/dL (%)	≥1.5	18.7 (17.0)	17.8 (15.9)	0.028
History of hypertension (%)	Yes	10.2 (9.3)	11.5 (10.3)	0.033
Transplant Variables				
Number of HLA mismatches (%)	0-2	8.5 (7.7)	7.9 (7.1)	0.029
	3-5	83.7 (75.9)	86.2 (77.0)	
	6	18.1 (16.4)	17.8 (15.9)	
CIT, hours (%)	<4	74.9 (67.9)	79.5 (71.0)	0.327
	≥4	34.2 (31.0)	25.3 (22.6)	
	missing	1.2 (1.1)	7.1 (6.4)	

SMD, standardized mean difference; ODD, overdosed deceased donor; BMI, body mass index; HLA, human leukocyte antigen; CIT, cold ischemic time.

The univariate Cox model showed that recipients of ODD hearts did not have significantly differing risk of death (HR: 1.28, 95% CI: 0.36 – 4.54, p = 0.704) compared to recipients of non-ODD hearts. After IPT weighting, the risk of death increased for recipients of ODD hearts (HR: 1.67, 95% CI: 0.42 – 6.62, p = 0.465) but after multivariable adjustment in the IPTW Cox model, risk of death for recipients of ODD hearts returned to the null with a marginally tighter

confidence interval (HR: 0.94, 95% CI: 0.22 – 4.07, p = 0.938) (Table 10). The proportional hazards assumption was visually adequate in all log -log survival plots. The functional form of donor and recipient age did not need to be assessed.

Table 10. Three models examining the relationship between overdose as a cause of donor death and recipient death.

	Model 1: Univariate Cox model		Model 2: Univariate IPTW Cox model		Model 3: Multivariable IPTW Cox model	
Variable	**HR (95% CI)**	**p**	**HR (95% CI)**	**p**	**HR (95% CI)**	**p**
Donor overdose status						
ODD	1.28 (0.36, 4.54)	0.704	1.67 (0.42, 6.62)	0.465	0.94 (0.22, 4.07)	0.938

ODD, overdosed deceased donors; IPTW, inverse probability of treatment weight; HR, hazard ratio; CI, confidence interval.

Model 2 is weight adjusted for recipient sex, age, race, BMI; donor overdose status, sex, age, race, BMI, last measured creatinine, history of hypertension; transplant number of HLA mismatches.

Model 3 is weight adjusted for all variables mentioned in Model 2 as well as adjusted for as covariates in the IPTW Cox proportional hazards model for recipient sex and organ cold ischemia time.

5.3 Discussion

Heart transplantation from ODDs increased over the study period in parallel with increases in overdose deaths in BC but did not see the same linear growth in utilization after 2016 compared to other organ groups. However, because fewer heart transplants are performed compared to other organ groups, the small number of ODD hearts utilized serve an important purpose; in 2017 ODD hearts represented 40% of all heart transplants in the province. Compared to recipients of non-ODD heart transplants, recipients of ODD heart transplantation had similar unadjusted survival probabilities at five-years post-transplant. Adjusted for donor and recipient characteristics, the three-year analysis found no association of ODD status on recipient survival however, confidence intervals were wide due to the small sample size (N = 110) as well as the few and varied outcomes recorded (9% of the analytical sample). Therefore, we refrain from making any conclusions regarding the effect of donor overdose death status on heart transplant recipient survival.

Durand et al. studied the national SRTR database between 2000-2017 utilizing similar IPTW methodology with standardized risk differences to examine 5-year survival rates for recipients of ODD heart transplantation, and also found no increased risk of death for recipients of ODD heart transplants compared to trauma death donor (0.8% [95% CI, −3.4% to 4.3%]) and medical death donor (3.9% [95% CI, −0.3% to 7.5%]) heart transplant recipients with a unadjusted 5-year survival rate of 79.2% for recipients of ODD hearts (46). Phillips et al. also conducted a study using the national SRTR database between 2010-2017, using a 5 year Kaplan-Meier comparison method and a 5 year Cox proportional hazards regression model (adjusted only for donor characteristics) on heart transplant recipients and found no difference in survival between recipients of ODD and non-ODD hearts with 5-year unadjusted ODD heart recipient survival below 85% (47). ODDs studied by Phillips et al. were more likely to be younger than 40 years of age, white, have a history of cocaine use, more likely to be HCV positive, more often had a history of cardiac arrest, and were more likely to have received cardiopulmonary resuscitation (47). Ising et al. studied the UNOS deceased donor and thoracic transplant databases between January 2005 and March 2015 comparing recipients of ODD and non-ODD hearts using propensity score (adjusted for select donor and recipient characteristics) matched Kaplan-Meier curves with comparisons done using the log-rank test. They found no difference in post-transplant survival and recorded a crude 5 year survival rate of 76% in both matched and un-matched cohorts (92). ODDs studied by Ising et al. were more likely to be female, smokers, with high serum creatinine, and were more likely to be flagged as IRDs (92). Warraich et al. studied the UNOS Standard Transplant Analysis and Research database between January 2000, and March 2014 to analyze heart transplant recipient survival from ODDs and non-ODDs at 10 years using Cox proportional hazards regression models adjusted for recipient and donor

characteristics; finding no difference in survival between the donor groups (50). They found ODDs were more likely to be female, white, have high serum creatinine, have risk factors for blood-borne disease transmission, and a history of substance abuse (50).

All these national studies in the US point towards the fact that donor overdose status is not a significant factor associated with heart recipient post-transplant survival. Similar with the American studies, the BC sample of heart ODDs were more likely to be younger, white, and flagged as exceptional distribution (equivalent to Public Health Increased Risk) donors. However, unlike the American studies, the BC sample of heart ODDs were mostly males with fewer comorbidities such as diabetes and hypertension. Of note, heart donor characteristic comparisons of ODD and non-ODD groups for the BC sample were not significantly different however, this is likely a result of small sample size.

A limitation of our study was the small sample size and few outcomes. Given we needed to account for all variables listed in Table 9, we were fortunate that donor and recipient characteristics compared between ODDs and non-ODDs were relatively balanced after IPTW allowing us to only adjust for three variables as covariates. Unfortunately, the small sample size also gave rise to an issue of power to detect a meaningful difference therefore our null results are not reliable. However, because unadjusted survival rates are high and risk of death is drastically reduced compared to staying on the wait list, we believe this analysis is worth pursuing with additional data. This analytical sample does not contain many ODDs who are older or more likely to have comorbidities such as diabetes or hypertension. Change in ODD demographics

may impact future results. Analysis for this organ group is inconclusive, additional data and further study is required.

Chapter 6: Liver Transplant Outcomes

6.1 Methods

6.1.1 Data

We studied recipients of liver transplantation between January 2013 – December 2019. Descriptions of data source, study population, and definitions of study variables are presented in **section 2.1**. Of note, the following variable categorizations specific to liver transplantation analyses include: recipient age categorized as 15-29, 30-39, 40-49, 50-59, 60-69, and 70-75 years; donor age categorized as 12-19, 20-29, 30-39, 40-49, 50-59, and 60-70 years; recipient race categorized as white, east & south & southeast Asian, and other; donor race categorized as white and other; recipient and donor BMI categorized as < 25, $25 – 29$, and ≥ 30 kg/m^2; and cold ischemia time categorized as < 12 and ≥ 12 hours. The analytical sample comprised of the first instance of liver transplant in the study period for each recipient. Past transplants were adjusted for using a binary variable (yes/no) indicating whether the transplant was the recipient's first transplant.

6.1.2 Descriptive analysis

The number of ODD and non-ODD liver transplantations were plotted annually over the study period. Donor and recipient characteristics were compared by donor overdose status using the methods described in **section 2.2.2**.

6.1.3 Analysis of post-transplant outcomes

Time to death was examined using the Kaplan-Meier method and the IPTW Cox proportional hazards model as described in **section 2.3.1** and **section 2.3.2**. Time to death was calculated as time from transplantation to date of death, censored at re-transplantation or end of follow-up.

The multivariable logistic regression model used to calculate propensity scores included recipient (sex, age, race, HCV), donor (sex, age, race, HCV, last measured creatinine, history of hypertension, history of diabetes, and deceased donor type), and transplant (first transplant) factors. Variable SMDs calculated for the weighted sample comparing donor overdose status groups that were greater than 0.1 were adjusted for in the multivariable IPTW Cox proportional hazards model. The proportional hazards assumption was assessed using log -log survival plots and functional form of continuous donor and recipient age was assessed if needed using plots of martingale residual against age.

The cumulative probability of experiencing the first episode of acute rejection at 1-, 3-, and 5-year post-transplant was analyzed using cumulative incidence curves as outlined in **section 2.3.1**.

6.2 Results

6.2.1 Descriptive analyses

From 2013-2019 there were 410 liver transplantations from donors who had an identifiable overdose death status. ODDs increased 440% from 5 in 2013 to 27 in 2017 then decreasing slightly to 18 in 2019. The yearly average number of ODD transplantations was 3.5-fold higher after 2016 compared to before 2016 (Figure 10). Increased ODD transplantations over time was

primarily driven by an increase in ODD utilization coinciding with the increased number of overdose deaths in BC. The annual pattern of transplantations mirrored the influx of ODDs during the study period (Figure 1).

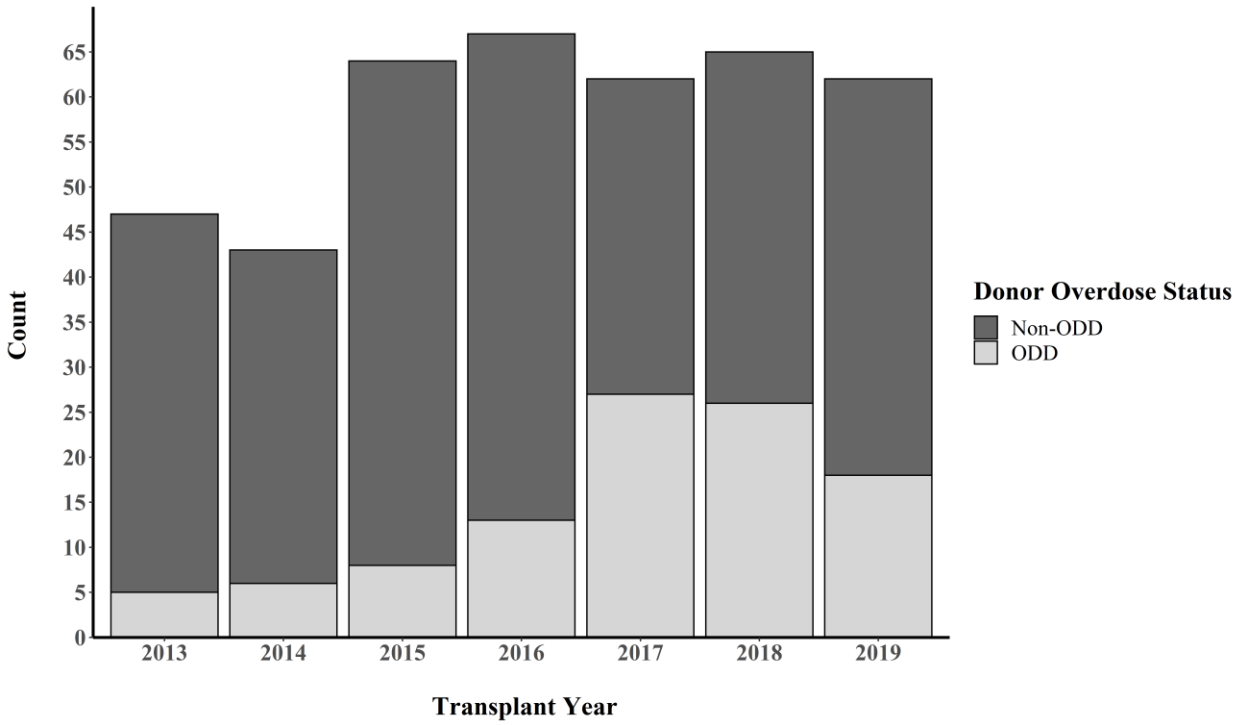

Figure 10. Bar graph showing the number of liver transplantations during the study period categorized by donor cause of death resulting from overdose (ODD) or not resulting from overdose (non-ODD).

Out of the 410 liver transplants, 6 kidney liver transplants were excluded. Of the 404 remaining liver transplants, 367 (91%) were first time liver transplants, 32 (8%) were second time liver transplants, and 5 (1%) were third time liver transplants. The analytical sample comprised of 382 liver transplants. Of these, 287 (75%) livers were from non-ODDs and 95 (25%) livers were from ODDs. Recipients of ODD transplantations were more likely to be male (73.7% vs 61.0%, $p = 0.034$) with other recipient traits showing similar distributions between donor overdose groups. ODDs were more likely to be younger (median age [Q1; Q3]): 31 [25, 38] years vs. 47

[31, 57] years, p < 0.001), white (86.3% vs 79.4%, p = 0.182), males (74.7% vs 62.0%, p = 0.033) with less comorbidities such as diabetes (2.1% vs 7.0%, p = 0.131) and hypertension (5.3% vs 19.9%, p = 0.001) but, were more likely to be flagged as exceptional distribution donors (83.2% vs 38.3%, p < 0.001) and were more likely to be HCV positive (5.3% vs 1.4%, p = 0.046). The majority of ODDs had cause of death due to hypoxia (98.9% vs 32.1%, p < 0.001). Of note, ODDs were more likely to have a cold ischemia time of ≥ 12 hours (34.2% vs 17.6%, p = 0.005) but were missing 25.92% of data for this variable (Table 11).

Table 11. First instance of liver transplant in the study period for each recipient: donor and recipient characteristics compared by overdose as the cause of donor death.

Characteristics	Level	Non-ODD (N = 287)	ODD (N = 95)	p
Recipient Variables				
Sex (%)	Male	175 (61.0)	70 (73.7)	0.034
	Female	112 (39.0)	25 (26.3)	
Age (%)	15-29 (min = 15)	20 (7.0)	4 (4.2)	0.515
	30-39	15 (5.2)	8 (8.4)	
	40-49	39 (13.6)	18 (18.9)	
	50-59	96 (33.4)	30 (31.6)	
	60-69	102 (35.5)	32 (33.7)	
	70-75 (max = 75)	15 (5.2)	3 (3.2)	
Median Age (Q1, Q3)		58.0 (48.5, 63.0)	56.0 (48.0, 62.0)	0.258
Race (%)	White	203 (70.7)	70 (73.7)	0.824
	East & South & Southeast Asian	51 (17.8)	16 (16.8)	
	Other	33 (11.5)	9 (9.5)	
BMI[1], kg/m2 (%)	<25	118 (45.6)	32 (38.1)	0.424
	25-29	81 (31.3)	32 (38.1)	
	≥30	60 (23.2)	20 (23.8)	
HCV (%)	Yes	68 (23.7)	24 (25.3)	0.864
Peak PRA[1] % (%)	<30	29 (90.6)	3 (75.0)	0.390
	30-79	1 (3.1)	0 (0.0)	
	≥80	2 (6.2)	1 (25.0)	
Donor Variables				
Sex (%)	Male	178 (62.0)	71 (74.7)	0.033
	Female	109 (38.0)	24 (25.3)	
Age (%)	12-19 (min = 12)	22 (7.7)	5 (5.3)	<0.001
	20-29	42 (14.6)	35 (36.8)	
	30-39	39 (13.6)	34 (35.8)	
	40-49	58 (20.2)	15 (15.8)	
	50-59	77 (26.8)	4 (4.2)	
	60-70 (max = 70)	49 (17.1)	2 (2.1)	
Median Age (Q1, Q3)		47.0 (31.0, 57.0)	31.0 (25.0, 38.0)	<0.001
Race (%)	White	228 (79.4)	82 (86.3)	0.182
	Other	59 (20.6)	13 (13.7)	

Characteristics	Level	Non-ODD (N = 287)	ODD (N = 95)	p
BMI, kg/m2 (%)	<25	126 (43.9)	43 (45.3)	0.925
	25-29	100 (34.8)	31 (32.6)	
	≥30	61 (21.3)	21 (22.1)	
History of diabetes (%)	Yes	20 (7.0)	2 (2.1)	0.131
History of hypertension (%)	Yes	57 (19.9)	5 (5.3)	0.001
HCV (%)	Yes	4 (1.4)	5 (5.3)	0.046
Creatinine, mg/dL (%)	<1.5	249 (86.8)	77 (81.1)	0.232
	≥1.5	38 (13.2)	18 (18.9)	
Cause of death (%)	Hypoxia	92 (32.1)	94 (98.9)	<0.001
	CVA	95 (33.1)	0 (0.0)	
	Trauma	72 (25.1)	0 (0.0)	
	Other	28 (9.8)	1 (1.1)	
Deceased donor type (%)	NDD	246 (85.7)	78 (82.1)	0.494
	DCD	41 (14.3)	17 (17.9)	
Exceptional distribution donor (%)	Yes	110 (38.3)	79 (83.2)	<0.001
Transplant Variables				
Number of HLA mismatches[1] (%)	0-2	14 (5.9)	5 (6.0)	0.661
	3-5	200 (84.4)	67 (80.7)	
	6	23 (9.7)	11 (13.3)	
CIT[1], hours (%)	<12	173 (82.4)	48 (65.8)	0.005
	≥12	37 (17.6)	25 (34.2)	
Transplant number (%)	first transplant	275 (95.8)	92 (96.8)	0.888

ODD, overdosed deceased donor; BMI, body mass index; CVA, cerebrovascular accident; HCV, hepatitis C virus; HLA, human leukocyte antigen; PRA, panel reactive antibody; NDD, neurologically determination of death; DCD, donation after circulatory death; CIT, cold ischemic time; Variable level frequencies between ODD and non-ODD organ recipients were compared using the chi-square test, Fisher's exact test, or the Wilcoxon rank sum test as appropriate.

[1]Missing: Recipient BMI (10.21%); Recipient peak PRA % (90.58%); Number of HLA mismatches (16.23%); CIT, hours (25.92%).

6.2.2 Outcomes analyses

6.2.2.1 Primary outcome

Survival after ODD transplantation was 93% at 1-year and 84%, at 3- and 5-year post-transplant. Survival after non-ODD transplantation was 92%, 84%, and 79% at 1-, 3-, and 5-year post-transplant (Figure 11). There was no difference in recipient survival between donor overdose groups in the first 5-years of post-transplant follow-up (log-rank, p = 0.67).

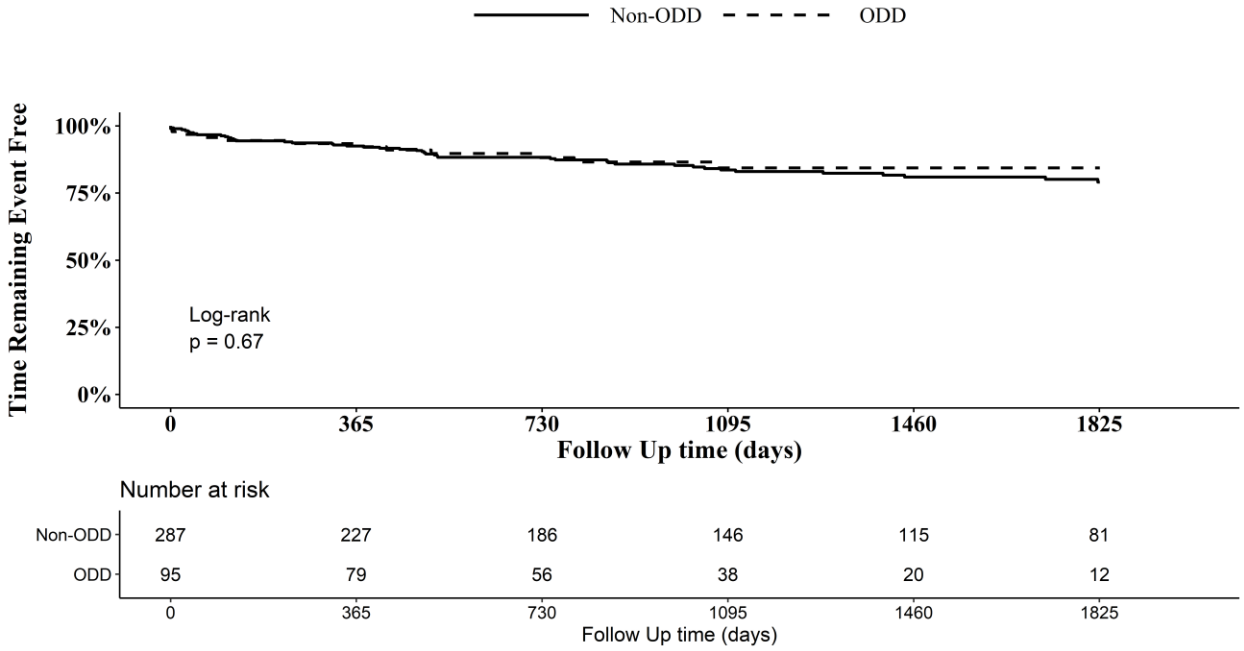

Figure 11. 5-year Kaplan Meier curves and corresponding risk tables for death among liver transplants compared by donor overdose death status.

After IPT weights were calculated from the propensity scores generated by the multivariable logistic regression model adjusted for variables listed in **section 6.1.3**; recipient sex, race, and donor age, deceased donor type, and transplant number had a SMD > 0.1 (Table 12) and were adjusted for in the multivariable IPTW Cox proportional hazards model.

Table 12. Standardized mean difference table after inverse probability of treatment weight assignment for liver analysis.

Characteristics	Level	Non-ODD (Weighted N = 385.1)	ODD (Weighted N = 342.2)	SMD
Recipient Variables				
Sex (%)	Male	248.0 (64.4)	240.1 (70.2)	0.123
	Female	137.1 (35.6)	102.2 (29.8)	
Median age (Q1, Q3)		58.0 (48.7, 62.3)	56.2 (49.0, 62.6)	0.038
Race (%)	White	273.4 (71.0)	231.7 (67.7)	0.110
	East &South & Southeast Asian	69.6 (18.1)	76.8 (22.4)	
	Other	42.2 (10.9)	33.8 (9.9)	
HCV (%)	Yes	90.9 (23.6)	85.1 (24.9)	0.030
Donor Variables				
Sex (%)	Male	251.4 (65.3)	233.8 (68.3)	0.065
	Female	133.7 (34.7)	108.4 (31.7)	
Median age (Q1, Q3)		42.0 (27.0, 54.0)	35.8 (28.0, 45.0)	0.231
Race (%)	White	312.0 (81.0)	272.8 (79.7)	0.033
	Other	73.1 (19.0)	69.5 (20.3)	
Creatinine, mg/dL (%)	<1.5	326.4 (84.8)	278.6 (81.4)	0.090
	≥1.5	58.7 (15.2)	63.7 (18.6)	
History of hypertension (%)	Yes	61.6 (16.0)	46.2 (13.5)	0.070
History of diabetes (%)	Yes	22.0 (5.7)	18.7 (5.5)	0.011
HCV (%)	Yes	7.6 (2.0)	8.3 (2.4)	0.031
Deceased donor type (%)	NDD	330.7 (85.9)	305.4 (89.2)	0.102
	DCD	54.4 (14.1)	36.8 (10.8)	
Transplant number (%)	first transplant	369.8 (96.0)	319.0 (93.2)	0.124

ODD, overdosed deceased donor; HCV, hepatitis C virus; NDD, neurologically determination of death; DCD, donation after circulatory death; SMD, standardized mean difference.

The univariate Cox model showed that recipients of ODD livers did not have significantly differing risk of death compared to recipients of non-ODD livers (HR: 0.95, 95% CI: 0.50 – 1.82, p = 0.886). After IPT weighting, the risk of death estimate for recipients of ODD livers did not greatly change (HR: 0.96, 95% CI: 0.45 – 2.04, p = 0.908). After multivariable adjustment in the IPTW Cox model, risk of death again did not greatly change (HR: 0.96, 95% CI: 0.42 – 2.20, p = 0.930) (Table 13). The functional form of donor age was visually adequate. The proportional hazards assumption was visually adequate in all log -log survival plots.

Table 13. Three models examining the relationship between overdose as a cause of donor death and recipient death.

	Model 1: Univariate Cox model		Model 2: Univariate IPTW Cox model		Model 3: Multivariable IPTW Cox model	
Variable	**HR (95% CI)**	**p**	**HR (95% CI)**	**p**	**HR (95% CI)**	**p**
Donor overdose status						
ODD	0.95 (0.50, 1.82)	0.886	0.96 (0.45, 2.04)	0.908	0.96 (0.42, 2.20)	0.930

ODD, overdosed deceased donors; IPTW, inverse probability of treatment weight; HR, hazard ratio; CI, confidence interval.

Model 2 is weight adjusted for recipient sex, age, race, HCV; donor overdose status, sex, age, race, HCV, last measured creatinine, history of hypertension, history of diabetes, deceased donor type, and transplant number.

Model 3 is weight adjusted for all variables mentioned in Model 2 as well as adjusted for as covariates in the IPTW Cox proportional hazards model for recipient sex, race; donor age, deceased donor type, and transplant number.

6.2.2.2 Secondary outcome

The probability of experiencing acute rejection for ODD liver transplantation was 22% at 1-year and 23% at 3- and 5-year post-transplant. The probability of acute rejection for non-ODD liver transplantation was 25%, 26%, and 29% at 1-, 3-, and 5-year post-transplant. Although recipients of ODD transplantation were less likely to have experienced acute rejection, there was no significant difference (log-rank, p = 0.49) in the first 5 years of follow up (Figure 12).

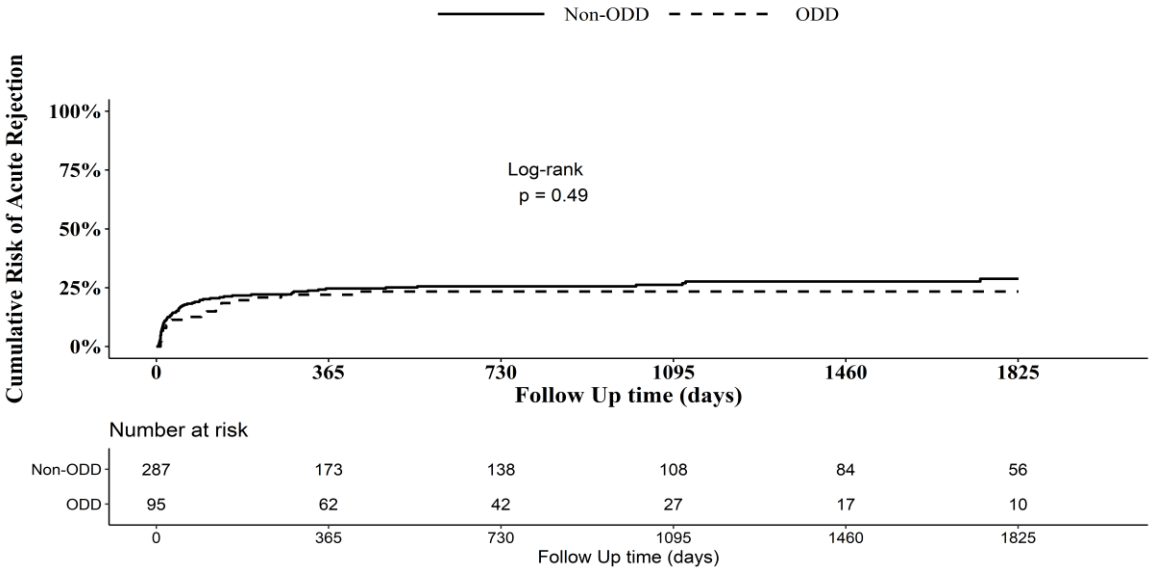

Figure 12. 5-year cumulative incidence curves and corresponding risk tables for first episode of acute rejection among liver transplants compared by donor overdose death status.

6.3 Discussion

Liver transplantation from ODDs increased over the study period, reaching a high in 2017 and slightly receding in 2019. ODD liver utilization trends followed overdosed donation trends because more livers from donors were transplanted compared to other organ groups such as double-lung and heart. Naturally this results in liver ODDs looking similar to the ODD population; more likely to be young, white, and male, with less comorbidities but a higher prevalence of HCV. Adjusted for donor and recipient factors, ODD status did not have a significant effect on recipient survival three-years post-transplant. Recipients of ODD liver transplantation had similar unadjusted survival probabilities at five-years post-transplant as well as similar probabilities of experiencing their first episode of acute rejection at five years post-transplant.

Literature comparing liver transplant recipient survival between donor overdose status groups is limited with Durand et al. and Wanis et al. being the most relevant. Durand et al. studied the national SRTR database between 2000-2017 using similar IPTW methodology with standardized risk differences to examine 5-year survival rates for recipients of ODD liver transplantation and found no increased risk of death for recipients of ODD livers compared to trauma death donor (-1.8% [95% CI, −5.3% to 2.1%]) and medical death donor (2.8% [95% CI, −0.6% to 6.5%]) liver transplant recipients with a unadjusted 5-year survival rate of 76.8% for recipients of ODD livers (46). Wanis et al. also studied the national SRTR database but only looked at DCD donors between 2006-2016 by estimating graft failure cumulative incidence curves standardized by baseline recipient, donor, and transplant characteristics finding no difference in graft failure between ODD and non-ODD liver transplant recipients. Wanis et al. reported a 5-year risk of

graft failure of 31% among ODD liver transplant recipients (49). Liver ODDs studied by Wanis et al. were more likely to have a history of cocaine or other drug use and similar to the BC ODD population were more likely to be younger with less comorbidities such as diabetes or hypertension. Recipients of ODD livers in BC recorded higher unadjusted survival rates at 5-year post-transplant compared to national 5-year survival rates in the US. Similar to double-lung analysis, we believe beyond demographics this is also partially due to improvement in care over time as both Durand et al. and Wanis et al. studied transplant recipients prior to 2010. These two national American studies align with our results confirming that ODD status does not affect liver transplant recipient survival.

A limitation of our study is the percentage of missing values for recipient peak PRA percentage at more than 90% which made this variable unusable. This may be because the variable is not important in liver transplantation due to livers having weaker rejection response compared to lungs and hearts (93). However, in our double-lung and heart analyses, peak PRA percentage was also not useable due to high missingness. The number of HLA mismatch, and organ cold ischemia time variables were missing more than 10% of data and were excluded from the calculation of propensity scores for the generation of IPT weights. As mentioned prior HLA mismatch was also not considered for adjustment because increased HLA mismatch has been shown to not be an independent risk factor for liver recipient graft loss (77,78). When adjusted for organ cold ischemia time with a missing level in the IPTW Cox proportional hazards model (results not shown), we still arrived at a less than one, non-significant estimate for donor overdose status indicating organ cold ischemia time does not confound the relationship between donor overdose status and survival.

ODD liver transplantation leads to high survival rates in the first 5-years post-transplant. This analytical sample does not contain many ODDs who are older or more likely to have comorbidities such as diabetes or hypertension. Utilization of livers from older ODDs with more comorbid conditions may not guarantee the same results. In the interest of reducing the waitlist, given current rates of survival, transplantation of ODD livers is safe.

Chapter 7: Kidney Transplant Outcomes

7.1 Methods

7.1.1 Data

We studied recipients of kidney transplantation between January 2013 – December 2019. Descriptions of data source, study population and definitions of study variables are presented in **section 2.1**. Of note, the following variable categorizations specific to kidney transplantation analyses include: recipient age categorized as 2-19, 20-29, 30-39, 40-49, 50-54, 55-59, 60-69, 70-81 years; donor age categorized as 12-19, 20-29, 30-35, 36-39, 40-49, 50-59, and 60-70 years; recipient and donor race categorized as white, Indigenous, east & south & southeast Asian, and other; recipient and donor BMI categorized as < 25, $25 – 29$, and ≥ 30 kg/m^2; cold ischemia time categorized as < 12 and ≥ 12 hours; and duration of dialysis prior to transplantation categorized as <1, 1-3, and >3 years. The analytical sample comprised of the first instance of kidney transplant in the study period for each recipient. Past transplants were adjusted for using a binary variable (yes/no) indicating whether the transplant was the recipient's first transplant.

7.1.2 Descriptive analysis

Donors were plotted by categories of KDRI to discern kidney quality by donor overdose status. The number of ODD and non-ODD kidney transplantations were plotted annually over the study period. Donor and recipient characteristics were compared by donor overdose status using the methods described in **section 2.2.2**.

7.1.3 Analysis of post-transplant outcomes

Time to ACGL was examined using the Kaplan-Meier method and the IPTW Cox proportional hazards model as described in **section 2.3.1** and **section 2.3.2**. To account for the possibility that a donor can appear twice in the analytical dataset due to each donor being capable of donating up to two kidneys; we used a robust estimate of coefficient standard errors in all Cox proportional hazards models to account for correlation between donors. Time until ACGL was calculated as time from transplantation to either date of death, date of re-transplantation, date of graft failure/return to dialysis, or censored at end of follow-up. The multivariable logistic regression model used to calculate the propensity score included recipient (sex, age, race, BMI, HCV), donor (sex, age, race, BMI, HCV, last measured creatinine, history of hypertension, history of diabetes, and deceased donor type), and transplant (number of years on dialysis prior to transplant, organ cold ischemia time, HLA mismatch, and transplant number) factors. Variable SMDs calculated for the weighted sample comparing donor overdose status groups that were greater than 0.1 were adjusted for in the multivariable IPTW Cox proportional hazards model. The proportional hazards assumptions were assessed using log -log survival plots.

We also looked at death with function and DCGL separately as these two outcomes combined amount to ACGL. The Kaplan-Meier method was used to look at the 1-, 3-, and 5-year cumulative probability of not experiencing death with function or DCGL as outlined in **section 2.3.1**. The cumulative probability of experiencing the first episode of acute rejection at 1-, 3-, and 5-year post-transplant was analyzed using cumulative incidence curves as outlined in **section 2.3.1**.

7.2 Results

7.2.1 Descriptive analyses

From 2013-2019, 558 donors with an identifiable overdose death status donated at least one kidney. The distribution of KDRI categories by donor overdose status shows that ODDs tended to have lower KDRI values and very few ODDs had KDRI values past 1.79 (Figure 13).

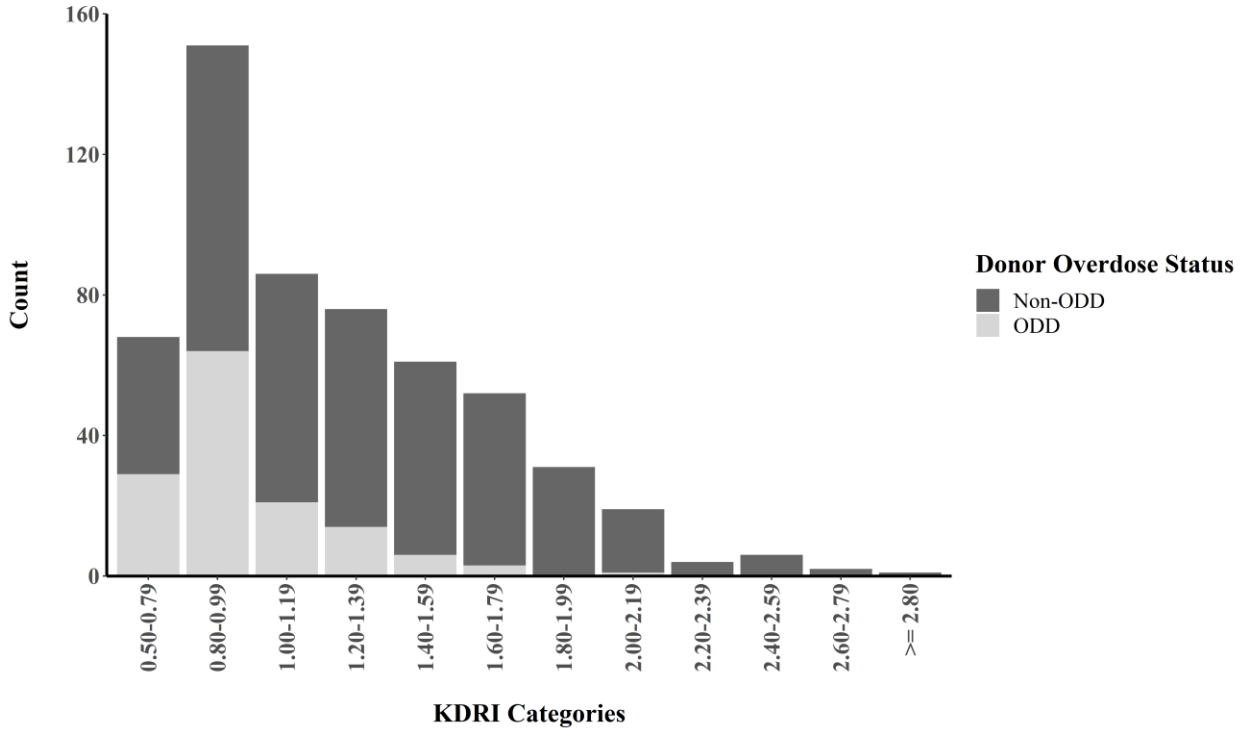

Figure 13. Donor KDRI categories compared by donor overdose status for all kidney donors with an identifiable donor overdose status in the study period.

From the 558 donors resulted 1,035 kidney transplantations for 1,032 recipients in the study period. ODD transplantation increased 640% from 10 in 2013 to 74 in 2018 then decreased to 45 in 2019 (Figure 14); this increase was primarily driven by an increase in ODD utilization coinciding with the increased number of overdose deaths in BC. This pattern of utilization

mirrored the influx of ODDs during the study period (Figure 1). The yearly average number of ODD transplantations was 6-fold higher after 2016 compared to before 2016.

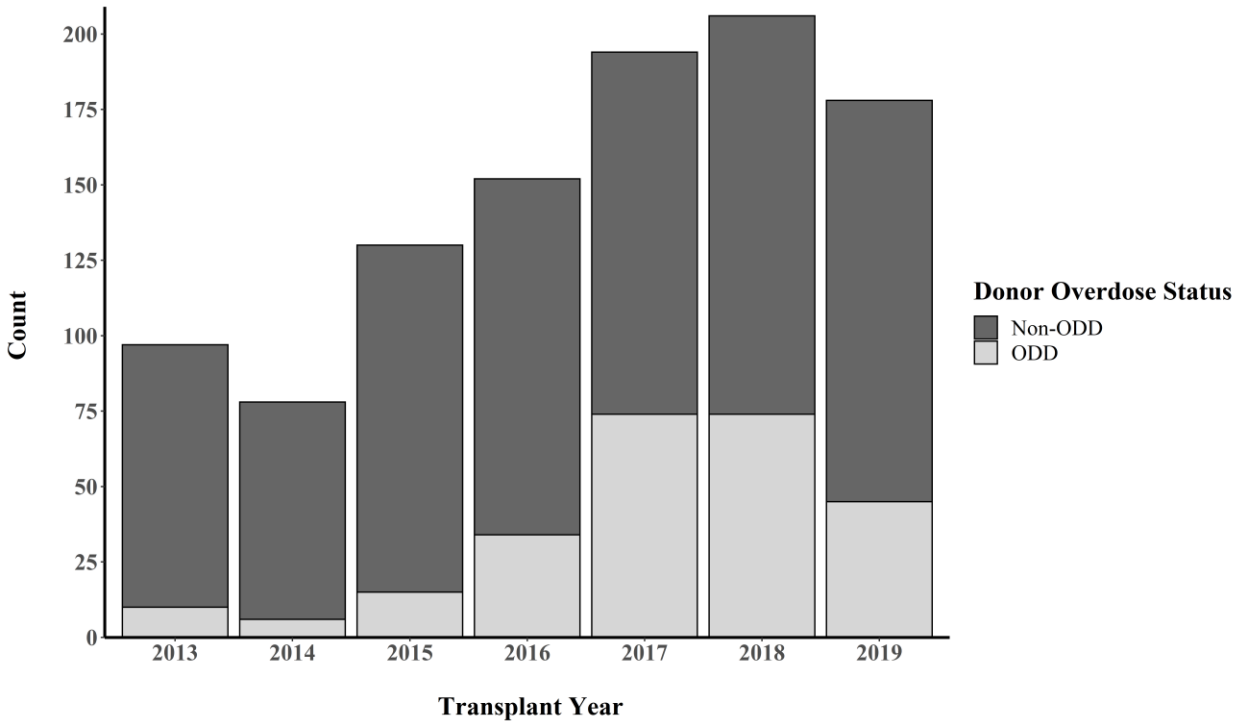

Figure 14. Bar graph showing the number of kidney transplantations during the study period categorized by donor cause of death resulting from overdose (ODD) or not resulting from overdose (non-ODD).

Twenty kidneys were excluded as they were combination transplants (2 kidney heart, 12 kidney pancreas, and 6 kidney liver). Of the 1,015 single kidney transplants, 910 (89.66%) were first, 92 (9.06%) were second, 11 (1.08%) were third, and 2 (0.2%) were fourth time kidney transplants. The analytical sample comprised of 1,012 kidney transplants. Of these, 760 (75%) kidneys were from non-ODDs and 252 (25%) kidneys were from ODDs.

Recipients of ODD transplantations were more likely to be younger (median age [Q1; Q3]): 51 [42, 59] years vs. 60 [48, 67] years, $p < 0.001$) with other recipient traits showing similar

distributions between donor overdose groups. ODDs were more likely to be younger (median age [Q1; Q3]): 35.0 [27.0, 42.2] years vs. 49.5 [34.0, 59.0] years, $p < 0.001$), white (84.1% vs 79.3%, $p < 0.001$), males (75.8% vs 58.9%, $p < 0.001$) who were less likely to be flagged as expanded criteria donors (4.8% vs 35.5%, $p < 0.001$) and had less comorbidities such as diabetes (1.6% vs 8.6%, $p < 0.001$) and hypertension (6.3% vs 24.9%, $p < 0.001$) but, were more likely to be flagged as exceptional distribution donors (82.1% vs 37.0%, $p < 0.001$), have a last measured creatinine ≥ 1.5 mg/dL (22.6% vs 11.6%, $p < 0.001$), and were more likely to be HCV positive (6.7% vs 1.7%, $p < 0.001$). The majority of ODDs recorded hypoxia as the primary cause of death (98.4% vs 30.0%, $p < 0.001$). Delayed graft function marked by dialysis within the first week occurred in similar frequencies between recipients of ODD and non-ODD kidneys (28.6% vs 29.3%, $p = 0.878$) (Table 14).

Table 14. First instance of kidney transplant in the study period for each recipient: donor and recipient characteristics compared by overdose as the cause of donor death.

Characteristics	Level	Non-ODD (N = 760)	ODD (N = 252)	p
Recipient Variables				
Sex (%)	Male	481 (63.3)	167 (66.3)	0.436
	Female	279 (36.7)	85 (33.7)	
Age (%)	2-19 (min = 12)	27 (3.6)	6 (2.4)	<0.001
	20-29	27 (3.6)	15 (6.0)	
	30-39	43 (5.7)	29 (11.5)	
	40-49	112 (14.7)	67 (26.6)	
	50-54	65 (8.6)	39 (15.5)	
	55-59	93 (12.2)	36 (14.3)	
	60-69	266 (35.0)	45 (17.9)	
	70-81 (max = 81)	127 (16.7)	15 (6.0)	
Median Age (Q1, Q3)		60.0 (48.0, 67.0)	51.0 (42.0, 59.0)	<0.001
Race[1] (%)	White	356 (47.0)	118 (46.8)	0.893
	Indigenous	33 (4.4)	11 (4.4)	
	East & South & Southeast Asian	330 (43.5)	113 (44.8)	
	Other	39 (5.1)	10 (4.0)	
BMI[1], kg/m2 (%)	<25	224 (29.6)	88 (35.3)	0.238
	25-29	274 (36.2)	82 (32.9)	
	≥30	258 (34.1)	79 (31.7)	
HCV (%)	Yes	19 (2.5)	2 (0.8)	0.164
Peak PRA[1] % (%)	<30	391 (60.2)	129 (55.8)	0.140
	30-79	173 (26.7)	77 (33.3)	

Characteristics	Level	Non-ODD (N = 760)	ODD (N = 252)	p
	≥80	85 (13.1)	25 (10.8)	
Donor Variables				
Sex (%)	Male	448 (58.9)	191 (75.8)	<0.001
	Female	312 (41.1)	61 (24.2)	
Age (%)	12-19	46 (6.1)	10 (4.0)	<0.001
	20-29	86 (11.3)	71 (28.2)	
	30-35	70 (9.2)	53 (21.0)	
	36-39	39 (5.1)	37 (14.7)	
	40-49	139 (18.3)	47 (18.7)	
	50-59	203 (26.7)	28 (11.1)	
	60-70	177 (23.3)	6 (2.4)	
Median Age (Q1, Q3)		49.5 (34.0, 59.0)	35.0 (27.0, 42.2)	<0.001
Race (%)	White	603 (79.3)	212 (84.1)	<0.001
	Indigenous	38 (5.0)	22 (8.7)	
	East & South & Southeast Asian	95 (12.5)	8 (3.2)	
	Other	24 (3.2)	10 (4.0)	
BMI[1], kg/m2 (%)	<25	287 (37.9)	104 (41.3)	0.168
	25-29	263 (34.7)	94 (37.3)	
	≥30	208 (27.4)	54 (21.4)	
History of diabetes (%)	Yes	65 (8.6)	4 (1.6)	<0.001
History of hypertension (%)	Yes	189 (24.9)	16 (6.3)	<0.001
HCV (%)	Yes	13 (1.7)	17 (6.7)	<0.001
Creatinine[1], mg/dL (%)	<1.5	670 (88.4)	195 (77.4)	<0.001
	≥1.5	88 (11.6)	57 (22.6)	
Cause of death (%)	Hypoxia	228 (30.0)	248 (98.4)	<0.001
	CVA	255 (33.6)	0 (0.0)	
	Trauma	204 (26.8)	0 (0.0)	
	Other	73 (9.6)	4 (1.6)	
Deceased donor type (%)	NDD	547 (72.0)	192 (76.2)	0.221
	DCD	213 (28.0)	60 (23.8)	
Exceptional distribution donor (%)	Yes	281 (37.0)	207 (82.1)	<0.001
Expanded criteria donor (%)	Yes	270 (35.5)	12 (4.8)	<0.001
Transplant Variables				
Number of HLA mismatches[1] (%)	0-2	55 (7.3)	21 (8.4)	0.646
	3-5	598 (78.9)	191 (76.1)	
	6	105 (13.9)	39 (15.5)	
CIT[1], hours (%)	<12	506 (68.0)	166 (66.9)	0.814
	≥12	238 (32.0)	82 (33.1)	
Dialysis duration prior to transplant[1], years (%)	<1	28 (3.7)	10 (4.0)	0.003
	1-3	286 (37.9)	125 (50.0)	
	>3	440 (58.4)	115 (46.0)	
Transplant number (%)	first transplant	691 (90.9)	219 (86.9)	0.086
Delayed graft function (%)	Yes	223 (29.3)	72 (28.6)	0.878

ODD, overdosed deceased donor; BMI, body mass index; CVA, cerebrovascular accident; HCV, hepatitis C virus; HLA, human leukocyte antigen; PRA, panel reactive antibody; NDD, neurologically determination of death; DCD, donation after circulatory death; CIT, cold ischemic time; Variable level frequencies between ODD and non-ODD organ recipients were compared using the chi-square test, Fisher's exact test, or the Wilcoxon rank sum test as appropriate.

Each donor may contribute more than one row of data for donor variable frequencies as each donor may donate up to two kidneys.

[1]Missing: Recipient race (0.2%); Recipient BMI (0.69%); Recipient peak PRA % (13.04%); Donor BMI (0.2%); Donor creatinine, mg/dL (0.2%); Dialysis duration prior to transplant, years (0.79%); Number of HLA mismatches (0.3%); CIT, hours (1.98%).

7.2.2 Outcomes analyses

7.2.2.1 Primary outcome

The probability of not experiencing ACGL after ODD transplantation was 98% at 1-year and 97% at 3- and 5-year post-transplant. The probability of not experiencing ACGL after non-ODD transplantation was 94%, 88%, and 83% at 1-, 3-, and 5-year post-transplant. Compared to recipients of non-ODD kidneys, recipients of ODD kidneys were significantly less likely to experience ACGL in the first 5-years of post-transplant follow-up (log-rank, $p < 0.001$) (Figure 15).

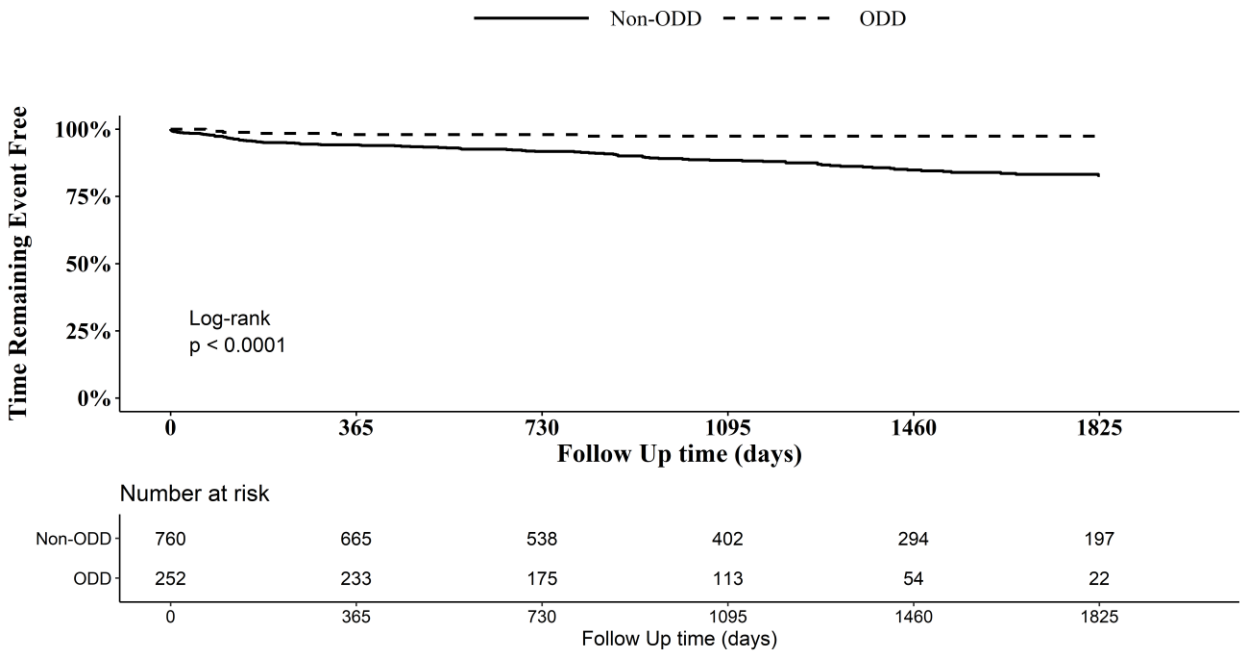

Figure 15. 5-year Kaplan Meier curves and corresponding risk tables for all cause graft loss among kidney transplants compared between donor overdose cause of death.

After IPT weights were calculated from the propensity scores generated by the multivariable logistic regression model adjusted for select variables listed in **section 7.1.3**; recipient age, race,

and donor sex, age, race, and BMI had a SMD > 0.1 (Table 15) and were adjusted for in the multivariable IPTW Cox proportional hazards model.

Table 15. Standardized mean difference table after inverse probability of treatment weight assignment for kidney analysis.

Characteristics	Level	Non-ODD (Weighted N = 1035.2)	ODD (Weighted N = 885.3)	SMD
Recipient Variables				
Sex (%)	Male	659.3 (63.7)	602.5 (68.1)	0.092
	Female	375.8 (36.3)	282.9 (31.9)	
Age (%)	2-19	33.1 (3.2)	35.3 (4.0)	0.182
	20-29	42.7 (4.1)	39.2 (4.4)	
	30-39	69.5 (6.7)	65.7 (7.4)	
	40-49	175.0 (16.9)	174.3 (19.7)	
	50-54	115.1 (11.1)	118.3 (13.4)	
	55-59	131.4 (12.7)	110.0 (12.4)	
	60-69	327.5 (31.6)	264.8 (29.9)	
	70-81	140.8 (13.6)	77.7 (8.8)	
Race (%)	White	473.6 (45.7)	417.4 (47.1)	0.096
	Indigenous	43.4 (4.2)	34.3 (3.9)	
	East & South & Southeast Asian	464.1 (44.8)	376.6 (42.5)	
	Other	52.1 (5.0)	57.0 (6.4)	
	missing	2.0 (0.2)	0.0 (0.0)	
Recipient BMI, kg/m2 (%)	<25	327.1 (31.6)	264.4 (29.9)	0.055
	25-29	362.9 (35.1)	306.0 (34.6)	
	≥30	338.5 (32.7)	310.4 (35.1)	
	missing	6.7 (0.6)	4.6 (0.5)	
HCV (%)	Yes	20.9 (2.0)	9.5 (1.1)	0.077
Donor Variables				
Sex (%)	Male	661.9 (63.9)	631.8 (71.4)	0.159
	Female	373.3 (36.1)	253.5 (28.6)	
Age (%)	12-19	56.4 (5.4)	52.0 (5.9)	0.170
	20-29	158.8 (15.3)	157.6 (17.8)	
	30-35	134.6 (13.0)	121.4 (13.7)	
	36-39	86.2 (8.3)	74.2 (8.4)	
	40-49	187.7 (18.1)	192.0 (21.7)	
	50-59	228.6 (22.1)	174.5 (19.7)	
	60-70	182.9 (17.7)	113.6 (12.8)	
Race (%)	White	816.5 (78.9)	709.1 (80.1)	0.297
	Indigenous	72.9 (7.0)	56.0 (6.3)	
	East & South & Southeast Asian	102.6 (9.9)	37.4 (4.2)	
	Other	43.2 (4.2)	82.8 (9.3)	
BMI, kg/m2 (%)	<25	397.8 (38.4)	368.7 (41.6)	0.131
	25-29	375.9 (36.3)	336.7 (38.0)	
	≥30	259.5 (25.1)	179.9 (20.3)	
	missing	2.0 (0.2)	0.0 (0.0)	
Creatinine, mg/dL (%)	<1.5	862.8 (83.3)	755.3 (85.3)	0.080
	≥1.5	170.4 (16.5)	130.0 (14.7)	
	missing	2.0 (0.2)	0.0 (0.0)	
History of hypertension (%)	Yes	205.4 (19.8)	145.4 (16.4)	0.089
History of diabetes (%)	Yes	69.2 (6.7)	40.6 (4.6)	0.091
HCV (%)	Yes	44.9 (4.3)	31.0 (3.5)	0.043
Deceased donor type (%)	NDD	765.8 (74.0)	627.8 (70.9)	0.069
	DCD	269.4 (26.0)	257.5 (29.1)	

Characteristics	Level	Non-ODD (Weighted N = 1035.2)	ODD (Weighted N = 885.3)	SMD
Transplant Variables				
Number of HLA mismatches (%)	0-2	75.1 (7.3)	54.3 (6.1)	0.047
	3-5	816.7 (78.9)	710.1 (80.2)	
	6	140.5 (13.6)	118.9 (13.4)	
	missing	2.9 (0.3)	2.0 (0.2)	
CIT, hours (%)	<12	696.7 (67.3)	595.8 (67.3)	0.034
	≥12	319.0 (30.8)	276.7 (31.3)	
	missing	19.4 (1.9)	12.8 (1.4)	
Dialysis duration prior to transplant, years (%)	<1	36.4 (3.5)	24.9 (2.8)	0.057
	1-3	436.4 (42.2)	390.8 (44.1)	
	>3	554.6 (53.6)	464.6 (52.5)	
	missing	7.7 (0.7)	5.0 (0.6)	
Transplant number (%)	first transplant	938.7 (90.7)	798.2 (90.2)	0.018

ODD, overdosed deceased donor; BMI, body mass index; HCV, hepatitis C virus; HLA, human leukocyte antigen; NDD, neurologically determination of death; DCD, donation after circulatory death; CIT, cold ischemic time; SMD, standardized mean difference.

The univariate Cox model showed that recipients of ODD kidneys had significantly decreased risk of ACGL (HR: 0.23, 95% CI: 0.10 – 0.53, $p < 0.001$) compared to recipients of non-ODD kidneys. After IPT weighting, the risk of ACGL did not greatly change for recipients of ODD kidneys (HR: 0.25, 95% CI: 0.10 – 0.62, $p = 0.003$) and after multivariable adjustment in the IPTW Cox model, ODD status was still significantly protective (HR: 0.30, 95% CI: 0.12 – 0.77, $p = 0.012$) (Table 16). The proportional hazards assumption was visually adequate in all log -log survival plots.

Table 16. Three models examining the relationship between overdose as a cause of donor death and recipient all cause graft loss.

	Model 1: Univariate Cox model		Model 2: Univariate IPTW Cox model		Model 3: Multivariable IPTW Cox model	
Variable	**HR (95% CI)**	**p**	**HR (95% CI)**	**p**	**HR (95% CI)**	**p**
Donor overdose status						
ODD	0.23 (0.10, 0.53)	<0.001	0.25 (0.10, 0.62)	0.003	0.30 (0.12, 0.77)	0.012

ODD, overdosed deceased donors; IPTW, inverse probability of treatment weight; HR, hazard ratio; CI, confidence interval.

Model 2 is weight adjusted for recipient sex, age, race, BMI, HCV; donor overdose status, sex, age, race, BMI, HCV, last measured creatinine, history of hypertension, history of diabetes, deceased donor type; transplant HLA mismatch, organ cold ischemia time, transplant dialysis duration prior to transplant, and transplant number.

Model 3 is weight adjusted for all variables mentioned in Model 2 as well as adjusted for as covariates in the IPTW Cox proportional hazards model for recipient age; donor sex, age, race, and BMI.

7.2.2.2 Secondary outcomes

The probability of not experiencing death with function for ODD kidney transplantation was 98% at 1-, 3-, and 5-year post-transplant. Only five recipients of an ODD kidney experienced death with function. The probability of not experiencing death with function for non-ODD kidney transplantation was 97%, 93%, and 89% at 1-, 3-, and 5-year post-transplant. Recipients of ODD transplantation were significantly less likely to have experienced death with function (log-rank, p = 0.005) in the first 5-years of follow up (Figure 16).

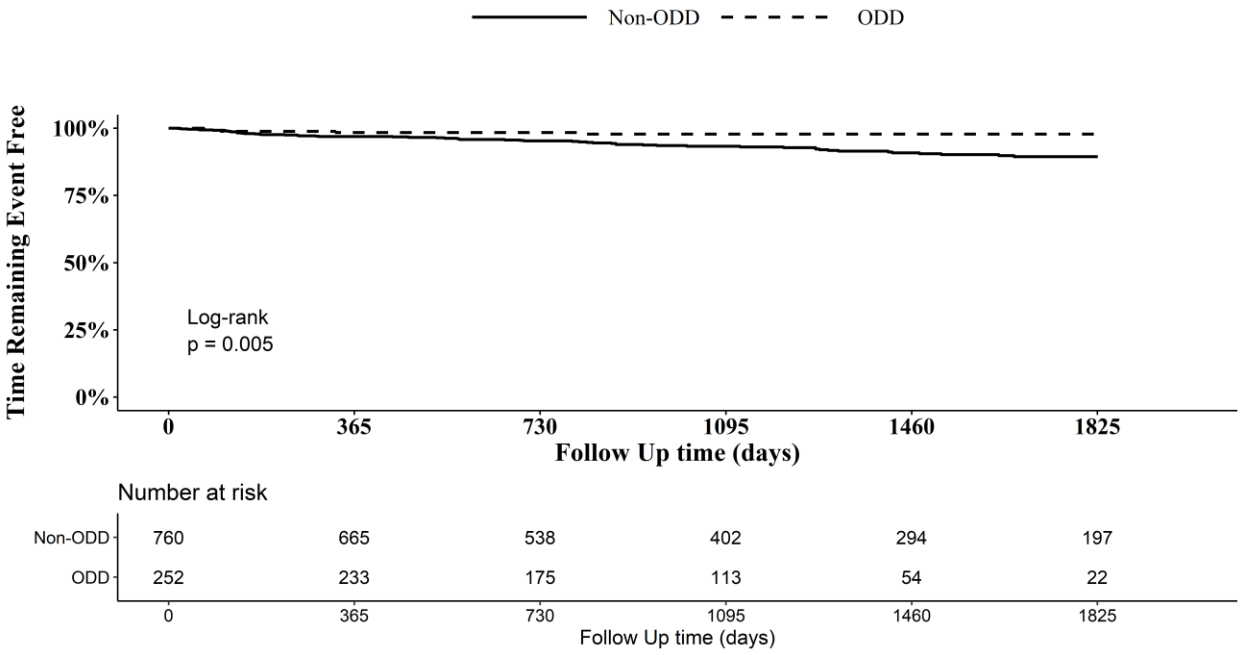

Figure 16. 5-year Kaplan Meier curves and corresponding risk tables for death with function among kidney transplants compared by donor overdose death status.

The probability of not experiencing DCGL for ODD kidney transplantation was 99.6% at 1-, 3-, and 5-year post-transplant. Only one recipient of an ODD kidney in the analytic sample experienced DCGL. The probability of not experiencing DCGL for non-ODD kidney transplantation was 97%, 95%, and 93% at 1-, 3-, and 5-year post-transplant. Recipients of ODD

transplantation were significantly less likely to have experienced DCGL (log-rank, p = 0.0012) in the first 5-years of follow up (Figure 17).

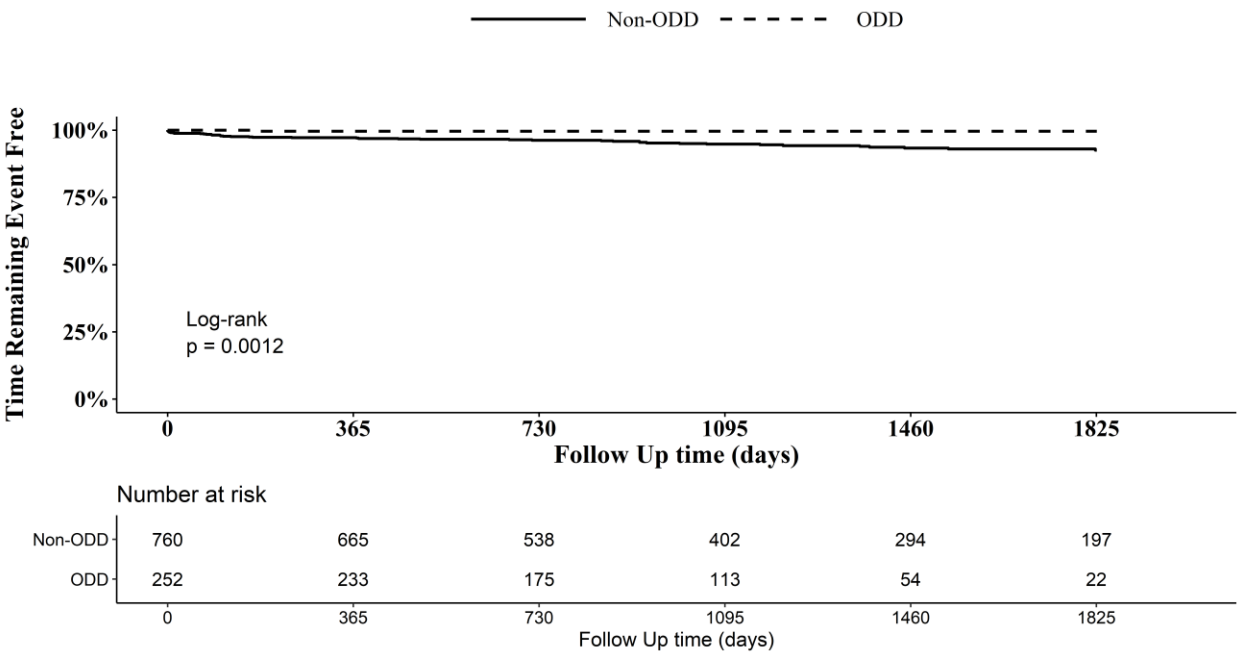

Figure 17. 5-year Kaplan Meier curves and corresponding risk tables for death censored graft loss among kidney transplants compared by donor overdose death status.

The probability of experiencing acute rejection for ODD kidney transplantation was 8%, 9%, and 11% at 1-, 3-, and 5-year post-transplant. The probability of acute rejection for non-ODD kidney transplantation was 8%, 10%, and 11% at 1-, 3-, and 5-years post-transplant. There was no significant difference (log-rank, p = 0.7) of acute rejection in the first 5-years of follow up between donor overdose groups (Figure 18).

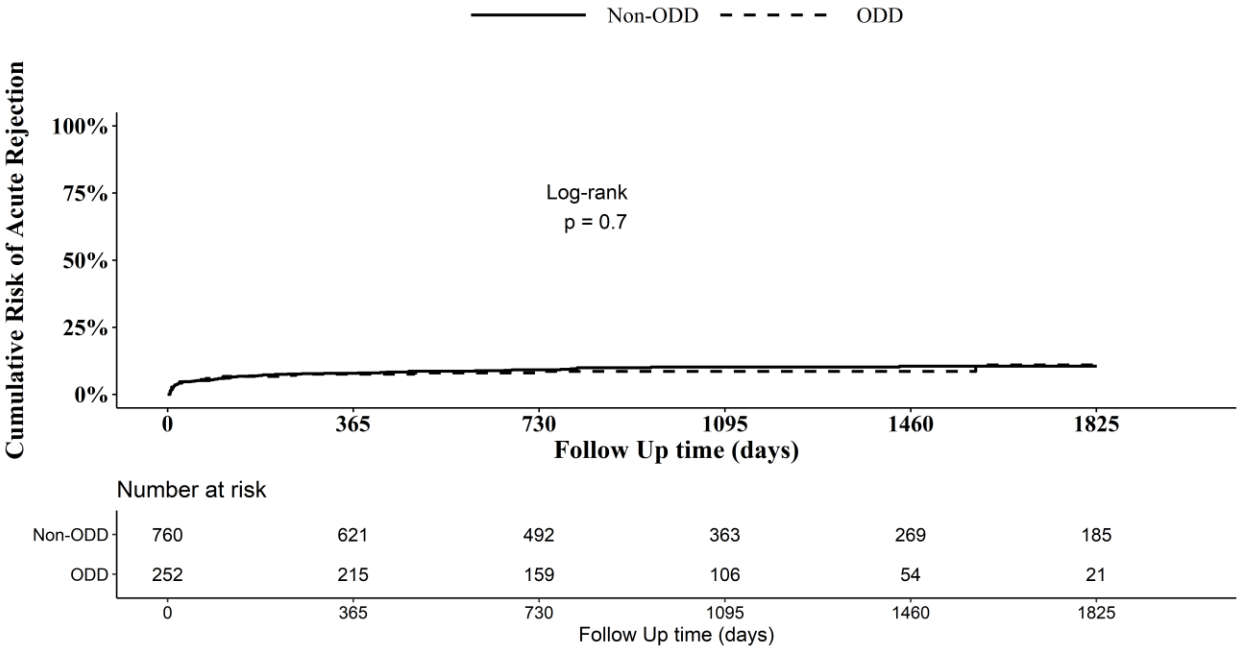

Figure 18. 5-year cumulative incidence curves and corresponding risk tables for first episode of acute rejection among kidney transplants compared by donor overdose death status.

7.3 Discussion

Kidney transplantation from ODDs increased over the study period, reaching a high in 2017 and 2018 then slightly decreasing in 2019. ODD kidney utilization trends mirrored overdosed donation trends because more than 90% of ODDs and non-ODDs donated at least one kidney in the study period. Naturally this results in kidney ODDs accurately representing the ODD population; more likely to be young, white, and male, with less comorbidities but higher last measured creatinine and a higher prevalence of HCV. Therefore, outcomes are more representative of the current ODD population; compared to recipients of non-ODD kidneys, recipients of ODD kidney transplantation were significantly less likely to experience ACGL, death with function, and DCGL at five-years post-transplant. Adjusted for donor and recipient characteristics, donor overdose status reduced risk of ACGL for kidney transplant recipients at 3-

years post-transplant. There was no difference in the probabilities of experiencing first episode of acute rejection at five-years post-transplant between donor overdose groups.

Literature comparing kidney transplant recipient survival between donor overdose status groups is limited with Durand et al. and Wanis et al. being the most relevant. Durand et al. studied the national SRTR database between 2000-2017 using similar IPTW methodology with standardized risk differences to examine 5-year survival rates for recipients of ODD kidney transplantation and found no increased risk of death for recipients of ODD kidneys compared to trauma death donor (-3.1% [95% CI, −8.0% to 0.02%]) and medical death donor (2.1% [95% CI, −2.8% to 5.3%]) kidney transplant recipients with a unadjusted 5-year survival rate of 86.3% and a unadjusted 5-year death-censored graft survival rate of 88.8% for recipients of ODD kidneys (46). ODDs studied by Durand et al. who donated a kidney were representative of the US national ODD population as most donors donated at least one kidney; ODDs were more likely to be from the Northeast and Midwest states, were more likely to undergo kidney biopsy and were more likely to donate after circulatory death. Similar to the BC ODD population, ODDs in the US were more likely to be younger, white, have higher last measured creatinine, and were less likely to have a history of diabetes or hypertension (46). Wanis et al. also studied the national SRTR database but only looked at DCD donors between 2006-2016 by estimating graft failure cumulative incidence curves standardized by baseline recipient, donor, and transplant characteristics finding no difference in graft failure between ODD and non-ODD kidney transplant recipients. Wanis et al. reported a 5-year risk of graft failure of 21.7% among ODD kidney transplant recipients (49). ODDs studied by Wanis et al. who donated a kidney were more likely to have a history of cocaine or other drug use and similar to the BC ODD population were

more likely to be younger with less comorbidities such as diabetes or hypertension. These two national studies in the US align with our hypothesis that ODD status does not affect recipient kidney transplant graft survival. However, adjusted for donor and recipient factors, ODD kidneys in BC showed a significant protective effect both in unadjusted and adjusted analyses compared to non-ODD kidneys. This means ODD kidneys were shown to improve graft survival. This is likely attributable to different donor and recipient demographics in BC compared to the US (expanded on in **section 8.2**). We are cautious in concluding that ODD kidneys offer significantly improved graft survival compared to non-ODD kidneys because although this was found to be statistically significant, we do not want to shift preferential treatment towards one type of donor. Especially given the crude rate of survival for recipients from both donor groups is high at 5-years post-transplant. There is also a greater probability that ODD demographics will shift drastically in the coming years (increasing/decreasing in number, getting older) compared to non-ODDs. Lastly, sample size differences exist between our kidney analytical sample and the national US analysis. A national Canadian study on ODD kidney quality would be more comparable and may yield different results.

There were no kidney specific analyses limitations. The kidney transplant group incorporated a large enough sample size as well as a reasonable number of outcomes. A strength to note is that although we used a robust estimate of coefficient standard errors to account for correlation between donors, we still arrived at a significantly protective hazard ratio for donor overdose status.

ODD kidney transplantation leads to high survival rates in the first 5-years post-transplant and has been shown to reduce risk of ACGL compared to non-ODD kidney transplantation. This analytical sample compared to other organ groups is comprised of a greater number of older ODDs but, older ODDs are still underrepresented compared to older non-ODDs. In the interest of reducing the waitlist, given current rates of survival, transplantation of ODD kidneys is safe.

Chapter 8: Conclusion

8.1 Summary

A public health emergency was called in 2016 following a precipitous rise in individuals dying of illicit drug overdose, primarily driven by an increased circulation of fentanyl. This resulted in increased organ donation from deceased individuals who died after drug overdose. This study examined how overdosed donors contributed to the deceased donor pool between 2013-2019 in BC and determined whether organs from these overdosed donors were safe for transplant recipients. Specifically, the objectives of this thesis were to 1) explore donor characteristics by donor cause of death (overdosed and non-overdosed), and 2) examine patient outcomes after receipt of an organ from an overdosed deceased donor, relative to outcomes after non-ODD transplantation

Chapters three to seven were written with the intent of publishing elsewhere. Strengths and limitations specific to each chapter have been discussed throughout the text. This concluding chapter aims to summarize key findings, identify common strengths and limitations, and describe how interpretation of results fit into the current landscape of overdose transplantation research.

8.2 Findings

Between 2013-2019, 605 local deceased donors donated a solid organ to 1,795 transplant recipients resulting in 1,857 transplantations in BC. During this period, we observed a three-times increase in annual ODD donation from 2017-2019 compared to 2013-2016. Survival at 5-years post-transplant for ODD double-lung (80%), heart (87%), and liver (84%) transplant recipients were high. Accounting for differences in donor and recipient characteristics, at 3-years

post-transplant donor overdose status did not significantly affect recipient survival for double-lung and liver analyses. Heart analyses was deemed to be inconclusive due to small sample size and few outcomes.

For ODD kidney transplant recipients, 97% survived and retained graft function at 5-years post-transplant. Accounting for differences in donor and recipient characteristics, at 3-years post-transplant donor overdose status was found to significantly reduce the risk of ACGL for kidney transplant recipients. BC kidney analysis results are notable because although the kidney organ group had the largest sample of transplantations compared to other organ groups, only 6 ODD kidney transplant recipients experienced ACGL (5 death with function, 1 DCGL) at 5-years post-transplant.

Similar results were found from the largest national registry study of overdose donor organ transplants in the US showing non-significance of donor overdose status on recipient survival across lung, heart, liver, and kidney organ groups (46). For comparability of kidney outcomes with Durand et al. who measured recipient death, we looked at the probability of not experiencing death with function which was also very high at 98%, 5-years post-transplant. Durand et al. found that ODD kidneys significantly reduced risk of recipient DCGL and only significantly reduced risk of recipient death in sensitivity analyses (46). No comparable studies analyzed ACGL as an outcome measurement for kidney transplantation. Compared to Durand et al., it is definitively clear that BC ODD kidney recipients had better outcomes compared to the US. These results could be attributable to multiple reasons. First, in BC, deceased donor kidneys are allocated to recipients based on age matching. For example, organs from donors 35 years or

younger are prioritized for patients 18-54 years of age, organs from donors aged 36-59 years are allocated irrespective of age to all patients on the waiting list, and donors 60 years of age or older or considered ECDs are allocated to recipients 60 years of age or older (37). The median age of individuals who died of overdose is 35 years and 53.2% of ODD kidneys in this study were ≤ 35 years whereas only 2.4% were aged ≥ 60 years. Prior to December 2014, kidney allocation in the US was age based but after December 2014 the US started using an improved kidney allocation system that focused on extending longevity by matching based on KDPI and expanding transplant opportunities for highly sensitized patients (high percentage panel reactive antibody) and certain demographic groups with long dialysis exposure prior to transplantation (94). The new kidney allocation system was implemented at a crucial period of time in the US when ODD utilization was increasing; after implementation, ODD kidneys may not have been matched to younger recipients in similar proportions compared to the BC age matching system. Second, there are also donor and recipient population differences between the Durand et al. study and our BC study; in BC there were fewer female ODDs and very few were African American. ODDs in BC also had lower prevalence of HCV, diabetes, and hypertension compared to ODDs in the US (46). For kidney transplant recipients, there were far fewer African American transplant recipients in BC (< 1%) compared to the US (> 25%) and lower prevalence of HCV among kidney transplant recipients in BC (approximately 2%) compared to the US (approximately 5%) (95). Lastly improvement in healthcare over time could also play a role; this was highlighted in the discussion of double-lung and liver analyses and is a factor in the entirety of this study as we started in 2013 whereas some US studies date back to the year 2000.

8.3 ODD acceptance: pros and cons of transplantation of organs from an ODD

8.3.1 ODD organ utilization

There is possible hesitancy from transplant professionals and transplant recipients when it comes to using and accepting ODD organs as they are more likely to be labeled “exceptional distribution” in BC (equivalent to “increased risk” in the US). In the US, a study of the SRTR between January 2005 to February 2009 as well as a study of the SRTR between January 2010 and December 2013 found that the increased risk donor (IRD) label negatively affected organ utilization, in particular kidneys being more often discarded when labeled as IRD despite the low risk of disease transmission (96–98). The use of exceptional distribution donors likely also varies across Canada however, there is a lack of primary data to confirm this. Kumar et al. conducted a national survey of Canadian transplant centers to gauge attitudes and willingness to use exceptional distribution donor organs. The study found that variation in attitudes and practice do exist and could be improved by increased availability of nucleic acid testing (NAT) to screen donors for HCV, HBV, or HIV in a timely manner. Unfortunately, it was found that fewer than half of Canadian transplant programs had access to real-time (results available prior to transplantation) nucleic acid testing (99).

8.3.2 Transplant recipient hesitancy

From a recipient’s perspective, Reese et al. found, through a small sample simulation survey, that regardless of organ quality, some patients would never accept organs with perceived increased risk (100). Donor labels whether it be exceptional distribution, IRD, HCV positive, or ECD may not matter as much as the perception of the label. Another study by Volk et al. found that a sizeable minority of patients would rather stay on the waiting list when given the option to accept

a “lower quality” liver that improves quality of life even if transplantation carried the same risk of death as staying on the waiting list. However, Volk et al. also found that when patients were presented with organs of differing survivability; feedback about organ availability and framing survival in terms of “average” organ quality rather than the “best” organ quality obtainable can change patient perceptions and increase their risk tolerance (101). Even with patient education, the BC patient population is not immune to this effect and a minority could reject ODD organs or exceptional distribution donor organs as they view the organs as being “lower quality” with concerns of bloodborne disease transmission.

8.3.3 HCV transmission

HIV positivity was not present in any donor or recipients in our analytic samples and only two donors were HBV positive. HCV transmission is the primary concern for disease transmission in BC at this time. The number of HCV infected donors in this study was very few (N = 22 (3.6%)), but this proportion was 3.5-fold higher in ODDs (8.2%) vs non-ODDs (2.2%). As more ODDs are used, the potential for HCV infected donors, and possible HCV transmission from donor to recipient will require ongoing monitoring. Donor HCV transmission to an HCV negative recipient is rare and is usually due to a donor’s recent infection resulting in a window period of undetectable antibodies by NAT. In the scenario that HCV transmission occurs, the risk of HCV infection for HCV-negative recipients is mitigated by the growing use of direct-acting antiviral (DAA) therapy with early small sample studies showing successful suppression of HCV viral load in lung, heart (102,103), and kidney transplant recipients (104–106). Although less common, for liver transplant recipients (HCV positive donor livers are usually transplanted to HCV positive recipients) DAA therapy is also a viable treatment (60,107). Some have cautioned

that these studies are small scale, have short-term follow up, and assume sufficient access to DAA therapy (108). Also, we have yet to understand the benefits of preemptive vs post-transplant DAA initiation and the possibility of infection relapse (109). However, given the rising number of ODDs and therefore the increased (but low) potential of HCV transmission for HCV negative recipients, DAA is a highly effective and safe solution to achieve sustained virologic response (110). BC does currently match NAT positive HCV donors with select transplant recipients.

8.3.4 Survival on the waitlist

A final consideration for the acceptance of ODD transplantation, is the risk of death while on the transplant wait list. Cox et al. showed that recipients of IRD lungs had significantly better cumulative survival when compared with recipients who refused IRD lung transplantation. After 1 year, 40% of studied individuals who refused IRD lung transplantation were in a similar or worse position (10.6% underwent IRD lung transplantation at a later date, 13.8% died or were removed from the waiting list because they were too sick to undergo transplantation, and 14.9% were still awaiting transplantation) (111). A recent study of the SRTR between 2010-2016 found that only 31% of patients who declined an IRD kidney ended up receiving a non-IRD kidney transplant, and patients who accepted an IRD kidney had a 48% reduced risk of death (112). UNOS data analyzed between 2007-2017 also showed survival benefit for those who accepted IRD hearts compared to those who did not accept IRD hearts. One year follow up of those who declined IRD hearts saw 12.4% requiring IRD heart transplantation, 7.9% died or withdrew due to inability to undergo transplantation, and 21.1% were still awaiting heart transplantation (113).

8.4 Strengths and limitations

Limitations to specific organ analyses were discussed in each organ chapter. Here we discuss limitations for general methods applicable to all organ groups in this study.

Again, the small sample size and few numbers of outcomes for some organ groups was the primary reason we incorporated IPTW methodology to adequately adjust for all confounders of interest without specifically adjusting for these variables in a multivariable regression model. The IPTW methodology requires assignment of weights that result in weighted samples sizes larger than the original sample. If the distribution of donor and recipient characteristics was highly heterogeneous within exposure groups, then large weights were assigned to observations that did not look like they belonged in either the exposed (ODD) or unexposed (non-ODD) groups. This occurred more often for ODD transplantations in our analyses because ODD transplantations always had a smaller sample resulting in a greater probability that outlier ODD characteristics would yield larger weights. These inflated weights in regression analyses can result in greater type I error (114). This issue was of concern for liver and kidney analyses. To correct for this, in sensitivity analyses, stabilized weights which achieve the same effect of balancing while retaining sample size were calculated for these two organ groups and regression results were produced (Table C - 1, Table C - 2). Results and conclusions from these sensitivity analyses were similar to primary analyses for both liver and kidney.

Of note for double-lung and liver analyses, this potential limitation was a strength. Our hypotheses were that ODD status would have no effect on recipient survival. Given we arrived at non-significant hazard ratios for these two organ groups despite using inflated IPT weights with

greater probability of type I error, we can feel more confident that donor overdose status was not associated with recipient transplant survival.

Other limitations of this study relate to the nature of registry data; we may be missing unmeasured confounders and observational data leaves us susceptible to selection bias, specifically collider bias related to the criteria that organ donation is only possible if an individual died in hospital. Most individuals who die as a result of overdose do not die in hospital; approximately 80% to 85% of overdosed deaths in BC occur in private (driveways, garages, trailer homes, decedent's own or another's residence) or other (hotels, motels, single room occupancy, shelters, social/supportive housing) residences (31) which means many overdosed deceased individuals were isolated at time of death and did not have the opportunity to be transferred to hospital in a timely manner. In Canada, for those who die in hospital, there exists strict selection criteria (e.g., age restriction, cause of death compatible with donation, no contraindications to donation, death on mechanical ventilation, and donor consent) resulting in estimates that only 7.7% of all in-hospital deaths are eligible for organ donation (17). Therefore, the subset of potential organ donors is not representative of the general deceased population. Given the extreme selection, we do not believe that the interpretation of results are biased, but are restricted to those who meet strict selection criteria, and cannot be extrapolated to all individuals who die as a result of overdose.

8.5 Considerations moving forward

In the year after the study, 2020, the COVID-19 pandemic resulted in national lockdowns and disruptions to healthcare. Despite disruptions, in 2020, BC transplant was able to process a high

number of deceased donor transplantations on par with previous years (N = 370) (115). Although we have yet to obtain data on ODDs in 2020, we expect ODD counts to be similar to 2019 if not greater due to the fact that the pandemic has exacerbated the opioid crisis. In 2020, the number of overdose deaths in Canada increased 71% from 3,658 in 2019 to 6,265 in 2020 with BC seeing a similar 72% increase from 1,015 in 2019 to 1,746 in 2020 (29). There has been a subtle shift in increasing proportions of individuals dying of illicit drug overdose from older age groups (31). As we have found, ODD organs have been proven safe for transplantation due to ODDs currently being mostly younger with fewer comorbidities except for a slight increase in HCV prevalence. As more overdose death individuals become donors, we need to assess future risks of possible ODD demographic shifts to older age groups and understand that binary classifications such as ODD status or exceptional distribution labels do not fully describe donor quality, nor were they created for such a purpose. All the while, we need to ensure risk is properly communicated and understood by transplant recipients.

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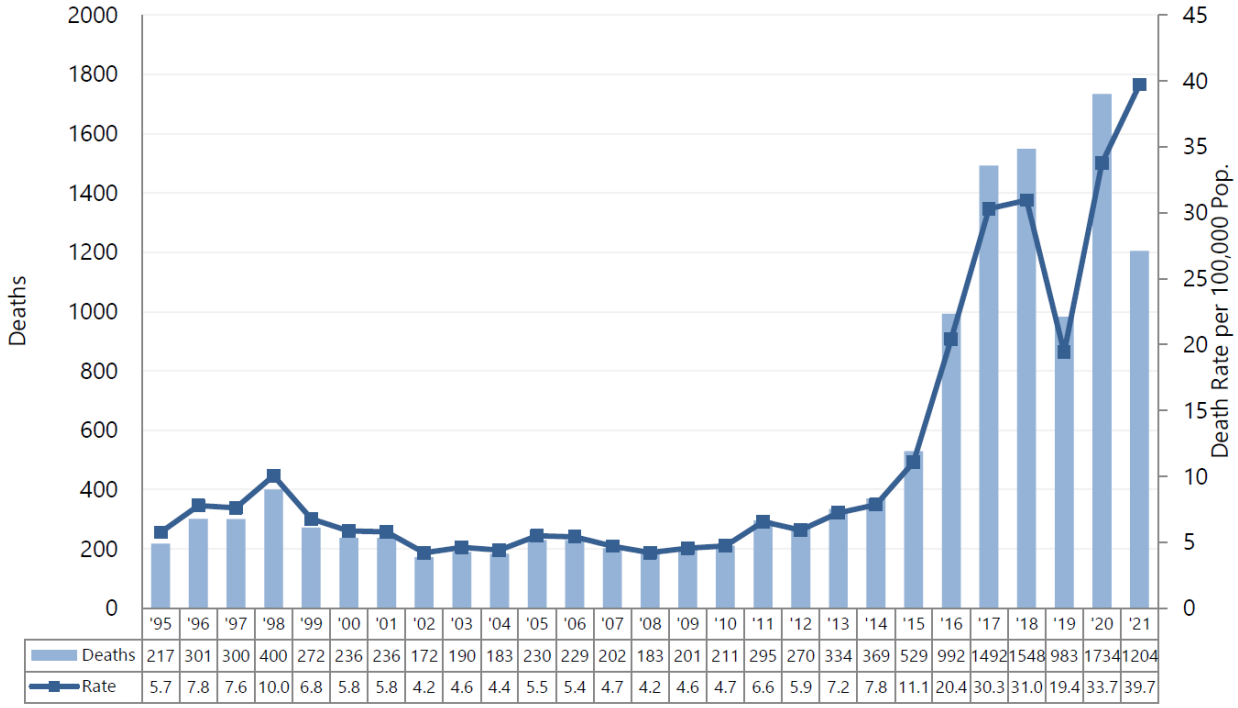
Appendices

Appendix A Supplementary materials from British Columbia Coroners report



	'95	'96	'97	'98	'99	'00	'01	'02	'03	'04	'05	'06	'07	'08	'09	'10	'11	'12	'13	'14	'15	'16	'17	'18	'19	'20	'21
Deaths	217	301	300	400	272	236	236	172	190	183	230	229	202	183	201	211	295	270	334	369	529	992	1492	1548	983	1734	1204
Rate	5.7	7.8	7.6	10.0	6.8	5.8	5.8	4.2	4.6	4.4	5.5	5.4	4.7	4.2	4.6	4.7	6.6	5.9	7.2	7.8	11.1	20.4	30.3	31.0	19.4	33.7	39.7

Figure A - 1. Illicit drug toxicity deaths and death rate per 100,000 population. This figure is from the BC Coroners Illicit Drug Toxicity Deaths in BC January 1, 2011 – July 31, 2021 report **(31)**.

Appendix B Cox proportional hazards model diagnostics

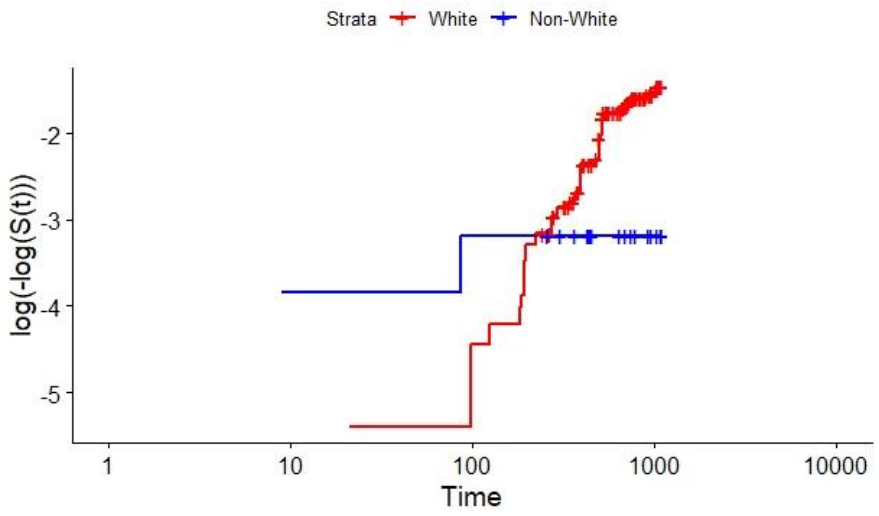


Figure B - 1. Double-lung analysis, log -log plot for recipient race.

Appendix C Sensitivity analysis results for liver and kidney transplantations using stabilized weights

C.1 Method for stabilized weights

Methods to estimate propensity scores, check for balance, and produce regression coefficients were not changed. Only the calculation of weights was altered in these sensitivity analyses. Xu et al. define stabilized weights as a method to reduce the weights of either those treated subjects with low propensity scores or those untreated subjects with high propensity scores (114). Stabilized weights involve an additional component; the probability of treatment without considering other covariates (p) defined as the number of subjects treated (ODD) divided by the total sample (ODD + non-ODD). Assuming Z is a dichotomous value representing the treatment received with 1 representing ODD and 0 representing non-ODD and *e* representing the propensity score, the stabilized weights (sw) can be derived via the equation:

$$sw = \frac{Zp}{e} + \frac{(1-Z)(1-p)}{1-e}$$

C.2 Results

Table C - 1. Three models examining the relationship between overdose as a cause of donor death and liver recipient death.

	Model 1: Univariate Cox model		Model 2: Univariate Stabilized Weighted Cox model		Model 3: Multivariable Stabilized Weighted Cox model	
Variable	**HR (95% CI)**	**p**	**HR (95% CI)**	**p**	**HR (95% CI)**	**p**
Donor overdose status						
ODD	0.95 (0.50, 1.82)	0.886	0.96 (0.45, 2.05)	0.914	0.89 (0.37, 2.14)	0.787

ODD, overdosed deceased donors; IPTW, inverse probability of treatment weight; HR, hazard ratio; CI, confidence interval.

Weights are calculated as stabilized weights.

Model 2 is weight adjusted for recipient sex, age, race, HCV; donor overdose status, sex, age, race, HCV, last measured creatinine, history of hypertension, history of diabetes, deceased donor type, and transplant number.

Model 3 is weight adjusted for all variables mentioned in Model 2 as well as adjusted for as covariates in the IPTW Cox proportional hazards model for recipient sex, race; donor age, deceased donor type, and transplant number.

Table C - 2. Three models examining the relationship between overdose as a cause of donor death and kidney recipient all cause graft loss.

	Model 1: Univariate Cox model		Model 2: Univariate Stabilized Weight Cox model		Model 3: Multivariable Stabilized Weight Cox model	
Variable	**HR (95% CI)**	**p**	**HR (95% CI)**	**p**	**HR (95% CI)**	**p**
Donor overdose status						
ODD	0.23 (0.10, 0.53)	<0.001	0.25 (0.10, 0.62)	0.003	0.30 (0.11, 0.79)	0.015

ODD, overdosed deceased donors; IPTW, inverse probability of treatment weight; HR, hazard ratio; CI, confidence interval.

Weights are calculated as stabilized weights.

Model 2 is weight adjusted for recipient sex, age, race, BMI, HCV; donor overdose status, sex, age, race, BMI, HCV, last measured creatinine, history of hypertension, history of diabetes, deceased donor type; transplant HLA mismatch, organ cold ischemia time, transplant dialysis duration prior to transplant, and transplant number.

Model 3 is weight adjusted for all variables mentioned in Model 2 as well as adjusted for as covariates in the IPTW Cox proportional hazards model for recipient age; donor sex, age, race, and BMI.

Appendix D Donor age distribution 2013-2019

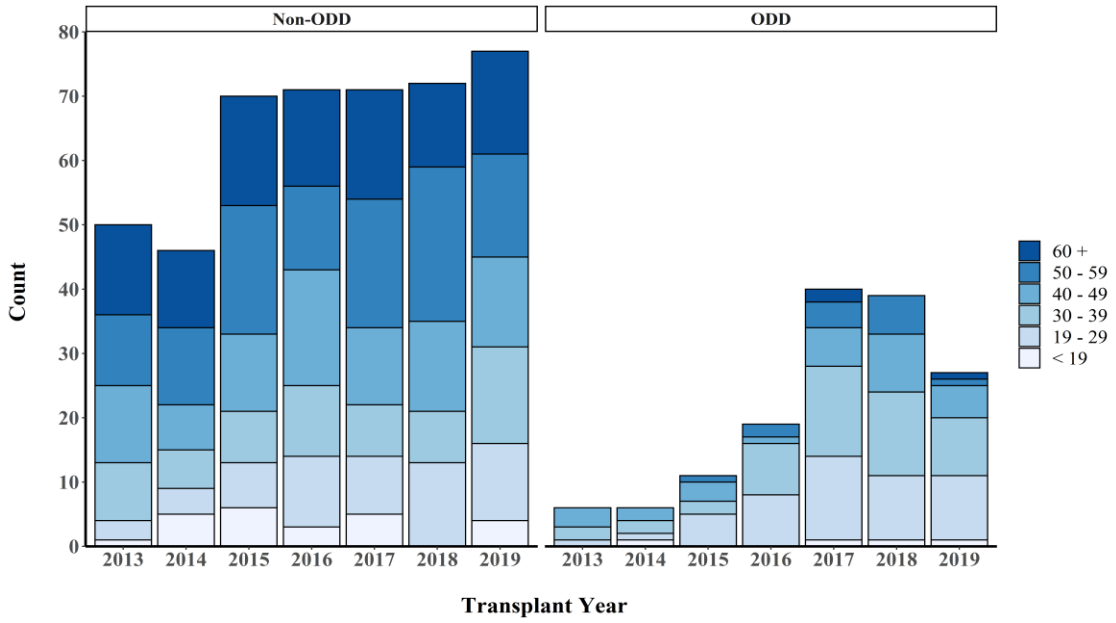


Figure D - 1. ODD and non-ODD count comparison between 2013-2019.

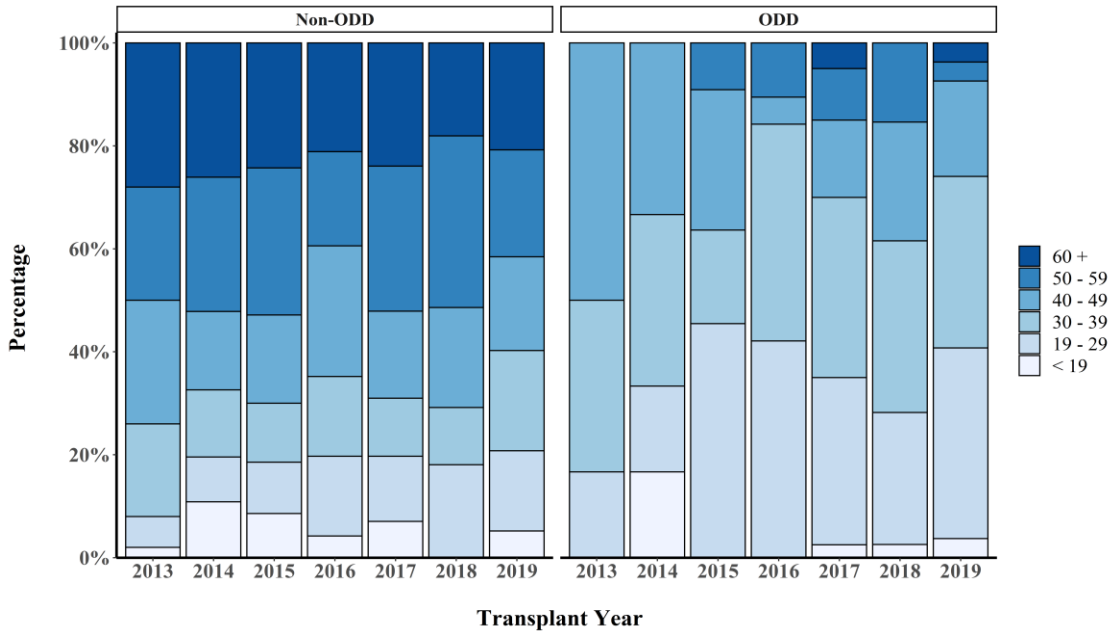


Figure D - 2. ODD and non-ODD percentage comparison between 2013-2019.