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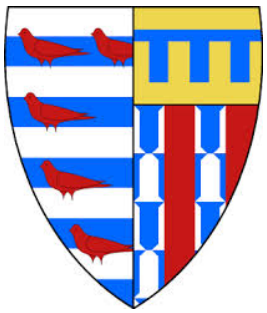
Maximising organ donation and transplantation through the use of organs from increased risk donors



Pembroke College

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This dissertation is submitted for the degree of Doctor of Philosophy

Submission date:

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Supervisors: Professor Christopher Watson, Professor J A Bradley, Professor James Neuberger

Declaration

- This dissertation is the result of my own work and includes nothing which is the outcome of work done in collaboration except as declared in the Preface and specified in the text.
- It is not substantially the same as any that I have submitted, or, is being concurrently submitted for a degree or diploma or other qualification at the University of Cambridge or any other University or similar institution except as declared in the Preface and specified in the text. I further state that no substantial part of my dissertation has already been submitted, or, is being concurrently submitted for any such degree, diploma or other qualification at the University of Cambridge or any other University or similar institution except as declared in the Preface and specified in the text.
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Maximising organ donation and transplantation through the use of organs from increased risk donors

Patrick Bernard Trotter

Abstract

Organ transplantation remains the best treatment for many patients with end organ disease. However, there is a discrepancy between organ supply and demand. Many donor organs are not used for transplantation because of risk attributes in the deceased donor ranging from infectious risks to specific risks associated with the cause of death.

The aims of this thesis were to identify the number of deceased donors with risk attributes and then quantify the risks associated with using organs from such donors. This information was then used to provide evidence to the transplant community on which to base their decisions on using organs from such donors.

This thesis used data in the UK Transplant Registry, which prospectively collects data on the clinical characteristics and follow-up of all donors and transplant recipients in the UK, and the Potential Donor Audit, which is a prospectively populated registry including all patients who die in UK critical care units of donation age.

The main findings of this thesis were that there are a large number of deceased donors with risk attributes, in particular donors with increased risk behaviour for blood borne viral disease or with hepatitis C virus infection, whose organs are currently not used for transplantation, but that could safely be used. The thesis also describes that the transmission of meningitis/encephalitis from deceased donors to transplant recipients is a rare but serious complication of transplantation, but that transplantation of usually excellent organs from such donors should not be contraindicated. Different transplant centres display marked variations in practice in using organs from donors with different risk attributes, but centres that display greater risk appetite in using organs from higher risk donors do not have worse transplant outcomes compared to centres with lower risk appetites.

Transplantation of organs from higher risk donors can result in excellent transplant outcomes. Wide variations in practice are seen across the UK, and to address this the UK aide memoire has been developed.

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Publications from this work

1. Trotter et al. Transplantation of Organs from Deceased Donors with Meningitis and Encephalitis: a UK Registry Analysis. Transplant Infectious Disease. December 2016; 18(6):862-871.

2. Trotter et al. Donors with Immune Thrombocytopenia: Do they pose a risk to transplant recipients? American Journal of Transplantation. March 2017;17(3):796-802.

3. Trotter et al. Deceased organ donors with a history of increased risk behaviour for the transmission of blood-borne viral infection: The UK experience. Transplantation. July 2017; 101(7):1679-1689.

4. Trotter et al. Use of organs from hepatitis C virus positive donors for uninfected recipients: a potential cost-effective approach to save lives? Transplantation. April 2018:102(4):664-672.

5. Trotter et al. Transplantation of kidneys from DCD and DBD donors who died after ligature asphyxiation: the UK experience. American Journal of Transplantation. June 2018. Epub ahead of print.

6. J. Neuberger, P. Trotter, R. Stratton. Organ Transplantation Rates in the UK. British Medical Journal. November 2017; 359:j5218.

7. O'Keefe et al. Mid- and Long-Term Health Risks in Living Kidney Donors: A Systematic Review and Meta-analysis. Annals of Internal Medicine. February 2018:168(4):276-284.

Awards from this work

1. Transplantation Society Young Investigators Award: 27th International Congress of the Transplantation Society, Madrid 2018.

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3. Kidney Research UK educational bursary, September 2017.

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3. Shortlisted for Williams Prize, Society of Academic Surgeons, January 2017

Abbreviations

AMR, Antimicrobial Resistance

AKIN, Acute Kidney Injury Network

BBV, Blood Borne Virus/Viral Disease

BMI, Body Mass Index

CIT, Cold Ischaemic Time

CLOD, Clinical lead in Organ Donation

CMV, Cytomegalovirus

CO, Carbon Monoxide

cRF, Calculated reaction frequency

DAKT, Dual Adult Kidney Transplant

DBD, Donation after Brain Stem Death

DCD, Donation after Circulatory Death

DGF, Delayed Graft Function

DLI, UK Donor Liver Index

eGFR, estimated glomerular filtration rate

EBV, Epstein-Barr Virus

GVHD, Graft Versus Host Disease

GP, Glycoprotein

HBsAg, Hepatitis B Virus Surface Antigen

HBV, Hepatitis B Virus

HCV, Hepatitis C Virus

HCVpos, Hepatitis C Virus antibody positive

HCVneg, Hepatitis C Virus negative

HIV, Human Immunodeficiency Virus

HLA, Human Leucocyte Antigen

HRSB, High Risk Sexual Behaviour

HTLV, Human T-Lymphotropic Virus

IRB, Increased Risk Behaviour

ITP, Immune Thrombocytopaenia

IVDU, Intravenous Drug User

KME, Known Cause Meningitis and Encephalitis

LCMV, Lymphocytic Choriomeningitis Virus

MDT, Multi-disciplinary team

EBV, Epstein Barr Virus

MDRO, Multi-drug resistant organisms

MELD, Model of End Stage Liver Disease

MHC, Major Histocompatability Complex

MSM, Men who have sex with men

NHS, National Health Service

NHSBT, NHS Blood and Transplant

NKAS, National Kidney Allocation Scheme

PDA, Potential Donor Audit

PNF, Primary non-function

PTLD, Post-transplant lymphoproliferative disorder

SaBTO, Advisory Committee in the Safety of Blood, Tissues and Organs

SNOD, Specialist Nurse in Organ Donation

SVR, sustained virological response

TMAT, Transplant Mediated Alloimmune Thrombocytopaenia

UK, United Kingdom

UKELD, United Kingdom End Stage Liver Disease Score

UKKDRI, UK Kidney Donor Risk Index

UKME, Unknown Cause Meningitis and Encephalitis

UKTR, UK Transplant Registry

US, United States

VAD, Ventricular Assist Device

WIT, Warm Ischaemic Time

WNV, West Nile Virus

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Organ transplantation remains a highly successful form of therapy for selected patients, either as lifesaving or life enhancing treatment (1).

However, in the United Kingdom (UK) there remains a large discrepancy between organ supply and demand (1). There are currently around 7000 people awaiting a solid organ transplant and of that number around 400 die every year on the transplant waiting list (Figure 1.1) (1). Every day an estimated 3 people die secondary to the shortage of organs available for transplantation and around 1 in 6 of those listed for a heart, lung or liver transplant die or become too unwell to receive a transplant (1,2). Due to this discrepancy between supply and demand it is imperative that organs from donors are not discarded unnecessarily, and it is important to assess groups of donors where utilization of organs could be improved.

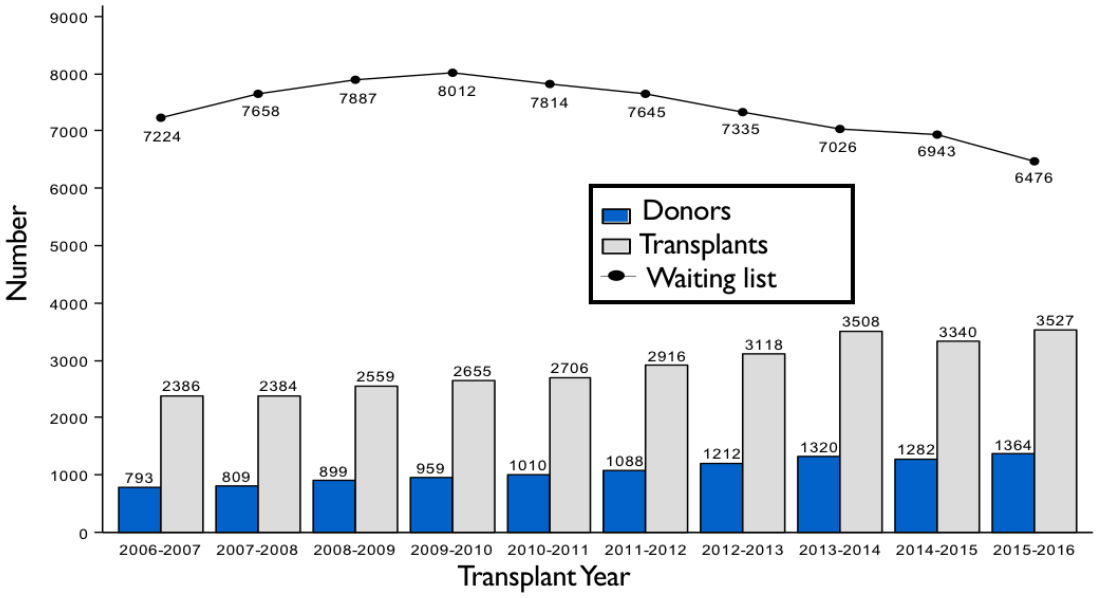


Figure 1.1. Number of deceased donors and transplants in the UK, 1st April 2006-31st March 2016, and patients active on the transplant list, taken from the NHSBT Organ Donation & Transplantation Activity report (3).

1.2 Waiting list mortality- Balancing of risks

The risk of using solid organs from donors considered to be of suboptimal quality because of donor factors such as older age or infection needs to be balanced against the risk of the patient dying following listing for organ transplantation (4). This consideration is important for all organ types, since although transplantation of livers, lungs or hearts is lifesaving as there is currently no viable alternative to transplantation, kidney transplantation has been shown to considerably improve a patient's quality and length of life compared to dialysis (4). As such, in the United States (US), 20-40% of patients listed for a solid organ transplant have died or been removed from the waiting list within 3 years (5).

The biggest risk of death for patients with end-stage renal failure awaiting a kidney transplant relates mainly to the negative health effects of renal dialysis, with some studies demonstrating patients on dialysis have up to a 30-fold increased risk of mortality compared to a matched healthy population (6,7,8). Dialysis has known severe effects on a patient's cardiovascular function and around 20% of deaths of patients on dialysis is secondary to cardiovascular disease (9). This effect of dialysis is seen most acutely in patients on dialysis with diabetes where mortality 5 years after starting dialysis can be upwards of 50% for certain age groups (9). Patients are also at increased risk for infection whilst on dialysis, in particular sepsis secondary to bacteraemia (9). However, dialysis remains a successful treatment and patients can be maintained for years successfully. Hence, the risk of not transplanting a kidney from a donor with risk attributes is very different to not transplanting other solid organs as dialysis is a viable treatment option.

The burden of liver disease in the UK is increasing, and liver disease is a common cause of death in the UK in those aged between 18 and 64 (10). The majority of liver disease is secondary to alcohol abuse, with obesity and viral hepatitis following alcohol as the second and third commonest reasons for liver failure (10-12). The median time from listing for a liver transplant to successful transplantation is around 150 days with some variation observed between different UK transplant centres. In the UK, of patients listed for a liver

transplant in the financial year 2012 to 2013, 68% of patients would have been transplanted within 1-year, 17% would still be waiting for a liver, 4% would have been removed from the list, and 11% will have died whilst awaiting a transplant (10-12). To be listed for a liver transplant, your 1 year risk of death of without a transplant should exceed the risk of death after transplantation, currently around 8%. Listed candidates are expected to have a greater than 50% chance of survival 5 years following transplantation with a quality of life that is acceptable to that candidate (10). Mortality on the liver transplant waiting list is mainly secondary to progression of the patient's disease and there being no viable treatment in lieu of transplantation (4). Hence there is a pressing need to increase the number of liver transplants performed due to ongoing high risk of mortality on the transplant waiting list. However, one of the major reasons for non-utilisation of livers is because of non-desirable risk attributes of the donor (13). As the deceased donor population changes, and more donors possess these undesirable risk attributes, it is imperative that the livers that can be safely used are not discarded (14). In addition, there is also a growing body of evidence that livers from donors with risk attributes may function as well as livers without such attributes (13,15).

Heart transplantation is an excellent treatment for patients with end stage heart failure, but due to the shortage of suitable hearts available for transplantation it remains a potential treatment option only for a select number of patients (16). In the UK, over the last 20 years, there have been increases in the number of patients on the heart transplant waiting list, but the number of heart transplants being performed has not increased at a similar rate (16). One of the major difficulties in heart transplantation is balancing the allocation of hearts to the sickest patients requiring transplantation, but also to ensure that the patients are well enough to survive the operation and the complications following transplantation (16). Current evidence seems to suggest that patients with stable heart failure might not necessarily benefit from transplantation (17).The number of patients on ventricular assist devices (VAD) has increased the number of patients on the heart transplant waiting list. VADs can be implanted in patients who otherwise would be likely to wait a

long time for a heart transplant, thus using the VAD as a bridge to transplant; VADs can reverse end-stage heart failure so that these patients can be discharged home. As well as the above group of patients, some patients who were not suitable transplant candidates, after a period of support on a VAD, may become transplantable. There are now a large number of patients with VADs on the heart transplant waiting list. This has increased transplant list numbers well beyond the numbers of performed transplants. However, most patients with VADs will be re-admitted to hospital with serious complications following insertion, so they are not free of complications (17). One of the major challenges to heart transplantation is the lack of suitable donors, and despite the UK reporting record numbers of deceased donors, only a small number of these donors will donate a heart for transplantation (3,17).

Lung transplantation is the gold-standard therapy for patients with end-stage lung disease (18,19). At present, suitable donor allografts are scarce. As such, organ allocation strategies are required to best allocate this limited resource (19). Lung transplant survival rates are lower than for other solid organ transplants, but as the patients listed for a lung transplant in the UK are a heterogeneous group across differing disease types, patients with different lung pathologies may derive varying levels of benefit from transplantation (18). An important consideration in lung transplantation is that some patients may be suitable for a single lung transplant or a bilateral lung transplant. The patients treated with a single lung transplant may be considered partially treated and may have reduced survival but due to lack of donor lungs single lung transplantation allows more patients to benefit from this scarce resource (18).

The risk of mortality on the waiting list varies for each patient and between organ types. Heart, liver and lung transplantation are lifesaving procedures, but not all patients will necessarily derive benefit from transplantation or derive benefit from the transplantation of any quality donor organ. Whilst not necessarily lifesaving, kidney transplantation confers a survival advantage compared to dialysis. The decision to utilise organs from donors with risk attributes, be it attributes that may affect organ function (e.g. older age,

comorbid disease) or may result in disease transmission (e.g. infection, malignancy) is always being weighed up against the risk of the patient dying without transplantation.

1.3 Deceased donation

The mainstay of organ transplantation is the use of organs from deceased donors. There are two main circumstances of deceased donation: Donation following brain stem death (DBD) and donation following circulatory death (DCD).

Brain stem death testing, also called neurological determination of death, has become an acceptable and common means of verifying death in the UK (20). The criteria require the patient to be deeply comatose, unresponsive, ventilated and have a known aetiology for their brain injury with potential reversible causes for their coma excluded (e.g. metabolic disturbances, hypothermia, sedative drugs, other neurological disorders etc.) (20). The donor must also have been shown to have no functioning brain stem reflexes. These conditions must be tested by two experienced doctors at separate times. DBD donors provide the majority of donor organs, despite brain stem death being relatively rare. An increasing number of donor organs are now coming from DCD donors. Prior to the acceptance of brain stem criteria for verifying death in 1979, all deceased donors were DCD donors. When brain stem testing became accepted, practice changed, recognising that the additional warm ischaemic insult that the donor organs are subjected to was deleterious to their subsequent outcome. Despite these concerns, over the last decade the number of organs from DCD donors being used for transplantation has continued to increase, with several large retrospective studies now demonstrating that for kidneys, the results are comparable to those for kidneys transplanted from DBD donors following adjustment for additional donor and recipient factors (21). Kidneys from DCD donors now make up 42.9% of the total number of renal transplants performed in the UK (3). While the use of livers from DCD donors is now part of standard UK transplant practice, despite the additional ischaemic injury being shown to have a higher incidence of graft failure, post-operative complications and

ischaemic cholangiopathy (22). The use of lungs from DCD donors provide a valuable resource of lungs for transplantation with good results being observed (23,24). However, they still make up a smaller proportion (~20%) of the total of deceased lung donors in the UK (24). Historically, the use of hearts from DCD donors is thought to be associated with poor outcomes (25). However, modern perfusion techniques mean this might become a viable option to help increase the number of heart transplants performed in the UK. Several studies demonstrate that the use of hearts from selected DCD donors convey good outcomes for patients (25-28).

There are two principal types of DCD donor, controlled and uncontrolled. Uncontrolled DCD refers to organ retrieval after a cardiac arrest that is unexpected and from which the patient cannot or should not be resuscitated(29,30), Controlled DCD takes place after death which follows planned withdrawal of life-sustaining treatment. The clinical circumstances of DCD are described by the Maastricht classification, and there are 4 major sub-types of DCD donor described by the Maastricht categories (Table 1.1) (29). Although some units in the UK have supported uncontrolled DCD, the vast majority of DCD donors in the UK are from controlled Maastricht category three patients (29,30).

Category	Type	Circumstances	Typical Location
1	Uncontrolled	Dead on arrival	Emergency Department
2	Uncontrolled	Unsuccessful resuscitation	Emergency Department
3	Controlled	Cardiac arrest follows planned withdrawal of life sustaining treatments	Intensive Care Unit
4	Either	Cardiac arrest in a patient who is brain dead	Intensive Care Unit

Table 1.1. The Maastricht classification of Donation after Circulatory Death (adapted from Summers et al 2015 (29).

1.4 Living donation

The use of kidneys from living donors has been taking place since 1954, when the first successful kidney transplant was performed by transplanting a kidney from a living donor into his identical twin. Improvements in immunosuppression in organ transplantation have resulted in transplantation being possible between non-genetically identical individuals and receiving a live donor kidney is now viewed as the gold standard in kidney transplantation. It is well documented that the use of kidneys from such donors results in improved outcomes for transplant recipients. While living kidney donation results in excellent transplant outcomes, it remains a complex ethical and moral issue. Living kidney donation is not without risk, but the risks are well quantified and low such that they are usually outweighed by the huge benefit experienced by the recipient. However, very few studies have assessed the mid to long term risks that living kidney donors could face. A recent systematic review and meta-analysis looking at the long-term outcomes of living kidney donors demonstrated that whilst all-cause mortality, cardiovascular disease and diabetes risk were similar for living kidney donors and the rest of the population, there was an increased risk of end stage renal disease, although this risk was still small (31). The review also demonstrated that female living kidney donors may have an increased risk of pre-eclampsia, albeit small in absolute terms (31). The findings of this analysis have implications on the consent process for living kidney donation and also on the follow-up of living kidney donors.

Living donor liver transplants remain uncommon in the UK, representing 3% of liver transplants performed, but living liver donation is the predominant form of liver transplantation in India and across Asia (32-34). In the UK they are performed for both Adult and Paediatric recipients, although this form of liver transplantation has been more common for paediatric recipients (34). The risks associated with living liver donation are significantly higher than for living kidney donation, with a complication rate in the donor around 21% (34-36). True mortality rates for living liver donors are unknown but in the US the mortality rate is roughly 0.2% (34). Reported outcomes from living liver donors

have been promising, and living liver donation remains a viable method by which to increase the number of liver transplants performed in the UK (34).

1.5 Allocation

1.5.1 National and Local Organ Allocation

Deceased donor organ allocation in the UK may be patient-specific offering, where the offering scheme has been developed with specific aims in mind using available evidence (e.g. kidney, pancreas, liver) or centre based offering, where the organ is deemed to be the responsibility of the transplant centre in whose zone the donor hospital lies, with the local transplant clinicians taking on the responsibility of selecting the most eligible recipient from their waiting list. In the latter situation transplant centres develop their own centre based allocation policies. Both types of organ allocation present different problems (37,38). Patient specific offering means that offers of organs from donors with specific risks may be declined, not because of the donor but because of the recipient. Centre-specific offering results in a large amount of responsibility being left to the transplanting clinicians to ensure fair allocation and the decision to accept an offered organ; in particular organs with potential infection transmission are often declined for transplantation (37,38). Solid organ allocation has undergone several changes over the last 20 years, with different allocation/offering schemes being introduced to try and reduce inadequacies or inequities in transplantation observed in prior schemes. A summary of the major changes in abdominal organ allocation in the UK is shown in Figure 1.2.

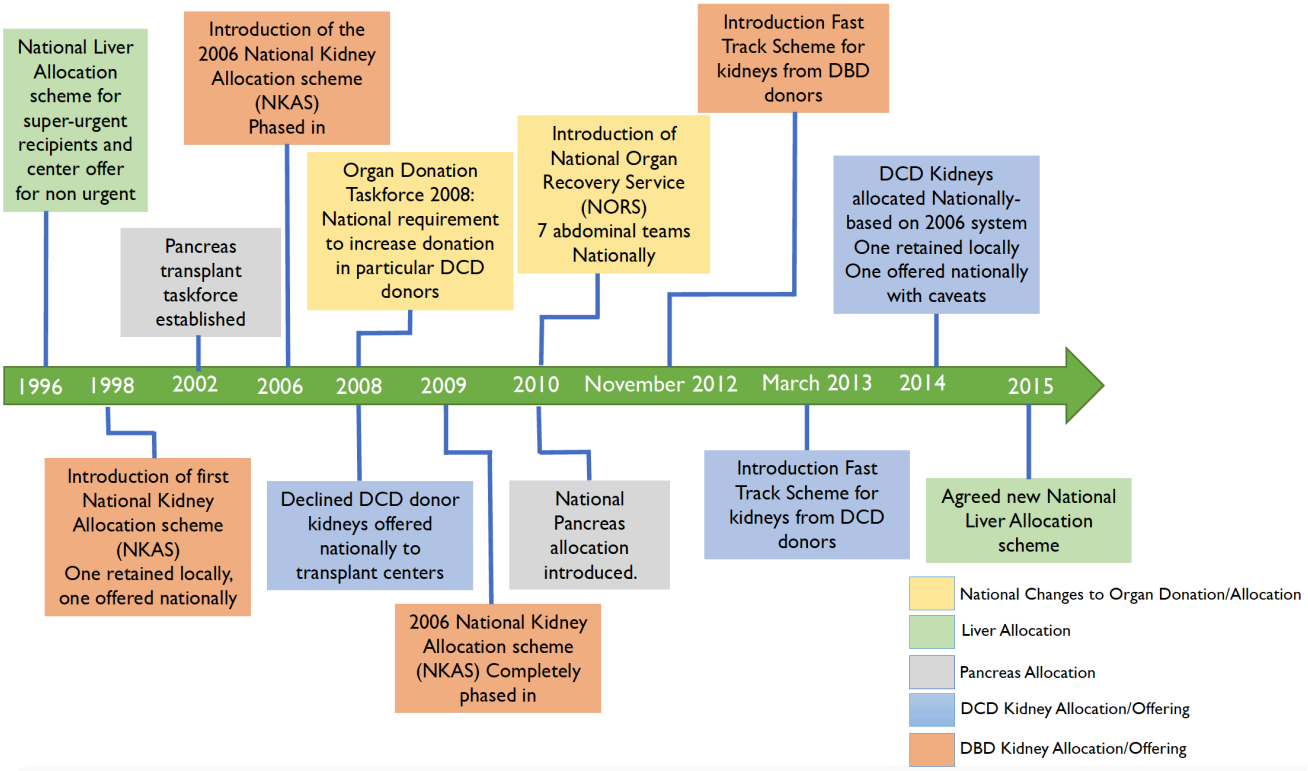


Figure 1.2. Timeline of major changes to abdominal organ allocation in the UK from 1996-2016.

1.5.2 Super-urgent recipients and fast-track of organs

For some patients awaiting organ transplantation, the severity of their organ failure may lead to death within a few days in the absence of successful transplantation. The most common situation this applies to is for liver recipients or heart recipients. Allocation schemes can recognise the urgent need for transplantation for such recipients and allocate the next organ available nationally to these recipients (39).

Fast-tracking of deceased donor organs refers to simultaneous offering of deceased donor organs to all UK transplant centres which have opted in to such schemes. The aims of the fast-track scheme are to reduce cold ischaemic time on deceased donor organs and also to improve utilisation of organs. The fast-track scheme for kidneys was introduced in November 2012 for kidneys from DBD donors and in March 2013 was expanded to include kidneys from DCD donors. The UK kidney fast-track scheme has resulted several hundred successful kidney transplants, and early allograft outcomes are favourable (40).

1.5.3 Human Leucocyte Antigen (HLA)-matching and compatibility

Immediately following consent for organ donation by the donor's next of kin, blood is taken from the potential donor, sent to a tissue typing laboratory, and the donor's HLA type and blood group determined. HLA is the human form of the major histocompatibility complex (MHC) (41). The HLAs corresponding to the MHC Class 1 are HLA-A, HLA-B and HLA-C. HLA is glycoprotein on the surface of cells that plays a major role in adaptive immunity(41). In transplantation, HLA class 1 and HLA class 2 play an important role. HLA class 1 is found on the surface of all nucleated cells and consists of a trans-membrane polymorphic heavy chain stabilized by a non-polymorphic surface structure the β-2 microglobulin. The heavy chain has three immunoglobulin like domains, α_1, $\alpha_{2,}$, and α_3. The α_1 and α_2 domains form a groove consisting of 2 α- helices and a β-pleated sheet which holds fragments of intracellular peptide. The α_1 and α_2 domains are incredibly polymorphic, whereas the α_3 domain is highly conserved and interacts with CD8 co-receptor of T-cells (42). There are several major sub-types of Class II HLA, namely HLA-DP, -DQ and –DR. Class II HLA molecules consist of two transmembrane glycoprotein chains, the α and β chains. Class II molecules are found on immune cells and they express endogenous peptide to CD4 T-helper cells (43). The major mechanisms by which a transplant candidate will have developed antibodies to non-self HLA is via blood transfusion, having been pregnant or had a previous transplant (41,44). If they have been exposed to non-self HLA by one of the above means they may develop anti-HLA antibodies. If they receive a transplant bearing HLA to which they have developed a prior antibody, this may result in hyper-acute rejection (within minutes of transplantation) or early acute antibody mediated rejection which can occur a few days after transplantation (41,45).

1.5.4 Kidney allocation

Due to the complexities and importance of HLA-matching in kidney transplantation, kidney allocation schemes have been developed to ensure that this national resource of donor kidneys are used for the best recipients. There have been several iterations of kidney allocation schemes in the UK.

The first national allocation system came into place in 1998 as the National Kidney Allocation scheme (NKAS) for heart beating donors (DBD donors) (46). This allocation hoped to compromise between equity and utility and kidneys were allocated based on tiers of HLA-matching (46,47). This allocation scheme was found to result in continued inequity of access to kidney transplantation for highly sensitised patients and patients of non-white ethnic origin. The 2006 NKAS replaced the 1998 NKAS because of this recognised inequity, and is still in place today. The main aim of the 2006 NKAS was equity of access to transplantation among all patients regardless of geographical location, ethnicity and rareness of HLA type. The 2006 scheme gave absolute priority to well matched patients, but that within that group, paediatric patients (<18 years) received absolute priority over adults. This allocation scheme improved access to transplantation, however inequity remained for highly sensitised and patients of non-white ethnicity. A new proposed kidney offering scheme has since been developed and will seek to address this (48).

Kidneys are only retrieved from a potential DCD donor when an implanting kidney transplant centre has indicated that they are provisionally prepared to transplant them, on the basis of the available donor information, including age, comorbidity, and risk of disease transmission (Figure 1.3) (49,50). There is marked variation between transplant centres in their willingness to use kidneys from DCD donors in the United Kingdom (51). Pre-2014, most DCD donor kidneys were allocated to patients living within the region associated with the donor hospital. From September 2014 one of the pair of DCD kidneys is allocated nationally and one donor kidney is retained for local use.

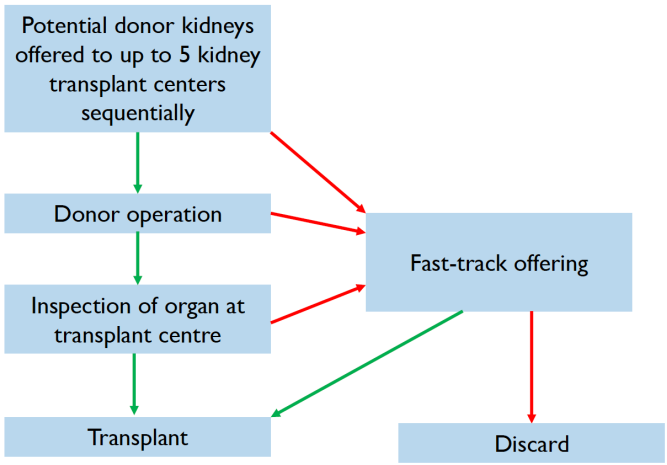


Figure 1.3. Summary of organ donation timeline from offer to transplant/discard. (modified from Summers et al. Kidney International 2015) (29).

1.5.5 Other organ allocation

Listing for liver, heart and lung transplantation is based on criteria that have been agreed and published nationally and an appeals panel exists to allow for exceptions to the agreed criteria(10,52-54). Each transplant unit has a designated zone in the UK, and the size of the zone is adjusted annually to ensure that the proportion of candidates on the Unit's waiting list is proportional to the proportion of deceased donors in the UK. There is considerable centre variation both in the numbers of patients on the wait list, the number of transplants done and the rates of acceptance (3). It is the responsibility of each Unit to decide whether to accept the offered liver, heart or lung and select the most appropriate recipient (54).
The sequence of offering of DBD livers is shown in Figure 1.4.

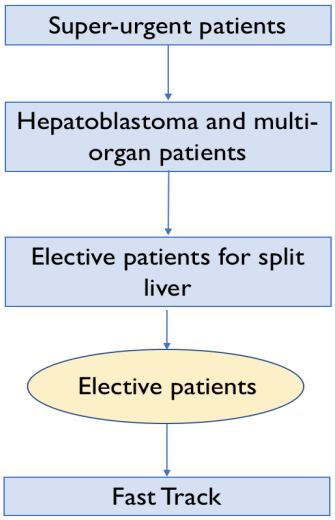


Figure 1.4. Summary of liver allocation in the UK under new 2015 National Liver Allocation scheme (54).

1.6 Infections in organ donation and transplantation

The prevention, diagnosis, and management of infectious disease in both organ donors and solid organ transplant recipients are some of the main contributors to the improved allograft outcomes observed in organ transplantation (55,56). The risk of serious infections in organ recipients is determined by a combination of factors, including the patients exposure to different infections and their level of immunosuppression. Donor transmission of infection is another factor that determines a transplant recipient's infection burden post-transplant, with the outcome of transmitted infections varying in severity (56,57). A timeline created by Fishman et al summarises the major infections that affect transplant recipients, and when post-transplant the patients might experience such infections (Figure 1.5) (58).

New quantitative molecular microbial assays and therapies have improved detection of infection in organ donors and transplant recipients and have helped to improve prevention and treatment of infection. Major hurdles that will likely impact on infection in transplant candidates include the shifting worldwide epidemiology of infections, in particular recent viral outbreaks in South America and Africa (58). Increasing antimicrobial resistance poses a major threat to organ transplantation. Several studies have now demonstrated

poor outcomes of transplant patients infected with multi-drug resistant organisms (MDRO), and also donor transmission of MDRO to transplant recipients (59,60). Other hurdles are suboptimal assays for the microbiological screening of organ donors, and virus-associated malignancies for which patient specific susceptibility is yet to be fully explored (61).

1.6.1 Current Microbiological screening in organ donors

The advisory committee for the safety of blood, tissues and organs (SaBTO) stipulate both mandatory and recommended screening of donor blood, tissues and organs. As demonstrated by Table 1, the requirements vary depending on what is being donated. Currently in the UK, all patients who have been consented for organ donation are screened for the presence of the following transmissible infections (63):

- Human immunodeficiency virus (HIV)
- Hepatitis C virus (HCV)
- Hepatitis B virus (HBV)
- Human T-lymphotropic virus (HTLV) (1 and 2)
- Toxoplasma gondii (Toxoplasmosis)
- Treponema Pallidum (syphilis)
- Epstein-Barr Virus (EBV)
- Cytomegalovirus (CMV).

Infection	Serological Test	Organs	Tissues	Haematopoietic progenitor cells, therapeutic cells and embryonic stem cells	Gametes and embryos
HIV1/2	Anti-HIV1/2Ab/HIV Ag combo	**M**	**M**	**M**	**M**
HBV	HBsAg	**M**	**M**	**M**	**M**
	Anti-HBc	**M**	**M**	**M**	**M**
HCV	Anti-HCV IgG	**M**	**M**	**M**	**M**
HTLV1/2	Anti- HTLV1/2	**R**	**M**	**M**	**M**
Syphilis	Anti-T. pallidum antibody	**R**	**M**	**M**	**R**
Toxoplasma gondii	Anti-T. gondii IgG	**R**	**NR**	**R**	**NR**
CMV	Anti-CMV IgG	**R**	**NR**	**R**	**R**
EBV	Anti-EBV IgG	**R**	**NR**	**R**	**NR**
HEV	HEV RNA	**R**	**R**	**R**	**NR**
Chlamydia trachomatis	n/a	**NR**	**NR**	**NR**	**M**

M= Mandatory test; R= Recommended test; NR= Not required/ not applicable.

Table 1.2 Mandatory and recommended screening of organ, tissue and cell donors (modified from SaBTO guidance 2017 (63)).

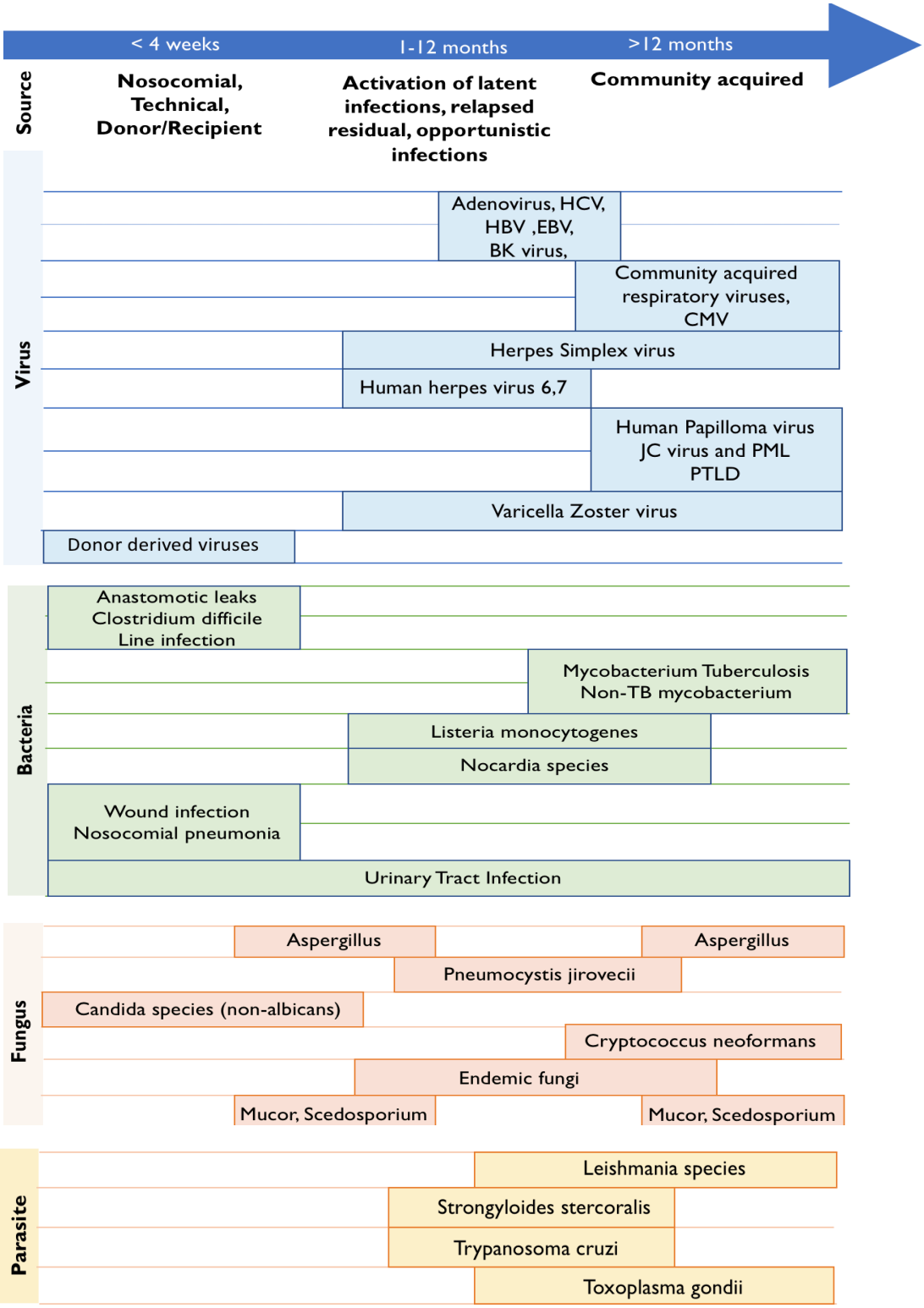


Figure 1.5. Timeline of infections following organ transplantation (adapted from Fishman et al (58).

1.6.2 Interpretation of microbiological results in transplantation

Following exposure to, and infection by a microbiological agent there is a period of time during which no microbe can be readily recovered from the host; this is classically called the eclipse period (Figure 1.6) (64-67). Donations taken during this period are unlikely to be infectious but in practice this would not be safe (63). The time from infection to the onset of detectable infectivity depends upon the method used for detection of infection. This period of infectivity which cannot be detected is colloquially called a "window" and represents the duration of undetectable infectivity. This "window" is shortest for genomic (nucleic acid technology testing (NAT)) and antigen tests, and longest for antibody tests. For practical purposes, the time from infection to first detection of a marker is referred to as the "window period" (58,65,67).

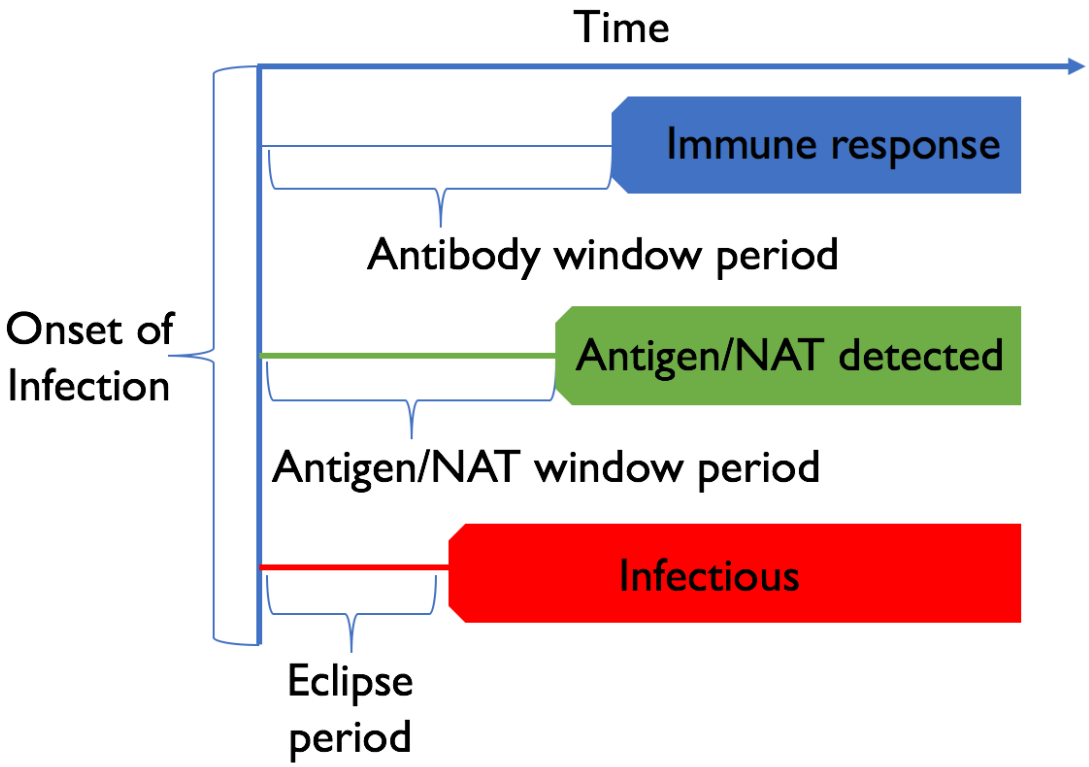


Figure 1.6. Demonstrating of the eclipse, antigen/NAT window, and antibody window period following infection. Modified from SaBTO 2017(63)

1.6.3 Common donor derived infections

If a potential donor is found to have either anti-EBV or anti-CMV antibodies, it does not immediately represent a contraindication for donation, as transmission of these viral infections has become an accepted part of transplant practice, largely due to the high prevalence in the donor population (63). Transmission of these viruses can, however, result in severe consequences for the transplant recipients (68-70). Transmission of EBV can result in post-transplant lymphoproliferative disorder (PTLD). The incidence of PTLD in the solid organ transplant recipients has never been accurately determined. Different incidences are reported depending on the organ that has been transplanted and the recipient's EBV serostatus pre-transplant (68-70). CMV, when transmitted or reactivated in the transplant recipient, can cause a whole host of inflammatory processes notably colitis and pneumonitis and can often prove fatal if treatment does not resolve the viraemia. It is also becoming more common for CMV to develop resistance to both valganciclovir and foscarnet through the mutations in UL54 and UL-97, resulting in significant morbidity or mortality in the recipient (71-73).

1.7 Increased risk organ donors

1.7.1 The impact of blood borne viral infections on donation and transplantation

A group of donors whose organs are often not used for transplantation are donors who have proven infectious diseases, particularly blood borne viral diseases (BBV) such as HCV, HBV, HTLV, and HIV. This is because of the likely transmission of the virus to the immunocompromised recipient.

1.7.2 HTLV

HTLV-1 is a retrovirus, in which infection in around 5-8% of non-immunocompromised patients results in one of two clinical disorders: HTLV-associated myelopathy and adult T-cell associated leukaemia / lymphoma (74). The impact that HTLV transmission has on immunocompromised individuals is not well understood, with several case reports suggesting rapid

progression of HTLV-associated myelopathy, but recent UK transmissions from a single donor to three recipients showed early infectious spread but no development of disease (74-76). Detection of antibodies to either HTLV-1 or –2 is a contraindication to organ and tissue donation in the UK (62,77,78).

1.7.3 Hepatitis C virology and epidemiology in donation and Transplantation

HCV is a RNA virus of the family Flavaviridae. Exposure to HCV can result in acute infection which in around 80% of individuals will result in chronic infection. The global prevalence of HCV (based on the presence of anti-HCV antibodies) is estimated to be around 1.6% (roughly 115 million people), with estimates of the global viraemic prevalence (i.e. the number of people with detectable HCV RNA) estimated at 1%, although these estimates may be an underestimate (79,80).

Prevalence of HCV infection shows variation across the globe. The countries with the highest prevalence for HCV are those with the greatest exposure to iatrogenic transmission of HCV. Currently around 250,000 people in the UK are thought to be infected with HCV and with increasing demand for organs for transplantation it is possible that selected Hepatitis C positive donors (HCVpos) may represent a source of organs for transplantation (Figure 1.7). However western countries account for a minority of the global prevalence of HCV (79). HCV infection also shows marked age distributions. In countries where the major route of transmission is through intravenous drug use (IVDU) the age of people infected is considerably lower than those who are infected by iatrogenic means.

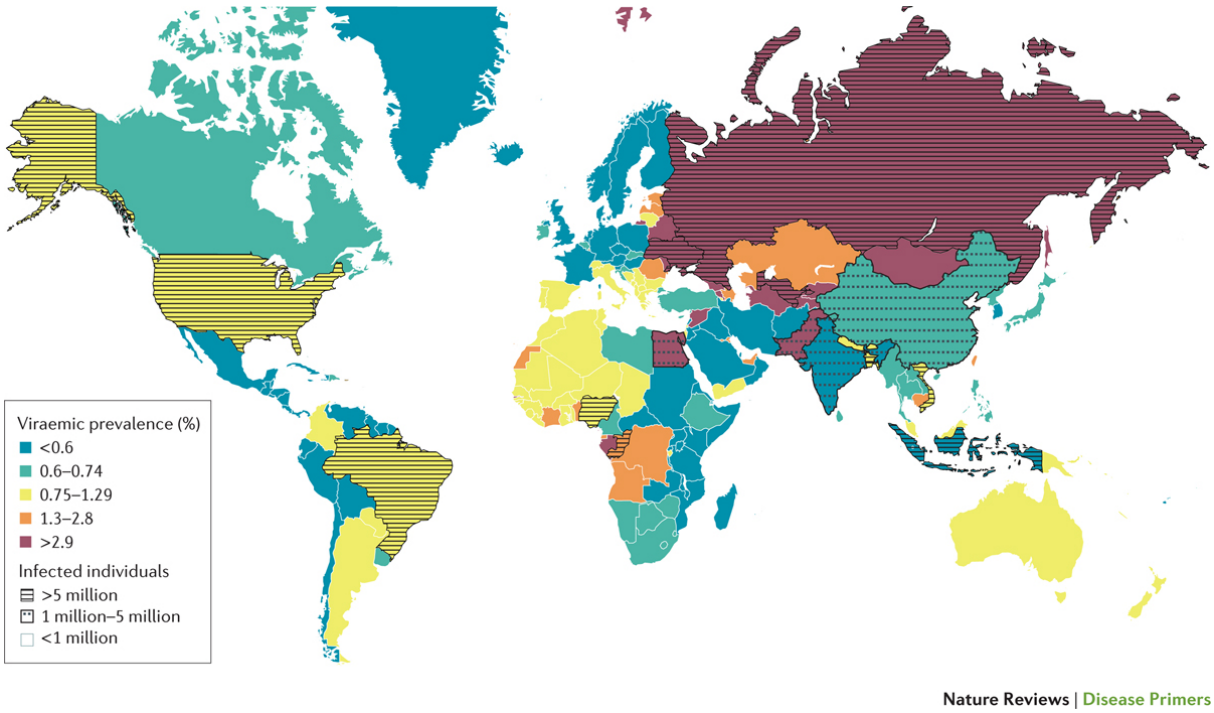


Figure 1.7. Viraemic prevalence of HCV around the world (from Manns, M. P. *et al.* (2017) (79)9

HCV is primarily transmitted through percutaneous blood exposure, such as through medical procedures or through the sharing of devices for IVDU. Vertical transmission and sexual transmission have also been reported, but are far less common. In the UK, iatrogenic spread of HCV has been significantly reduced since screening of blood products was introduced and through leucodepletion of blood products, leaving IVDU as the major route of HCV transmission (78). Other important risk factors for HCV include occupational exposure (i.e. working in healthcare and sustaining a needle stick injury) and tattooing. Nevertheless, in many cases no risk factor is identified.

HCV is a very heterogeneous virus with seven main genotypes, designated 1-7. These genotypes have many subtypes identified by lower case letters (e.g. 2a,2b…). The HCV genotype influences disease course and response to treatment.

1.7.4 Diagnosis of HCV

In organ transplantation, HCV is often identified through the presence of anti-HCV antibodies in the donor blood. Following detection of these anti-HCV

antibodies the transplant centre will then test for HCV RNA or detectable HCV antigen via PCR or NAT testing. There is often a window period following infection until detection of HCV antibodies can occur (the antibody window period) (Figure 1.7). Due to this infection window period the history of the donor for any behaviour that would place them at increased risk of blood borne viral disease is heavily relied upon for donor characterisation and assessing the safety of the organs for transplantation. This behavioural history therefore influences a clinician's likelihood of accepting the organs from an RNA negative HCV antibody positive individual (81,82).

1.7.5 HCV and transplantation

The progression of chronic HCV infection is from hepatic fibrosis to cirrhosis and hepatocellular carcinoma. HCV infection is a common cause of liver failure and requirement for transplantation (10). In addition to the hepatic complications seen in HCV there are a number of extrahepatic complications including cryoglobulinaemia, renal failure secondary to cryoglobulins or glomerulonephritis (GN) (in particular type 1 mesangiocapillary GN), and Hodgkin's lymphoma (79). In addition, patients have increased insulin resistance leading to diabetes mellitus, as well as increased cardiovascular disease and risk of stroke (83). The role HCV plays in end organ damage is therefore multifactorial and patients with chronic HCV can often require transplantation of organs other than the liver. At present, organs from HCV antibody positive (HCVpos) deceased donors are seldom used for transplantation because of the high probability of disease transmission, with an accelerated risk of cirrhosis and liver failure. National guidance in the US and UK currently strongly cautions against the use of organs from HCVpos donors (55,57,62). Until recently, treatment of HCV in the allograft recipient was expensive, toxic and relatively ineffective (84). However, the advent of highly effective direct acting anti-viral agents (DAA) has greatly improved the outcome for HCV infected patients, with over 95% achieving sustained virological response (SVR) (85,86). Hence, transmission of HCV could come to be viewed in a similar light to EBV and CMV transmission (87).

1.7.6 Mechanism of action of DAA

There are four classes of DAAs, defined by their mechanism of action and target. The four classes are non-structural proteins 3/4A (NS3/4A) protease inhibitors (PIs), NS5B nucleoside polymerase inhibitors. The NS3/4A protease was identified as a major target for antiviral intervention, as its blockade shuts down the intracellular life cycle by inhibiting maturation of the viral polyprotein (79). Replication has been identified as a major target for antiviral drugs. Replication can be directly inhibited by NS5B inhibitors. These include nucleotide analogues, which function as RNA chain terminators, and non-nucleoside inhibitors of NS5B that target allosteric sites of the enzyme and make it non-functional. NS5A inhibitors alter the regulatory role of NS5A and seem to disorganize the replication complex thereby inhibiting HCV replication in a potent manner, enhanced by their ability to also inhibit viral assembly and release (79).

1.7.7 Hepatitis B virus

HBV is a double stranded enveloped virus of the hepadnaviridae, with its primary replication occurring in the liver, hence the risk of transmission is highest following liver transplantation. Recently, there has been a trend towards using organs from donors who test positive for HBV as around 1/3rd of the global population has serological evidence of past infection or current infection. An estimated 400 million people are infected with HBV worldwide, with variation in prevalence depending on geographic region (88). Despite effective measures to prevent HBV infection via immunization and also effective anti-viral therapy, HBV infection remains a common blood borne viral disease and an important cause of end stage liver failure and requirement for liver transplantation (89). The first advances in HBV treatment were with Hepatitis B immunoglobulin and lamivudine which resulted in improved survival rates for patients with HBV. Following this, nucleoside(tide) analogues have demonstrated that they can prevent the need for liver transplantation for some patients by preventing end stage liver disease. These analogues also have meant that recurrence of HBV post-liver transplant is now rare. Deceased donors who are anti-HB virus core antibody

positive are being increasingly used for liver transplantation. However, without effective prophylaxis, HBV transmission has been estimated to be as high as 86% (89).

1.7.8 Human Immunodeficiency virus (HIV)

The presence of HIV infection in an organ donor is currently a contraindication to donation in the UK except in exceptional or lifesaving circumstances (63). Despite this guidance indicating there are situations where the organs from these donors could be used, there remains a reluctance to use organs from such donors. Over the last decade there has been an increasing number of reports describing successful organ transplantation of HIV positive donor organs to HIV positive recipients. Current epidemiological analysis suggests that since the introduction of highly active anti-retroviral therapy, life expectancy with treated HIV is roughly two-thirds that of the general population (90,91). Although several reports indicate that episodes of acute rejection are significantly higher in HIV infected individuals, in general transplant outcomes were favourable (92). As an increasing number of patients with HIV develop ESRD, the use of HIV positive donor organs for transplantation could become more common in order to address the discrepancy between organ supply and demand. It has also been proposed that HIV infected patients on the waiting list could be allocated HIV infected organs. Preliminary experience of transplanting kidneys from HIV infected donors to HIV infected transplant recipients in South Africa has been reassuring and the first UK case of transplanting HIV infected kidneys to two HIV infected recipients has demonstrated that it is safe and effective (93).

1.7.9 Increased ischaemic risk donors

Death secondary to hanging, drowning or carbon monoxide (CO) inhalation results in global tissue hypoxia, and may have severe detrimental effects on organs that might be used for transplantation (94,95). However, thus far there has been no convincing evidence to refute or uphold this assertion. As such, there is no current guidance in the US, UK or Europe as to whether organs from such donors should be used for transplantation.

Suicide by hanging is one of the most common suicide methods and suicide remains a common cause of death, especially in the younger population (96,97). During hanging there is compression of the carotid arteries, jugular veins and the trachea resulting in raised intracranial pressure, cerebral oedema and brain death. In addition to the above, the suicide victim also develops pulmonary oedema and multi-organ failure secondary to global tissue hypoxia (94,98). Hence, donors who died by the above mechanism may have greater risk for hypoxia driven organ damage. There are also concerns regarding the amount of down time that the patient may have had prior to organ retrieval, and hence an unknown amount of ischaemic insult to the organs. With regards to the lungs from donors who have drowned, there is concern about possible infectious complications (99).

The effect that these causes of death have on the quality of donor organs has never been fully established and due to the ongoing shortage of organs available for transplantation, organs from these donors have been used for transplantation.

1.7.10 Other donor diseases

There is growing concern over the possibility of transmission of donor autoimmunity to the recipient (100-102). The risks that these donors pose, in particular donors with immune thrombocytopaenia (ITP), has never before been quantified.

There is also concern over the presence of donor connective tissue disease such as Ehlers-Danlos and Marfans and how this may affect the organ and the ability of the surgeon to implant it. The presence of these conditions may also result in graft dysfunction or failure (103).

1.8 PhD Aims

1.8.1 PhD project objectives

The objectives for this PhD were to:

1. Describe the proportion of organ donors in the UK who died of meningitis and encephalitis and their corresponding transplant recipient outcomes
2. Describe the rate of autoimmune disease transmission from donors with ITP
3. Describe the different types of behaviour associated with increased risk of viral transmission in the UK donor population and to what extent their use results in unexpected blood borne viral disease transmission
4. Describe the UK experience of using organs from donors with HCV and evaluate the benefit in organ donation and transplantation if organs from these donors could be used.
5. Evaluate the effect that donor death by ligature asphyxiation has on renal transplant outcomes.
6. Describe how variations in risk appetite between renal transplant centres impacts on renal transplant outcomes and survival from listing

Methods

1.9 The UK Transplant Registry

Information is collected about the donor, the transplant procedure and the recipient for every transplant carried out in the UK and this is recorded in the UK Transplant Registry (UKTR). These data are collected from a variety of different sources including specialist nurses in organ donation (SNODs), donor and recipient transplant coordinators, transplant surgeons and clinicians and the staff involved in tissue-typing. This information is then relayed, often in paper form, to National Health Service Blood and Transplant (NHSBT) for input into the registry. In addition to the above, NHSBT formely employed data collectors who were given authorisation to access transplant follow-up data (graft and patient survival). This has since been replaced, and most centres now report their own follow-up to NHSBT. While much information is entered into specific fields, a large amount of information on deceased organ donors and recipients is recorded in the UKTR as free text entries. For deceased donors, this typically includes information about specific medications the donor may have been taking, causes of death that are not coded in the registry, and any other information deemed to be important by the transplant team to record at time of donation. With regards to transplant recipients, information held in the free text entries often relates to pre-transplant organ failure that is not coded in the registry and any causes of post-transplant organ failure or death that don't correspond to a specific cause stated in the UKTR. These free text entries could be accessed and analysed through coding for specific search terms, followed by manual review of the notes of the deceased donors or recipients identified from the code. Specific statistical code to search the free-text entries is shown in Appendix 1.

1.10 The Potential Donor Audit

The Potential Donor Audit (PDA) is a prospective registry of all patients aged less than 80 years who died in critical care units of acute hospitals in the UK, irrespective of their medical suitability to become organ donors. The PDA was established to determine the potential number of solid organ donors and

provide information regarding different hospital practices about donation, as one of a series of measures aimed to improve organ donation in the UK. For the present analysis information from the PDA was only analysed from 2009 onwards when the coded reasons for why potential donors did not proceed to donation was made more comprehensive with a choice of 24 coded 'contraindications' to donation (e.g. Haematological malignancy; HIV) and 14 'reasons' why organ donation did not proceed (e.g. family refusal; coroner refusal). Up to 2013 only deaths in critical care units of patients up to the age of 75 years were included in the PDA, but from 2013 the age limit was increased to 80 years.

Initially patients who died in cardiothoracic intensive care units were not included in the audit, but from 2013 such patients have also been included in the audit.

1.11 Incident Reporting

Prior to 2010, recipient centres were expected, according to UK guidance, to report any adverse outcomes in recipients relating directly to the organ donation process to NHSBT, including, in the case of donors with meningitis/encephalitis, transmission of the causal agent. This reporting requirement became mandatory when the 2010 European Union Organ Donation Directive (EUODD) was written into UK law in the Quality and Safety of Organs for Transplantation Regulations (2012).

1.12 Changes in SaBTO guidance

Over the last 18 years the SaBTO guidance has changed three times to reflect changes in transplant practice. These guidelines have therefore changed over the course of the study periods for each results chapter. In order to present the findings of the results chapters in the context of guidelines at the time, the major changes in SaBTO guidance are summarised in table 2.1.

Chapter and study period	SaBTO Guidance- publication year		
	2000 (64)	**2011 (62)**	**2017 (63)**
Chapter 3- Donors who die from Meningitis and Encephalitis in the UK Study period 1st January 2003 to 31st December 2014	***Bacterial meningitis-*** *Acceptable for transplantation if* no visible damage or local infection in organ at retrieval-donation acceptable with appropriate recipient antibiotic prophylaxis covering donor organism.	***Bacterial meningitis*** No significant change	***Bacterial Meningitis*** No significant change
	Meningitis unknown aetiology Not specifically mentioned but included in the following: Donor has any history of neurodegenerative disease of unknown aetiology- Donations can never be accepted from a donor with a degenerative neurological disease of unknown aetiology	***Meningitis unknown aetiology*** **Change:** Material from meningitis cases from whom no organism is cultured should not be used for donation	**Meningitis unknown aetiology** **Change:** Material from cases of death from meningo-encephalitis where no organism is cultured should not be used for donation, except in the circumstance that the following conditions are met: - The infection is thought due to a bacterium by clinicians caring for the patient. - Microbiological cultures are negative because they were taken after antibiotics had been started. - Appropriate and adequate antibiotic treatment has been given to the recipient. - Expert microbiological advice has been obtained. Addition of decision aide flow chart
	Viral meningo-encephalitis: Herpes simplex (HSV) or varicella zoster infection (VZV)- contraindication to donation unless HSV/VZV treated for 7+days, if treated less then 7 days, recipient should have anti-viral prophylaxis Other aetiology, donor not abroad- careful expert case consideration by case assessment required Other aetiology, donor abroad recently- contraindication to donation.	***Viral meningo-encephalitis*** **Change**: If HSV or VZV CNS infection is diagnosed as a manifestation of systemic viral infection (as seen in neonates and the immunosuppressed), donation of organs, tissues and cells is contraindicated as the viruses may be disseminated widely with associated viraemia. HSV encephalitis without evidence of systemic infection can be treated with antiviral therapy and the likelihood of disseminated infection in the donor is small, even without antiviral therapy. In this situation antiviral prophylaxis should be considered for the recipient. Eyes must not be donated if the donor has a past history of, or active infection with, either HSV or VZV.	***Viral Meningo-encephalitis*** **Change:** addition of decision aide flow chart

Chapter 5- The potential to increase organ donation from deceased organ donors with a history of increased risk behaviour for the transmission of blood-borne viral infection Study period: 1st January 2003 to 31st December 2015	Cautions against use if risk behaviour identified within preceding 12 months. ***Information on donors to be collected:*** The following information should be gained from living donors or, for dead donors or living donors not capable of discussing these matters, from their most relevant life partner or close family member. Is the donor or their partner known to have HIV, Hepatitis B or Hepatitis C ? For men, has the donor ever had sex with another man? Has the donor ever received money or drugs in payment for sex? Has the donor ever injected or snorted drugs, even once? In the last 12 months, has the donor had sex with: someone who is, or may be, HIV positive? a man who has had sex with another man (if the donor is female)? a person who receives money or drugs in payment for sex? anyone who has ever injected or snorted drugs? anyone who has been sexually active in parts of the world where the main route of HIV infection is heterosexual sex?	**Change:** No advice on appropriateness of patients for organ donation ***Information on donors to be collected:*** **Change:** Any behavioural history that could have put the donor at risk of blood-borne viruses. This will include questions about risk behaviours such as recreational drug use, men who have sex with men (MSM), and risks such as accidental body fluid exposure;	**Change:** Advises specific consent on additional risk that donor poses and said discussion to be recorded in patients notes ***Information on donors to be collected:*** **Change:** Behavioural history that could have put the donor at risk of transmissible pathogens This will include questions about risk behaviours such as recreational drug use, men who have sex with men (MSM), sex with commercial sex workers, sex with a partner know to have a sexually transmissible disease, acupuncture, tattooing and body piercing.
Chapter 6 Potential and actual deceased donors with HCV Study period: 1st January 2000 to 1st January 2016	***Donor HCV antibody*** Contraindication to donation. Consider only in life-saving situations (after discussing all implications with organ recipient or those close to the patient) if the patient is already infected with HCV ***Donor HCV RNA/NAT positive*** Not addressed in guidance	***Donor HCV antibody/antigen positive and Donor HCV RNA/NAT positive*** **Change:** Contraindication to donation- caveat in exceptional circumstances, a life-preserving donation from an infected donor may be released for clinical use in a recipient who also is infected with or has cleared HCV in accordance with. In exceptional circumstances a life-preserving donation from a donor whose serum is concordantly repeatably reactive for, or contains, anti-HCV may be released for clinical use providing HCV RNA is	***Donor HCV IgG antibody positive-*** Relative contraindication to donation ***Donor HCV RNA NAT or HCV combination Ab/Ag ("combo") test*** Relative contraindication to donation **Change:** New "HCV infection in the potential donor does not amount to an absolute contraindication to donation of material for life-preserving transplantation, however the net benefit of transplantation must be considered against the risk of not receiving that specific transplant.

		undetectable, bearing in mind that this does not absolutely exclude infectivity. Consider seeking expert advice concerning HCV management in recipient.	This risk/benefit analysis allows for the potential use of a transplant from a HCV infected donor to a non-infected recipient" (63).

Table 2.1. Summary of the changes in SaBTO guidance (2000-2017) as pertains to each relevant results chapter.

1.13 Donor Risk Indices

In order to estimate the potential graft survival of discarded donor kidneys the UK Kidney Donor Risk Index was used (UKKDRI). This risk index takes into account variables that significantly impacted on graft survival and uses coefficients from a multivariate analysis to generate an equation that is used to predict the risk of graft failue.

UKKDRI was calculated by the following equation:

UKKDRI = exp{0.245 x (donor age <40)+ 0.396 x (donor age ≥60) + 0.265 x (history of hypertension) + 0.0253 x [donor weight (kg) 75]/10) + 0.00461 x (days in hospital)+ 0.0465 x (adrenaline)(104).

Similarly, an equation has been generated in order to predict the likelihood of liver graft failure post transplanted. The UK *Donor Liver Index* (DLI) is calculated using the following equation:

DLI = exp{1.61 + 0.0084 x age − 0.012 x height[m] − (0.17 if female) + (0.64 if DCD) + (0.49 if split liver) + (0.16 if smoker) + 0.0092 x bilirubin [in µmol/L] (105).

There is currently no UK donor cohort validated risk index for heart, lung, or multi-visceral deceased organ donors. The Pancreas Donor risk index constructed using the Scientific Registry of Transplant Recipients in the US, has been validated on the UK donor population to predict allograft survival following simultaneous kidney-pancreas (SPK) transplantation (106). It did not predict allograft survival following pancreas transplant alone or pancreas after kidney transplantation (106).

1.14 Estimated glomerular filtration rate (eGFR)

Calculated from the modification of diet in renal disease calculation (MDRD) equation (107):

$=186 \times (Creat / 88.4)^{-1.154} \times (Age)^{-0.203} \times (0.742 \text{ if female}) \times (1.210 \text{ if black})$

1.15 HLA, UKELD and MELD definitions

HLA-mismatch level was defined according to UK allocation policy for kidneys from brain-death donors and was based on the mismatch between donor and recipient at the HLA-A, -B, and -DR loci: level 1 was a 000 HLA-A, -B, and -DR mismatch; level 2 was a 0 HLA-DR plus 0 or 1 HLA-B mismatch; level 3 was a 0 HLA-DR plus 2 HLA-B mismatch or a 1 HLA-DR plus 0 or 1 HLA-B mismatch; and level 4 was a 2 HLA-DR or a 1 HLA-DR plus 2 HLA-B mismatch (50).

The United Kingdom End-Stage Liver Disease (UKELD) and Model of End Stage Liver Disease (MELD) scores were used when assessing differences in liver recipient characteristics. UKELD score is calculated based on the patient's international normalized ratio (INR) of prothrombin times, serum creatinine, serum bilirubin, and serum sodium (108). MELD score is calculated based on recipient serum bilirubin and creatinine levels, INR and underlying cause of liver disease (109,110)

1.16 Statistical Analysis

1.16.1 Univariate Analysis

Principal univariate analysis was carried out using t-test for parametric continuous data and Wilcoxon for non-parametric continuous data. To test for normality the Anderson-Farling method was used.

Fisher's exact test and chi-squared (χ^2) were used to compare categorical data.

1.16.2 Survival Analysis and Kaplan-Meier tables

Survival data in medicine is concerned with the time it takes an individual to reach an end point of interest. The survival analyses in this paper are concerned with the time it takes a transplant patient to die following organ transplantation (patient survival) or the time it takes for the patient's transplant allograft to fail (graft survival). Survival data is characterized by two features:

1. Length of time for the patient to reach the end point of interest (e.g. death)
2. Censoring of the data

Survival times reflect the time from the 'starting point' (for most of this work that will be the time of transplantation) until the outcome of interest is reached. Often it is not known when this endpoint of interest is reached, only that the patient remained free of this endpoint over the specified study period (i.e. the patient may have experienced graft loss following the study period or it may not be known if the graft failed because the patient was lost to follow-up). These patients are described as being 'right-censored'. 'Right-censored' means the patients were known to not have reached the endpoint of interest when they were last followed-up. 'Left-censored' data refers to when follow-up for the study begins after the baseline date.

Kaplan-Meier (KM) estimates of survival curves were first proposed in 1958 by Kaplan and Meier (111).The Kaplan-Meier method of calculating survival curves give the cumulative probability (the survival probability) of an individual remaining free of the endpoint at any time after the baseline (Figure 2.1). The survival probability changes when a specific endpoint is reached, giving the KM curve a stepped like appearance.

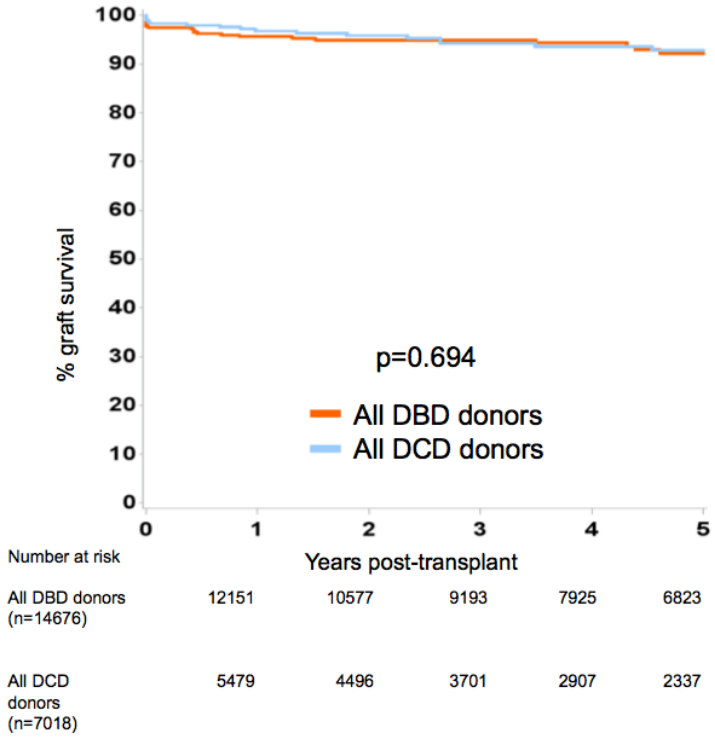


Figure 2.1. Example KM curve showing 5-year death censored graft survival of recipients of kidneys from DBD donors compared to DCD donors.

As Figure 2.1 demonstrates it is often required to compare the survival between two cohorts of patients. This thesis will often compare the survival of recipients based on the presence/absence of a risk attribute in the deceased donor. To statistically assess whether or not there is a difference between the survival of the two groups the log-rank test or regression methods can be used. The log-rank test is used throughout this thesis to describe differences in mortality curves, and the test works by detecting a consistently different event rate between the groups, with the null hypothesis being that there is no difference between the two groups. This generates a p-value as shown in Figure 2.1. For this thesis, all p-values less than 0.05 were deemed to be statistically significant, unless otherwise stated in the chapter.

1.16.3 Multivariate Analysis of survival data

The limit of the log-rank test is that it cannot assess the independent role of more than one factor at a time on survival. In order to do this multivariable regression models can be used to quantify the relationships between one or more factors on survival. The model used throughout this piece of work is

Cox-proportional hazards model. This model can test the independent effects of a number of explanatory variables to a hazard. This regression takes the form of: $h_i(t) = \exp(\beta' x_i)h_0(t)$

where $h_i(t)$ is the hazard for an individual i at time t, $h_0(t)$ is a baseline hazard and x_i are the explanatory variables in the model and β are the corresponding coefficients of these variables. From this model we are then able to get hazard ratios. These ratios give the estimated hazard of a disease for the variable xj = x+ 1 relative to the individual with variable xj=x +0, while adjusting for all the other variables in the equation. The hazard ratio is interpreted as: >1 raised hazard, <1 decreased hazard, 0: no increase or decrease in hazard at the endpoint.

An important assumption of Cox proportional hazards regression model is the proportionality of hazards i.e. a hazard remains constant throughout time for the variables included in the model. To assess proportionality of hazards log-cumulative hazard plots were used.

1.16.4 Logistic regression

Logistic regression is a regression model that can be used when your outcome is a binary variable (e.g presence/ absence of a condition) and there are a large number of explanatory variables. Logistic regression is used extensively throughout this thesis, primarily to investigate the role that different donor risk attributes have on the likelihood of a deceased donor to proceed or not proceed to organ donation, or to have their organs used/ not used for transplantation. In these situations, not proceed/ not transplant=0 and proceed/transplant=1. The logistic regression equation appears as follows:

$$Logit(p)=a +b1x1+b2x2+\ldots bkxk.$$

Where x_i is the *i*th explanatory variable e.g. (1 or 2 in the equation above); p is the value of b the true probability that the individual has the disease/ outcome of interest, given their values for x; a is a constant term; and b is the estimated logistic regression coefficients. The exponential of these particular **b**

coefficients results in the estimate of the odds ratio. As with the hazards ratio, the odds ratio gives estimates of odds of **a** diseases for values of **x**. i.e. the odds for a disease of x+1 relative to x + 0, whilst adjusting for all the other x's in the equation, hence resulting in *a* an adjusted odds ratio. Again, like for the hazards ratio an odds ratio >1 corresponds to increased odds of having the outcome of interest, and a value below 1 indicates decreased odds.

1.16.5 Multivariable analysis-building the models

Multivariable analysis was carried out using logistic regression analysis for binary outcomes, linear regression for assessing the impact of different factors on post-transplant eGFR and creatinine, and for survival Cox proportional hazards. These methods have been used extensively throughout this thesis.

Both multivariate techniques require you to build a model in a step-wise manner or with donor and/or recipient characteristics that have been deemed important clinically. For both logistic regression and Cox-proportional hazards regression the model is assessed following the addition of each new variable through Akaike's information criterion (AIC):

$$AIC = -2\log L + \alpha q$$

The AIC decreases as your model improves. In this equation -2logL, is -2x the logarithm of the likelihood of estimates, 'αq'= a constant multiplied by the number of unknown 'β' parameters included in the model. As changes in -2LogL have a χ^2 distribution, the change in -2LogL following the addition of each new variable can be used to assess the significance of said variable in the model.

1.17 Multiple Imputation

In order to handle the missing data in the registry multiple imputation was performed when stated. Multiple imputation replaces each missing observation with a set of plausible values that represent the uncertainty about the right value to impute. The use of multiple imputation allows for analysis of the imputed data sets with no missing information. The imputation method

depends on the pattern of the missing data. A monotone missing pattern infers that once a missing variable is observed for a group/unit, all variables following this will also be missing. An arbitrary missing pattern can be either monotone or non-monotone, and was the pattern for most missing data in the UKTR. The FCS method of imputation was used using FCS regression for continual variables, FCS logistic regression for binary/ordinal variables and FCS discriminant function in SAS for binary/nominal variables.

The imputation models should be congenial to, or consistent with, your analytic model, Including, at least, the same variables as the analytic model.

Multiple imputation assumes the data are missing at random given the covariates in the model.

1.18 Statistical Software

The software used for data analysis for this research was Statistical Analyses Software 9.3 (SAS 9.3), from SAS institutes in Cary, North Carolina (112). It is a code based program that has three main functions. Firstly, it allows SQL programming, and hence easy interaction with the databases such as those that compose the NHSBT UKTR. Secondly it has a powerful statistics package. Thirdly, it has a macro language that enables extensive customization of the SAS program.

Results

Donors who die from Meningitis and Encephalitis in the UK

Publications from this work: *Trotter et al. Transplantation of Organs from Deceased Donors with Meningitis and Encephalitis: a UK Registry Analysis. Transplant Infectious Disease. December 2016; 18(6):862-871.*

1.19 Background

The demand for organs for transplantation far exceeds supply and increasing consideration is being given to the use of organs from sub-optimal donors, including those perceived to pose a potential increased risk of disease transmission to the recipients (113). Donors who have a died as a result of meningitis and encephalitis are of potential concern because of the risk of transmitting life threatening meningitis or encephalitis to the immunocompromised recipient (57,113,114) . This risk was highlighted by a recent case in the UK where a donor who died of an encephalitis of unknown cause transmitted a fatal encephalitis to two renal transplant recipients (115). Cases of meningitis and encephalitis transmission have been observed in the US and Europe, with the transmission often proving fatal (116-122). The risk of disease transmission, however, needs to be evaluated and balanced against the potential benefit of additional donor organs for transplantation to the recipient population.

UK guidelines from the SaBTO (2017) state that ‘if there is any possibility of acquisition of a neurotropic infection from abroad the donation is contraindicated owing to the risk of rabies, West Nile virus or other exotic neurotropic infections’ (63). The guidelines also state that ‘Material from cases of meningo-encephalitis for which no infection is identified should not be used for donation’. However, there is a caveat in the guidance that recognises there may be a clinical need for transplantation of such urgency that it is appropriate to consider the use of organs and tissues for life-preserving purposes from donors who would not otherwise be considered eligible to donate, due to a

known or perceived risk of disease transmission (123). SaBTO guidance also states that 'if bacterial meningitis has been confirmed, but there is no visible damage or local infection in the organ or tissues required at retrieval, the donation of the organs, tissues and cells are acceptable' for transplantation (123). US guidance (2013) also states that donors dying of encephalitis without a proven cause should be avoided; the two exceptions to this general caution include donors with proven bacterial meningitis and donors with proven *Naegleria fowlerii* meningoencephalitis' (57). The UK and US guidance is mirrored by that from the Council of Europe (2015), which states 'if the aetiology of an active infection cannot be established the donor is not a suitable candidate for donation' (124). Despite current guidance, organs from donors where the cause of meningitis and encephalitis is not known continue to be used for transplantation, as clinicians balance the risk of donor transmitted disease against that of death on the waiting list whilst awaiting a graft. I reviewed the UK experience, to better understand the extent to which organs from deceased donors with meningitis and encephalitis (of both known and unknown cause) have been used for transplantation, and to determine the associated recipient outcomes.

1.20 Methods

1.20.1 Identification of deceased donors who died of Meningitis and Encephalitis

The UKTR was examined to identify deceased donors between 1st January 2003 and 31st December 2014, where the cause of death was meningitis and/or encephalitis, and who donated one or more organs for transplantation. All UK deceased donors whose cause of death was coded in the UKTR as 'meningitis' were readily identified. However, the designated codes for cause of death in the UKTR are limited to any one of 65 possible causes and there is no code for encephalitis on the registry currently, leaving the data entry team the option of coding cases of encephalitis as 'meningitis', 'infection-type unclassified', 'other', 'other-please specify' and 'unknown' and using the free text entry to specify encephalitis as the cause of death. All free text entries in the registry for donors whose primary cause of death was coded as

'meningitis,' were fully reviewed to identify if the infection had been recorded as viral, bacterial, was not known or was unstated, and whether the causal infectious agent had been recorded. For deaths coded as 'infection-type unclassified', 'other', 'other-please specify' and 'unknown', free text entries were searched using the search terms 'Meningitis', 'Encephalitis', 'Meningo-encephalitis', and common misspellings of these terms to identify any additional donors where the cause of death was meningitis/encephalitis and to find whether the causal agent had been identified. The information on organ donors entered into the UKTR is that entered at time of donation, and any subsequent changes in cause of death or in causative agent for meningitis or encephalitis are relayed to the recipient centres but not changed on the registry.

1.20.2 Identification of potential donors who died of meningitis and encephalitis

The PDA was examined to identify all non-proceeding potential donors who died of meningitis and encephalitis over the study period. Potential organ donors were identified in the same way as those in the UKTR, with cause of death coding supplemented by free-text searches.

1.20.3 Identification of recipients who received organs from donors who died of known and unknown causes of meningitis and encephalitis

Recipients of organs from donors who died of known and unknown causes of meningitis/encephalitis in the UK between 1st January 2003 and 31st December 2014 were identified using the UKTR. Information on recipient survival and death censored graft survival was collected from the UKTR.

1.20.4 Statistical Analysis

Principal univariate analyses reported deceased donor and recipient characteristics by donor meningitis and encephalitis status (known cause meningitis and encephalitis (KME), unknown cause meningitis and encephalitis (UKME), other) using percentages, means or medians and standard deviations or interquartile ranges as appropriate. Univariate analysis

was carried out using t-test for continuous data. Comparisons between groups were made using χ^2–tests for categorical data, and unpaired difference tests for continuous data (one-way ANOVA if normality can be assumed, Kruskal-Wallis test otherwise).

Kaplan-Meier curves were used to compare death-censored graft survival and patient survival across donor cause of death groups. The univariate log-rank test was used to calculate p-values from this.

Cox proportional hazards regression model was fitted in a stepwise selection method in order to identify the combined effect of factors on patient and graft survival. Log cumulative hazard plots were drawn and proportionality of hazards was checked using log-log plots of the hazard. There was no evidence of non-proportionality of hazards.

Donor related variables included in the multivariate model were donor age, donor type (DBD or DCD), ethnic group, gender, past medical history of diabetes and hypertension, liver disease, cardiac disease, previous drug abuse, smoking history and if the donor died of a known or unknown cause of meningitis/encephalitis. Recipient factors included were recipient age, ethnicity, gender, sensitization (for the renal model), primary renal, liver or heart disease, HLA group, and cold ischaemic time (CIT).

1.21 Results

1.21.1 Identification of donors who died from meningitis and encephalitis

A total of 258 (2.4%) of the 11,530 deceased donors, who donated one or more organs for transplantation, were identified as having died of a meningitis and encephalitis over the 12-year study period. Of the 258 organ donors identified, 214 (1.9%) were directly coded by the UKTR as having died of meningitis (Figure 3.1). A further 44 donors were not coded as meningitis but it was clear from free text entries that they had died of meningitis or encephalitis/meningo-encephalitis. Further analysis of free text entries in the UKTR for these donors showed that 85.7% had meningitis and the remaining 14.3% had encephalitis or meningo-encephalitis.

There were 221 organ donors who died from meningitis of which 169 (76.5%) had a bacterial cause, 2 (1.4%) a viral cause and in 50 cases (22.6%) the aetiology was unknown or unstated (Figure 3.1). Thirty-seven donors died from encephalitis and/or meningo-encephalitis, of which a bacterial cause was thought to be responsible in 11 (29.7%), a viral cause in 6 (16.2%) and in 20 (54.1%) of cases, the cause was unknown or unstated. Where the cause of meningitis and encephalitis was thought to be known, the causative infectious organism was stated in 63% of meningitides and 19% of encephalitides (Table 3.1). Most of the bacterial meningitides were attributed to a streptococcal or meningococcal cause.

Meningitis			
Bacterial	**n = 140**	**Viral**	**n = 1**
Streptococcal	85	Varicella-Zoster Virus	1
Meningococcal	32		
Staphylococcal	7		
Other gram positive organism	6		
Listeria	4		
Other gram negative organism	3		
Klebsiella	2		
Enterococcus	1		

Encephalitis			
Bacterial	**n = 6**	**Viral**	**n = 1**
Streptococcal	4	Varicella-Zoster Virus	1
Meningococcal	2		

Table 3.1. Causal infectious agents in organ donors who died from meningitis and encephalitis. Of the 258 donors who died from meningitis/ encephalitis 148 (57.4%) had a causal agent stated.

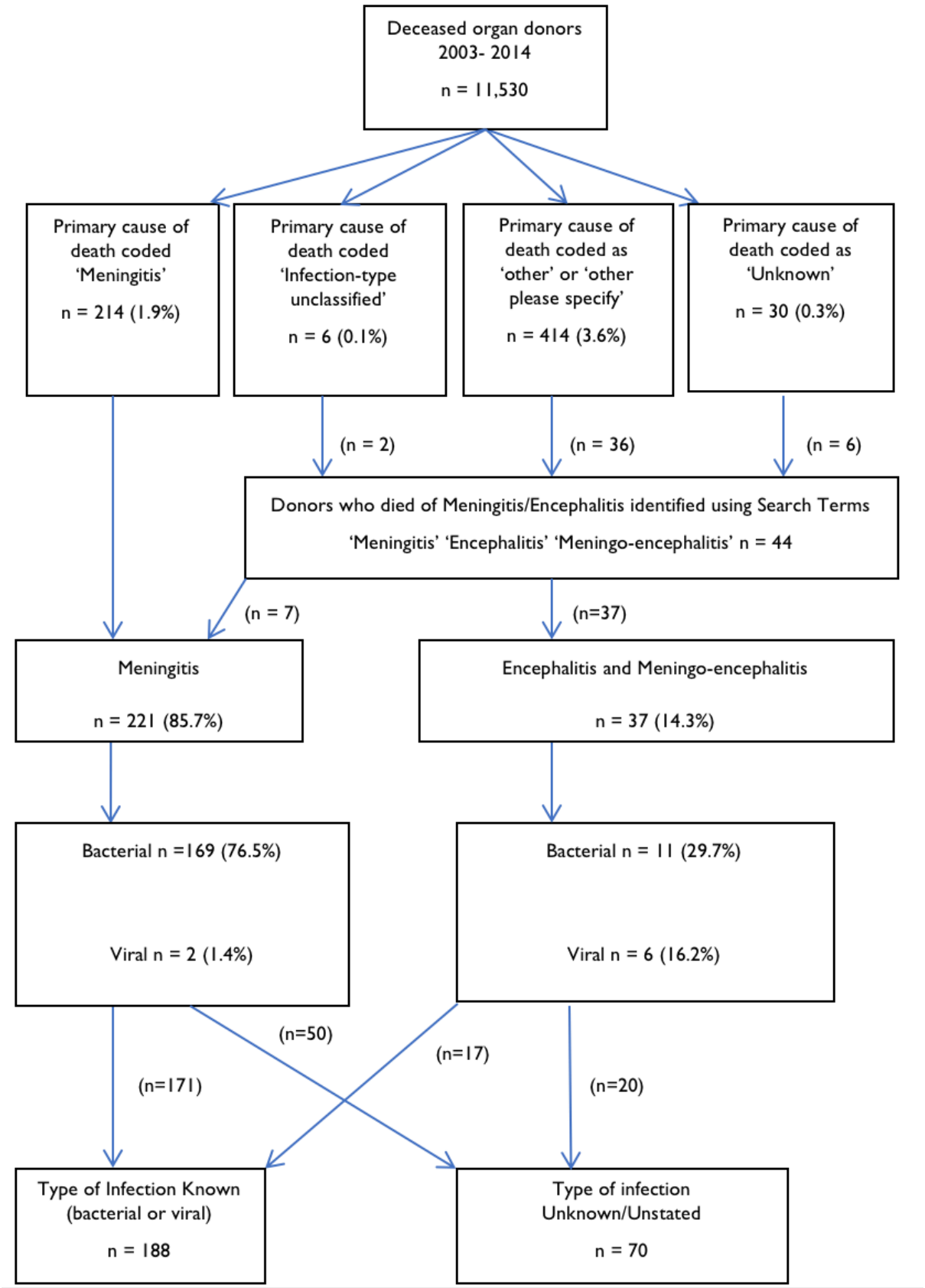


Figure 3.1. Flow diagram for organ donors identified as dying from meningitis and encephalitis

The UK PDA was scrutinized to identify patients less than 80 years with meningitis and encephalitis that did not proceed to organ donation and therefore were not entered on the organ donor transplant registry.

Over the 12-year study period, a total of 668 patients died of meningitis/encephalitis did not donate organs for transplantation. Whereas the number of patients who died of meningitis and encephalitis was greater in the latter part of the study period, the number of actual organ donors dying of meningitis and encephalitis remained relatively constant throughout the study period (Figure 3.2). Clinical details in the PDA of why potential donors did not proceed to organ donation were limited. Analysis of the reasons coded in the database or available in free text entries indicated that 85 (12.7%) of the 668 potential organ donors were declined based on their cause of death, i.e. meningitis and encephalitis.

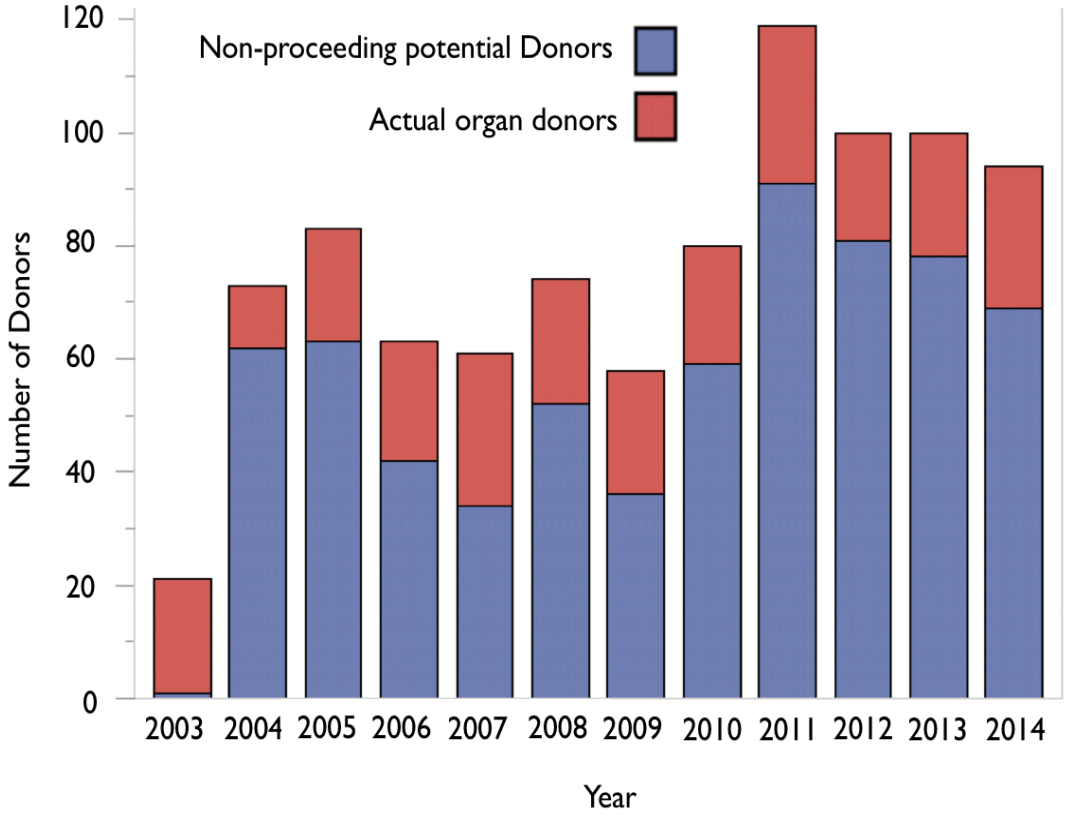


Figure 3.2. The number of non-proceeding potential organ donors with meningitis and encephalitis and, the number of actual organ donors with meningitis and encephalitis.

1.21.2 Characteristics of donors who died of meningitis and encephalitis

The clinical characteristics of the 221 organ donors with meningitis and the 37 donors with encephalitis were very similar and were, therefore, combined and compared to those who died of all other causes during the study period (Table 3.2). Organ donors who died of meningitis/encephalitis were younger and there were more DBD than DCD donors. They also, on average, donated more organs and more of the donated organs were transplanted. Overall, donors with meningitis/encephalitis had a lower body mass index (BMI) and lower incidence of hypertension, cardiac disease, and were less often smokers.

1.21.3 Characteristics of recipients receiving organs from donors who died of meningitis and encephalitis

The 258 organ donors with meningitis and encephalitis provided a total of 899 solid organs that were transplanted (455 kidneys, 237 livers, 71 hearts, 44 lungs, 7 heart and lung, 72 pancreata (including simultaneous kidney pancreas transplant (SPK)) and 13 other solid organ transplants). The types of organs transplanted were similar in deceased donors with known and unknown causes of meningitis and encephalitis.

	All other deceased donors (n = 11272)	Donors with Meningitis and Encephalitis (n = 258)	P value
Age (y)*	48.0 ± 16.6	34.0 ± 19.9	<0.001
Male/ Female (%)	54/ 46	52/ 48	0.602
DBD/ DCD (%)	69/ 31	88/ 12	<0.001
Number of Organs donated/donor	3.5 ± 1.5	4.0 ± 1.7	<0.001
Number of Organs Transplanted/donor	3.0 ± 1.5	4 ± 1.5	<0.001
BMI	26.3 ± 5.6	25.1 ± 6.9	<0.001
Diabetes			0.767
Yes/ No	714 (6%)/10182 (90%)	13 (5%)/239 (93%)	
Missing/Unknown	376 (3%)	6 (2%)	
Hypertension			<0.001
Yes/ No	2902 (26%)/ 7891 (70%)	22 (9%)/230 (89%)	
Missing/Unknown	479 (4%)	6 (2%)	
Cardiac Disease**			0.019
Yes/No	1129 (10%)/9637 (85%)	13 (5%)/240 (93%)	
Missing/Unknown	506 (5%)	5 (2%)	
Liver disease			0.125
Yes/No	367 (3%)/10316 (92%)	3 (1%)/249 (97%)	
Missing/Unknown	589 (5%)	6 (2%)	
Alcohol Abuse			0.022
Yes/No	1563 (14%)/9280 (82%)	21 (8%)/230 (89%)	
Missing/Unknown	429 (4%)	7 (3%)	
Drug Abuse			0.301
Yes/No	663 (6%)/10151 (90%)	10 (4%)/242 (94%)	
Missing	458 (4%)	6 (2%)	
Smoking History			<0.001
Yes/No	5065 (45%)/5846 (52%)	79 (31%)/174 (67%)	
Missing	361 (3%)	5 (2%)	
Cause of death stated as Cerebrovascular accident or Hypoxic brain injury	8485 (75%)	0	

Table 3.2 Clinical characteristics of organ donors who died of known and unknown causes of meningitis and encephalitis and donors who died from all other causes

UK centres transplanted a total of 455 kidneys from donors who died of known and unknown causes of meningitis and encephalitis. All 24 UK transplant centres accepted kidneys from donors with both KME and UKME (Figure 3.3). Over the entire study period, these comprised 1-11% of the total number of renal transplants performed (Figure 3.3). There was no clear relationship between the volume of transplant activity at a particular centre and the proportion of transplants performed using kidneys from donors with KME and UKME. The clinical characteristics of recipients who received kidneys from donors who died with an unknown cause and those with a known cause (bacterial or viral) of meningitis and encephalitis are shown separately and are compared with the recipients of non-meningitis/encephalitis organs (Table 3.3). There were no major clinical differences between recipients who received kidneys from donors who died of known and unknown causes of meningitis and encephalitis. Overall, however, recipients who received kidneys from donors with meningitis and encephalitis were markedly younger than those who received kidneys from deceased donors who died from other causes. The recipients of kidneys from donors with UKME and KME received kidneys, which had a better HLA-match than those from donors who died from other causes.

	Transplant recipients from donors with UKME (n =122)	Transplant recipients from donors with KME (n= 333)	Transplant recipients from all other causes of death donors (n =19092)	P value
Age (y)*	40.6 ± 15	41.1 ± 16.9	47.6 ± 14.9	<0.001
Gender				0.884
Male	83 (68%)	202 (61%)	11847 (62%)	
Female	39 (32%)	131 (39%)	7235 (38%)	
Not stated	0	0	10 (0.5%)	
Ethnicity				0.466
White	102 (83%)	261 (78%)	15165 (79%)	
Other/Not specified	20 (16%)	72 (22%)	3927 (21%)	
cRF>85%**	12 (10%)	37 (11%)	1677 (9%)	0.309
Wait time	531 (996)	638 (1085)	770 (1075)	0.004
Previous Transplants	19 (16%)	65 (20%)	2858 (15%)	0.131
HLA Mismatch				0.005
1 (well matched)	20 (16%)	52 (16%)	2570 (13%)	
2	44 (36%)	126 (38%)	6202 (33%)	
3	42 (35%)	102 (31%)	7944 (42%)	
4 (poorly matched)	15 (12%)	50 (15%)	2316 (12%)	
Missing/Unspecified	1 (1%)	3 (1%)	60 (<0.5%)	
Primary Renal Disease				0.041
Glomerulonephritis	10 (8%)	36 (11%)	2788 (15%)	
Polycystic Kidney Disease	11 (9%)	30 (9%)	2066 (11%)	
Diabetes (types 1 and 2)	20 (16%)	42 (13%)	2823 (15%)	
Other/Not reported	81 (66%)	225 (67%)	11404 (59%)	

Table 3.3. Clinical characteristics of kidney transplant recipients from organ donors who died of known and unknown causes of meningitis and encephalitis, and from donors who died of all other causes.

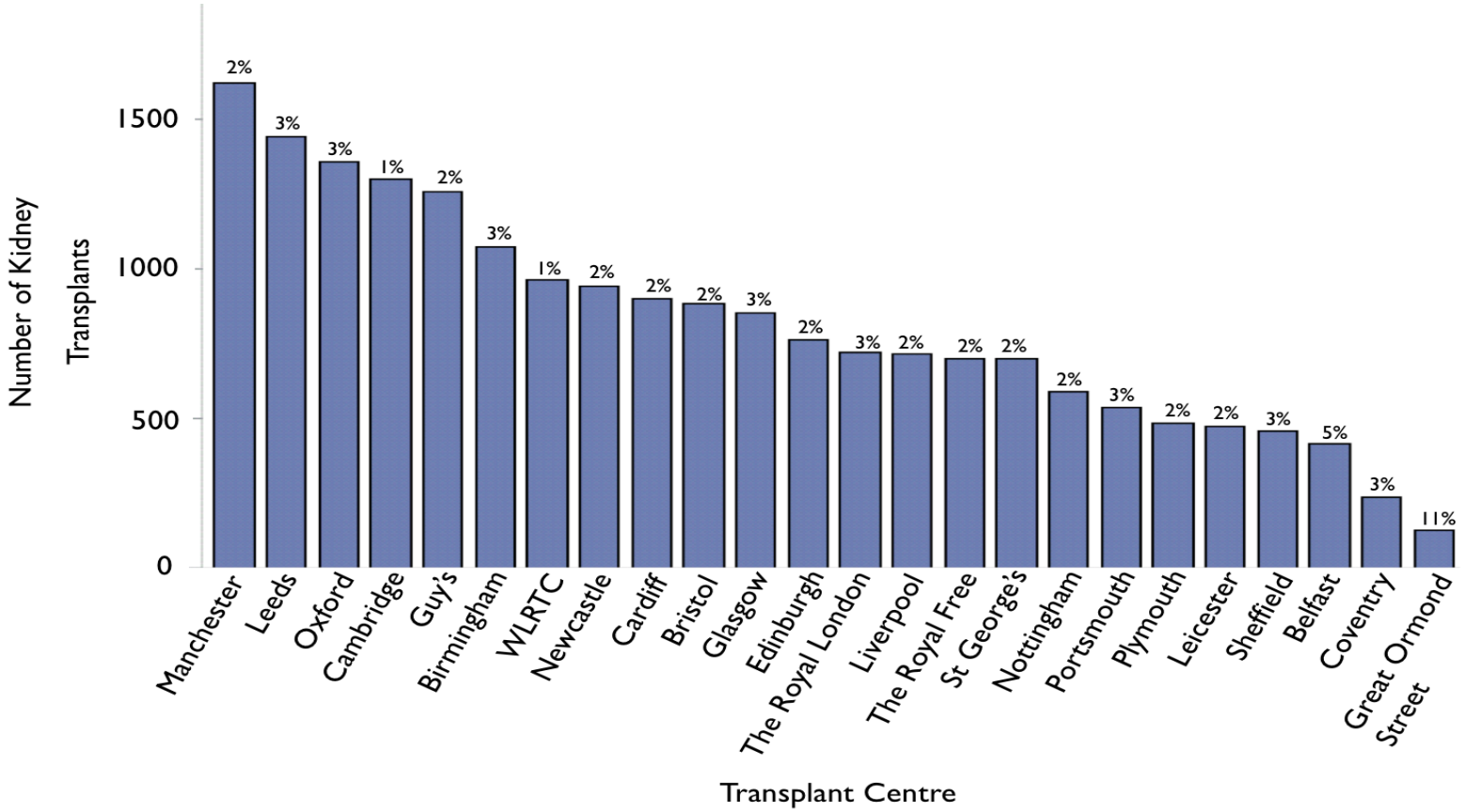


Figure 3.3. Total number of deceased donor kidneys transplanted in UK renal transplant centres from the 1st January 2003 to 1st of January 2015.

For each centre, the number of kidneys transplanted from donors with known and unknown causes of meningitis and encephalitis are shown as a percentage of the total number of deceased donor kidney transplants performed.

1.21.4 Liver Transplant Recipients

The clinical characteristics of the 237 liver transplant recipients who received livers from organ donors with KME and UKME are shown in Table 3.4 along with the characteristics of recipients of livers from donors who died of all other causes. The recipients of livers from KME donors and UKME donors were significantly younger than recipients of livers from donors who died of all other causes. Livers from UKME donors were more frequently allocated to recipients on the super-urgent waiting list (the most urgent category).

	Transplant recipients from UKME donors (n = 70)	**Transplant recipients from KME donors (n =167)**	**All transplants from donors who died of all other causes (n =8246)**	**P value**
Age (y)	36.4 ± 23.0	33.4 ± 23.7	45.2 ± 18.6	<0.001
Gender				0.415
Male / Female	38 (54%)/ 32 (46%)	94 (56%)/ 73 (44%)	4937 (60%)/ 3308 (40%)	
Not Stated	0	0	1 (<0.5%)	
Ethnicity				0.182
White / Other or Not specified	61 (87%)/ 9 (13%)	132 (80%)/ 34 (20%)	6973 (85%)/ 1273 (15%)	
Previous Transplants	9 (13%)	14 (8%)	806 (9%)	0.990
UKELD	54 ± 7	54 ± 6	54 ± 6	0.889
Urgent status	16 (23%)	27 (16%)	1220 (14%)	0.151
Primary Liver Disease				0.828
Primary Biliary cholangitis	10 (14%)	6 (4%)	597 (7%)	
Hepatitis C liver cirrhosis	6 (9%)	15 (9%)	1023 (13%)	
Alcoholic Liver disease	7 (10%)	18 (11%)	1540 (18%)	
Other/Not stated	47 (67%)	128 (76%)	5086 (62%)	

Table 3.4. Clinical characteristics of liver transplant recipients from organ donors who died of known and unknown causes of meningitis and encephalitis, and from donors who died of all other causes

1.21.5 Heart Transplant Recipients

Over the study period 71 hearts were transplanted from donors who died of meningitis and encephalitis (Table 3.5). Recipients from donors who died of meningitis/encephalitis were younger, and were much more likely to require a heart urgently in comparison to recipients of hearts from donors who died of all other causes (Table 3.5).

	Transplant recipients from donors with UKME (n=15)	**Transplant recipients from donors with KME (n=56)**	**Transplants recipients from all other cause of death donors (n=1482)**	**P-value**
Age (y)*	31.4 ± 26.6	31.2 ± 23.8	38.5 ± 18.7	<0.008
Gender				0.342
Male	8 (56%)	38 (68%)	1041 (70%)	
Female	7 (44%)	18 (32%)	441 (30%)	
Ethnicity				0.197
White	12 (80%)	53 (95%)	1304 (88%)	
Other/Not specified	3 (20%)	3 (5%)	178 (12%)	
Previous Transplants	0	0	30 (2%)	0.481
Urgent status	9 (60%)	40 (71%)	750 (50%)	0.008
Primary Heart Disease				0.935
Idiopathic Dilated Cardiomyopathy	7(46%)	14 (25%)	524 (35%)	
Congenital Heart Disease	1 (7%)	8 (14%)	133 (9%)	
Coronary Heart Disease	1 (7%)	8 (14%)	234 (16%)	
Other/Not stated	6 (40%)	26 (46%)	591 (40%)	

Table 3.5. Clinical characteristics of heart transplant recipients from organ donors who died of known and unknown causes of meningitis and encephalitis, and from donors who died of all other causes

1.21.6 Recipient outcomes after transplantation

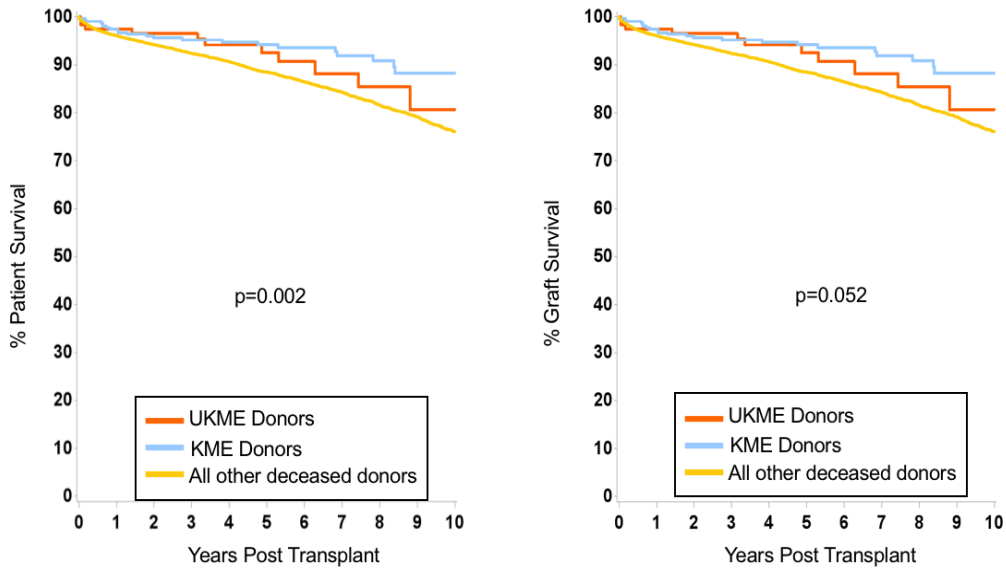
Of the 899 recipients who received transplants from donors with UKME and KME there were 2 early deaths attributable to donor transmission of encephalitis. The donor was a 39-year-old male who died in hospital with a

meningo-encephalitis of unknown aetiology. The renal recipients, males aged 67 and 42, died of encephalitis 17 days and 19 days respectively following transplantation. On post-mortem examination, the transmitted organism was found to be the nematode infection *Halicephalobus gingivalis*. It is the first documented UK case and first documented human-to-human transmission of this organism, and only the 6th, 7th and 8th documented cases of human infection. The UKTR did not include any other reports of death, graft loss or major morbidity secondary to disease transmission from any of the other donors with UKME or KME. Only one other of the 455 recipients of kidneys from donors with UKME or KME died within 30 days of transplantation, and death in this case was attributed to cardiovascular disease, giving a thirty day mortality of 0.7%, which is similar to the thirty-day mortality in renal transplant recipients who received kidneys from donors who died of all other causes (153 deaths in 19,095 recipients (0.8%)). In the 444 recipients of non-renal organs from donors with UKME and KME, there were 14 deaths within 30 days (3.2% 30 day mortality rate vs. 3.7% in recipients of organs from donors without UKME or KME), of which 3 deaths were attributed to a neurological cause and in all of these death followed a cerebrovascular accident (CVA). Of the three deaths from CVA, one recipient died of an ischemic stroke 11 days after receiving a liver from a donor with an unknown cause of encephalitis who also donated 2 kidneys for transplantation, one recipient died of a stroke (type unstated) 28 days after receiving a liver from a donor with a unknown cause of meningitis who also donated 2 kidneys for transplantation, and one recipient died of a haemorrhagic stroke 12 days after receiving a heart from a donor with *E.coli* meningitis who donated 2 kidneys and a liver for transplantation. In none of these three patients was any mention made in the free text entries to suggest the CVAs were in any way related to the transmission of infection.

Overall patient survival was significantly better in recipients of kidneys from donors with KME (p=0.002). After adjustment using Cox proportional hazard model the survival advantage was secondary to lower donor age, lower recipient age, a greater proportion being DBD donors and the donors possessing fewer comorbidities (p=0.06). Death censored graft survival for

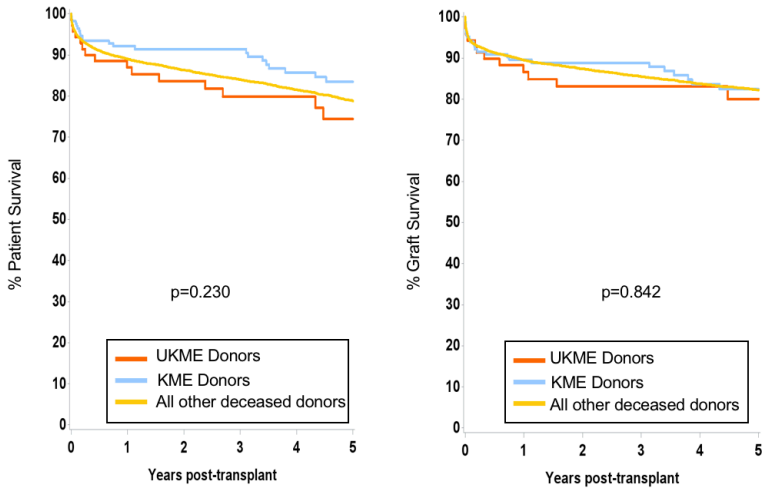
recipients of kidneys from donors with KME was greater than that for recipients of kidneys from donors who died of any other cause of death, but this difference failed to reach statistical significance (Figure 3.4). Patient and graft survival was similar for kidney recipients from UKME donors and recipients from donors who died from other causes.

Death-censored graft survival and patient survival were comparable for heart and liver recipients from UKME and KME donors when compared to all other cause of death heart and liver transplant recipients (Figure 3.5 and Figure 3.6).



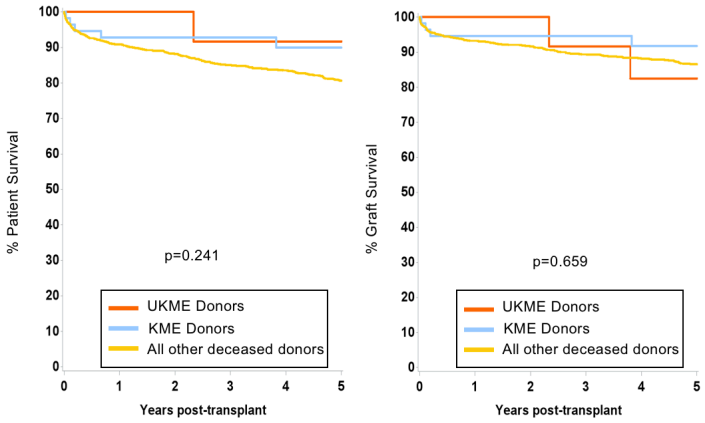
Donor Type	Total Number	5 years Patient Survival: Number at risk	10 years Patient survival: Number at risk
UKME	122	58 (93%)	12 (82%)
KME	333	167(94%)	37 (88%)
All other deceased donors	19092	8307 (89%)	1967 (76%)

Figure 3.4. Patient and death censored Graft Survival for recipients of kidneys from organ donors who died of known and unknown causes of meningitis and encephalitis, and organ donors who died from all other causes. P-value corresponds to score test of the overall null hypothesis that there are no differences in survival curves for all groups i.e. comparing survival for all groups.



Donor Type	Total Number	1 year Patient Survival: Number at Risk	5 years Patient Survival: Number at Risk
UKME	70	56 (87%)	26 (73%)
KME	167	136 (92%)	74 (84%)
All other deceased donors	8246	6613 (89%)	3204 (79%)

Figure 3.5. Patient and death censored Graft survival for recipients of livers from organ donors who died of unknown and known causes of meningitis and encephalitis, and organ donors who died from all other causes. P-value corresponds to score test of the overall null hypothesis that there are no differences in survival curves for all groups i.e. comparing survival for all groups



Donor Type	Total Number	1 year Patient Survival: Number at risk	5 years Patient Survival: Number at risk
UKME	15	13 (100%)	8 (92%)
KME	56	46 (93%)	24 (90%)
All other deceased donors	1482	1273 (91%)	694 (81%)

Figure 3.6. Patient and death censored Graft Survival for recipients of hearts from organ donors who died of unknown and known causes of meningitis and encephalitis, and organ donors who died of all other causes. P-value corresponds to score test of the overall null hypothesis that there are no differences in survival curves for all groups i.e. comparing survival for all groups.

1.22 Discussion

The analysis was undertaken to determine the extent to which organs from deceased donors who died of meningitis or encephalitis were transplanted in the UK, and to determine the outcome of recipients who received such organs. Over the 12-year study period, a total of 899 organs were transplanted from 258 donors who died of meningitis or encephalitis. The number of actual organ donors who died of meningitis or encephalitis over the 12-year study period remained relatively constant, and all UK transplant units accepted organs from such donors for transplantation. In the case of kidney transplants, there was evidence that the threshold for accepting kidneys from donors who died of meningitis or encephalitis varied between centres. However, such variability did not correlate with the volume of transplant activity undertaken by the centre.

While donors with meningitis or encephalitis comprised only a small proportion (2.3%) of the total number of deceased organ donors over the study period, they made an important contribution to transplant activity, leading to 455 kidney transplants and 444 non-renal transplants. Moreover, such donors tended to be younger with favourable donor characteristics and overall they donated more organs per donor. The majority (66%) of the entire donor cohort in this analysis who died of meningitis had a known cause of meningitis and therefore the use of their organs for transplantation was not, according to current UK guidelines, contraindicated. Nevertheless, a large proportion (34%) of those who donated organs died of an unknown or unstated cause of meningitis or encephalitis. Use of organs from such donors is cautioned in the UK guidelines, although it is recognised that their use in life saving situations may be appropriate. In the present study, donors with an unknown cause of meningo-encephalitis donated not only lifesaving organs but most (91%) donated at least one kidney for transplantation. We cannot exclude the possibility that, at least in some of these donors, additional reassuring clinical information relating to the aetiology of the meningo-encephalitis (e.g. expert opinion suspecting a bacterial cause that could not be proven) may have been made available to the transplanting centres, but was not recorded in the registry.

In the present analysis, there was no recorded incidence of transmission of the causative agent for meningitis or encephalitis from any of the donors where the causative agent was identified prior to donation. It is important to appreciate that clinical decision making informed the use of organs from donors with meningitis or encephalitis/meningo-encephalitis and it cannot be assumed that if organs from the potential, rather than actual, organ donors with a known cause of meningitis had been used that they also would not have posed a risk of disease transmission. One (2.7%) of the 37 organ donors with encephalitis (representing one (5%) of the 20 organ donors with an unknown cause of their encephalitis) transmitted infection to two renal allograft recipients. In both cases the transmitted infection, which was subsequently shown to be the nematode *H. gingivalis,* was fatal. There were no other recorded cases of disease transmission for patients who died of an unknown cause of meningitis and encephalitis. Overall, recipients of organs from donors who died as a result of a meningitis or encephalitis (known or unknown causes) had similar patient and graft survival to that observed in recipients of organs from donors who died from other causes. Where a bacterial cause of donor meningitis or encephalitis/ meningo-encephalitis was identified, this information would have been available to the recipient transplant centres and it is likely that most, if not all, recipients of such organs would have received prophylactic antibiotic treatment in keeping with clinical guidelines.

The number of actual organ donors with meningitis or encephalitis was around a third of the number of potential donors identified from the UK PDA dying with meningitis or encephalitis but whose organs were not used for transplantation. This figure is considerably higher than the overall percentage of actual to potential organ donors identified from the UK PDA (51). Unfortunately, the data available in the UK PDA was not sufficiently detailed to allow us to determine precisely why potential donors with meningitis and encephalitis did not proceed to become actual organ donors, but in at least 18.7% of cases the reason cited was the underlying cause of death, and presumably concern by recipient centres about disease transmission. It is impossible to estimate how many of these unused potential organ donors

could have transmitted a fatal disease to recipients, and hence how many potential lives were saved through not using these organs for transplantation.

The findings arising from the present analysis may allow clinicians at transplanting centres to make a more informed decision about the risks of disease transmission when considering the use of organs from potential donors with meningitis and encephalitis. The decision to transplant an organ from a donor with meningitis and/or encephalitis, especially where the cause is unknown, should be taken after fully informing the potential recipient of the associated risks.

There are several published case studies that describe examples of donor-derived infection causing meningitis and encephalitis in transplant recipients (116-122). A wide range of pathogens responsible for such disease transmission have been implicated and often it had not been clear before organ transplantation that the donors had meningitis and encephalitis (116-122). An emerging concern in the US is the transmission of West Nile Virus (WNV) from affected donors to transplant recipients, which has been seen in 8 different clusters. Transmission of Lymphocytic Choriomeningitis Virus (LCMV), Balamuthia Mandirallis and Rabies have also been reported (116-122). In the clusters of donor derived infection of meningitis and encephalitis, a wide variety of causes of death of the donors were reported, ranging from urinary tract infection, diabetic ketoacidosis, trauma and stroke (119,120,125). The current literature suggests that the risk of donor transmission of meningitis and encephalitis is omnipresent and exclusion of such donors, who are often relatively young and previously healthy, would not fully address this risk because, in reported cases, the cause of donor death was not always known to be meningitis and encephalitis. It was not possible from the analysis undertaken for the present analysis to determine the number of donors with unrecognized meningitis or encephalitis.

There are also other limitations to the present analysis: encephalitis and meningo-encephalitis were not specifically coded as a cause of death in the UKTR. Nor are the definitions made clear so there may have been some lack of consistency and accuracy between the diagnosis of encephalitis, meningitis and meningo-encephalitis. There is a possibility that the numbers quoted in

this chapter are an underestimate of those who died from these causes. Attempts were made to minimize this possibility by using multiple search terms (and common misspellings of these), and careful review of the free text entries. There is a possibility that cases of disease transmission from donors with meningitis or encephalitis were not reported to NHSBT, as the reporting requirement only became part of UK law in 2012. However, over the entire study period NHSBT has had close oversight of all UK transplant units and it is very unlikely that any transmission of meningitis or encephalitis occurred without NHSBT being made aware of this. Moreover, analysis of the causes of death in the 14 patients who died within 30 days after receiving organs from donors with UKME or KME showed that only 3 were listed as dying from neurological cause (all CVA), and in none of these was infection noted as a contributory cause of death. A further limitation of this analysis is its applicability to the wider global transplant community. Given the relatively limited geographical area of the UK there is limited variation in infectious pathogens. Hence, in other much larger countries, such as the US, where different infectious agents vary geographically and by time of year, additional consideration should be given to the risk that donors with meningitis or encephalitis may pose and what organism could be causing their illness.

Organ donors who die from Immune Thrombocytopaenia in the UK: What risk do they pose to transplant recipients

Publications from this work: Trotter et al. Donors with Immune Thrombocytopenia: Do they pose a risk to transplant recipients?
American Journal of Transplantation. 2017;17(3):796-802.

1.23 Background

The transfer of immunocompetent donor lymphocytes originating from transplanted organs, notably the liver, may result in the development of graft versus host disease (GVHD)(126). GVHD following liver transplantation has been reported in between 0.1-2% of liver transplant recipients and may progress to a fatal multi-system disease (126,127). Donor plasma cells or B-lymphocytes transmitted with an allograft are also known to cause transient haemolysis when donor specific antibodies react against recipient red cells (the passenger lymphocyte syndrome (PLS)) (128,129). In addition to GVHD and PLS, there have been very occasional case reports documenting the transmission of ITP from organ donors to liver transplant recipients with serious consequences (130-132).

Primary ITP is an autoimmune disorder characterized by isolated thrombocytopenia (peripheral blood platelet count <100 x 10^9/L) in the absence of other causes or disorders that may be associated with thrombocytopenia. ITP may also be secondary, when associated with other conditions such as infection, immunodeficiency syndromes, systemic autoimmune disease or malignancy. There is currently no definitive clinical or laboratory parameters that can define ITP and this remains a diagnosis of exclusion after considering alternative causes of thrombocytopenia such as liver disease, medications or bone marrow disorders (133,134). However, there are a number of antibodies to specific platelet glycoproteins that have been identified in patients with ITP. Testing for these antibodies is not recommended as platelet associated IgG is not specific to ITP, and has been detected in non-immune thrombocytopaenia (134). ITP typically presents with bruising and mucosal bleeding. Although many patients have no bleeding or minimal bruising, serious and sometimes fatal intracranial or gastrointestinal

bleeding can occur (135). Primary ITP is a rare disorder with an age-adjusted prevalence of 9.5 per 100,000 in the United States (US) and an incidence of 2.7 per 100,000 in Northern Europe (136). In children, ITP may follow viral infection and resolve spontaneously. In contrast, ITP in adults can have a subtle onset and is usually chronic in nature.

First line treatment for ITP is usually steroids or intravenous immunoglobulins (IVIg). Subsequent therapy may involve immunosuppression (e.g. rituximab, mycophenolate or azathioprine), surgical splenectomy or thrombopoietin receptor agonists (e.g. eltrombopag or romiplostim) (134).

In Transplant-Mediated Alloimmune Thrombocytopaenia (TMAT), donor leucocytes from an organ donor with ITP produce anti-platelet antibodies that bind platelet membrane epitopes such as glycoprotein (GP) IIb/IIIa common to both donor and recipient. Only 5 cases of TMAT have been previously reported, all following liver transplantation. In all cases TMAT was distinguished by severe and sudden onset thrombocytopaenia with platelets $<10 \times 10^9$/l within three days of liver transplantation (130-132). While TMAT is a rare complication of liver transplantation, there has been no attempt to estimate the risk of disease transmission from organ donors with recent or past history of ITP. Consequently, there is no current guidance in the UK or the US with regards to the safety of using organs from donors with ITP. To help inform policy on the use of organs from donors with a history of ITP we undertook a retrospective registry analysis to establish the number of donors with ITP from which organs were used for transplantation and their associated recipient outcomes.

1.24 Methods

1.24.1 Identification of Donors who died of ITP

The UKTR was used to identify all organ donors with a diagnosis of ITP. The UKTR was interrogated using the search terms *'ITP' 'Idiopathic Thrombocytopaenic Purpura', 'Immune Thrombocytopaenia'* (and common misspellings and alternative combinations of these words) for all UK deceased and living organ donors between 1st January 2000 and 31st December 2015.

In donors identified as having a pre-donation diagnosis of ITP, a search was made of their records to establish: the duration of ITP, what treatments (if any) had been received and their platelet counts at time of death. A diagnosis or a past medical history of ITP recorded in the UKTR meant that the donor was included in the analysis.

1.24.2 Identification of Recipients from Donors with ITP

The recipients of organs from donors who had ITP were identified from the UKTR. Information regarding patient and graft survival was collected from the registry. The platelet count on the third post-operative day and any subsequent history of TMAT or ITP in the transplant recipient was obtained from the recipient's respective transplant centre.

1.25 Results

1.25.1 Organ Donors with ITP

Over the 16-year study period there were 20,440 potential deceased donors of which 24 had diagnosis of ITP at the time of organ donation. None of 11,843 living donors over this time period were known to have ITP. Of the 24 deceased donors with history of ITP, information on whether specific treatment was given for ITP was available for 14 of them. Of these, two of the patients with ITP died of ICH before any specific treatment was administered. Of the remaining 12 patients, treatment comprised IVIg and/or steroids (n=9), splenectomy alone or splenectomy plus rituximab, eltrombopag and romplistim (n=2), and IVIg plus rituximab (n=1). Twenty-one of the 24 potential deceased donors with ITP proceeded to organ donation. Three donors with ITP did not proceed to organ donation, because of withdrawal of family consent (n=1), positive Human T-Lymphotropic Virus (HTLV) n=1), and prolonged time to asystole after withdrawal of life supporting treatment (n=1).

1.25.2 Clinical Characteristics of Donors with ITP

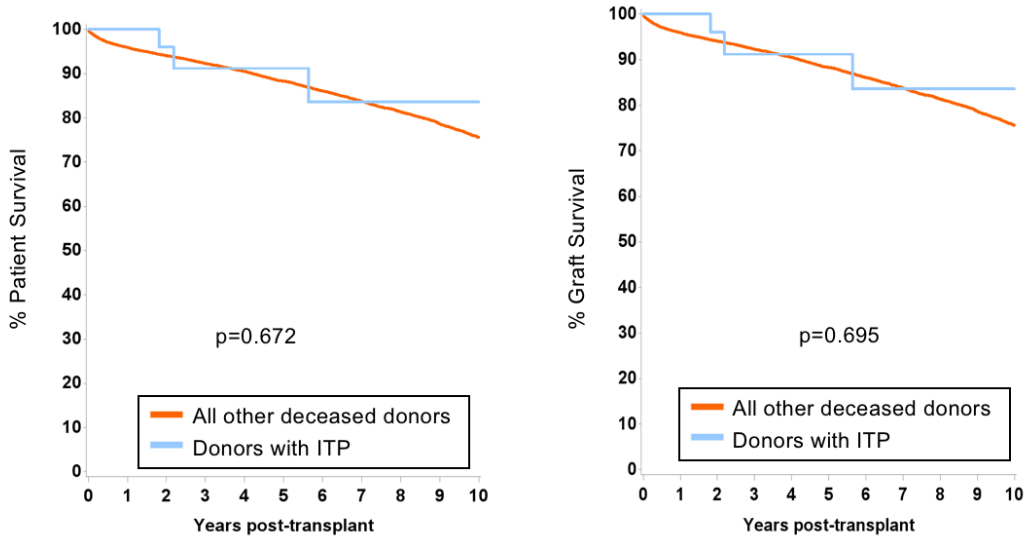
Compared with deceased organ donors who did not have ITP, organ donors with ITP were of similar age (median 49, Interquartile range (IQR) (23-63) vs.

49 (36-59), p=0.520), and gender (10 (48%) male vs. 7400 (54%) male, p=0.666). Donors with ITP were significantly more likely to have died from ICH (18 (85%) vs. 7864 (57%), p<0.001) and have a lower platelet count at donation (median 56 $x10^9$/l IQR (33-90) vs. median 203 x 10^9/l IQR (147-267), p<0.001) compared to donors without ITP. Donors with ITP donated organs, which led to 49 organ transplants [31 kidney transplants (including 3 simultaneous kidney-pancreas (SPK) transplants), 14 liver transplants and 4 heart transplants].

1.25.3 Clinical Characteristics of Kidney transplant recipients

The 31 kidney transplant recipients from organ donors with ITP and recipients of kidneys from those without ITP were of similar age (median 43.0 IQR (35-58) vs. median 48.0 IQR (37-58), p=0.272), gender (17(55%) male vs.14165 (62%), p=0.875), ethnicity (22 (71%) white vs. 18260 (80%) white, p=0.214), and HLA mismatch level (39% mismatch level 1 and 2 vs. 49% mismatch level 1 and 2, p=0.545). None of the 31 recipients developed ITP or TMAT in the early post-transplant period, although one recipient developed what was assumed to be sporadic ITP 8 years post-transplantation. The median platelet count on day-three after transplantation with a kidney from a donor with ITP was 179 $x10^9$/l (IQR 124-210).

Survival analysis comparing renal transplant recipients from donors with ITP and from all other deceased donors demonstrated no difference in 10-year death censored graft survival (p=0.672) and recipient survival (p=0.695) (Figure 4.1).



Donor Type	Total Number	5-year patient survival: Number at risk	10-year patient survival: Number at risk
Donor with ITP	31	13 (92%)	4 (84%)
All other deceased donors	22848	11651 (88%)	4593 (76%)

Figure 4.1. Patient and Graft survival of renal transplant recipients from organ donors with ITP and all other deceased organ donors

1.25.4 Clinical Characteristics of Liver transplant recipients

The 14 liver transplant recipients from organ donors with ITP and recipients of livers from those without ITP were of similar age, gender, ethnicity, UKELD score, primary liver disease, and had the same proportion of recipients that were listed urgently for a liver transplant (Table 4.1).

Platelet counts were recorded for all liver transplant recipients on day zero and day three post transplantation, with a median platelet count on day three of 49 x 10 ^{9}/l (IQR 24-76) and a median platelet count drop of 38 x 10^{9}/l (IQR 17-70) from day zero to day 3 (figure 4.2). The platelet count of liver transplant recipients fell in 12 of the 14 cases (86%) (Figure 4.2). These platelet counts were compared to the last 3 years of liver transplant recipients' day 0 and day 3 platelet counts at Addenbrooke's hospital in Cambridge (n=259). The median day 3 platelet count in this cohort was 44 x 10^{9}/l (IQR 30-58) and when the platelet counts dropped post liver transplantation, the

median platelet count drop was 18x10^9/l (IQR 10-31), which was not significantly different to the drop observed in liver recipients from organ donors with ITP (p=0.456). None of the liver transplant recipients from Cambridge had a platelet count <10x 10^9/L on day 3-post transplantation.

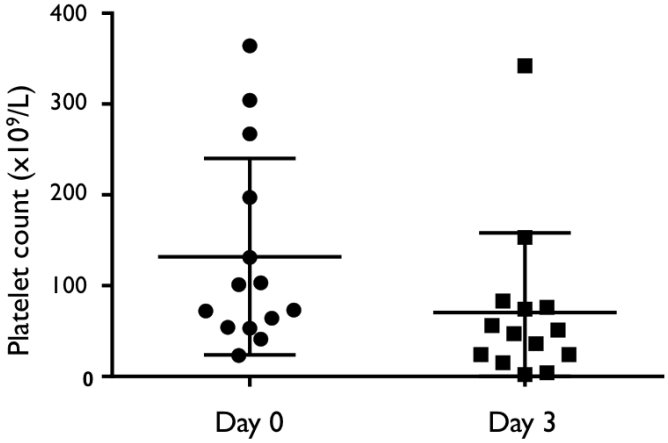
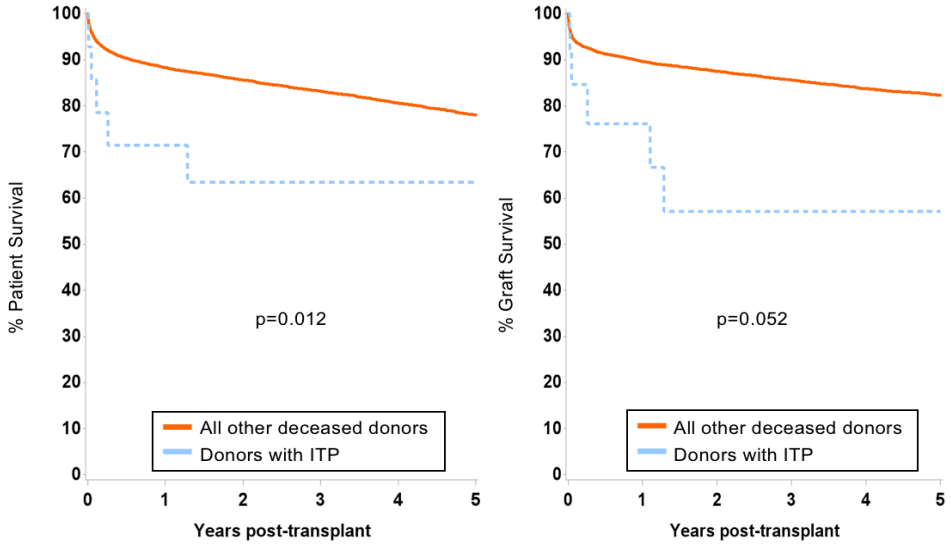


Figure 4.2. Liver transplant recipients from donors with Immune thrombocytopenia day 0 and day 3 platelet counts

In all cases the recipient centres were contacted regarding any possible diagnosis of TMAT. One of the liver recipients, a 61-year-old male, developed TMAT post transplantation. His platelet count dropped on day three to 2 x 10^9/l, and he subsequently died 18 days post liver transplantation secondary to pulmonary haemorrhage and multi-organ failure. Platelet antibodies specific to GPIb\XI identified in the donor were also found in the recipient following transplantation, but were absent from the recipient's serum sample taken 14 days prior to transplantation. The donor liver time-zero biopsy showed marked extramedullary haematopoiesis. There was no evidence of TMAT in the recipient of a single kidney from the same donor. One liver transplant recipient developed hepatic artery thrombosis and needed urgent re-transplantation and one died secondary to haemorrhage from a ruptured vascular aneurysm (Table 4.1). Graft and patient survival were inferior in recipients of livers from donors with ITP compared to those who received livers from all other deceased donors (Figure 4.3), although, when the death of the single patient with TMAT was excluded, patient and graft survival were similar in recipients of livers from donors with ITP and all other deceased donors (p=0.19) (Figure 4.3). None of the other early causes

of death or graft failure in the liver recipients from donors with ITP were thought to be secondary to TMAT.



Donor Type	Total Number	1 year patient survival: Number at risk	5 year patient survival: Number at risk
Donors with ITP	14	11 (79%)	9 (64%)
All other deceased donors	10494	9441 (90%)	8909 (85%)

Figure 4.3 Patient and death censored Graft survival of liver transplant recipients from organ donors with ITP and from all other deceased organ donor

1.25.5 Heart Recipients

The four recipients of hearts from organ donors with ITP were of similar age (median 43.0, p=0.736) ethnicity (75% white vs. 90% white, p=0.307), and gender (75% male vs. 62% male, p= 0.604) to all other deceased donor heart transplant recipients. The day three platelet counts were 143, 96, 53, and 96 x 10^9/l respectively. Two of the recipients developed thrombocytopenia more than three days post-transplant. In one case, this was attributed to use of anti-thymocyte globulin (ATG). The other was investigated extensively for their low platelet count, and anti-platelet antibodies were absent (anti-GPIIb/IIIa, GPIa/IIa, GPIb/IX, HLA, CD109). The nadir of their thrombocytopenia was a platelet count of 34 x 10^9/l seven days post cardiac transplantation. The recipient died 12 days post- cardiac transplantation from

allograft dysfunction and donor organ failure. The thrombocytopenia was thought to be secondary to continuous haemofiltration.

	Transplant recipients from donors with ITP (n = 14)	**All transplants from donors without ITP (n =10499)**	**P value**
Age (y)	46.0 (28-51)	50.0 (36-58)	0.190
Gender			0.642
Male/Female (%)	10 (71%)/4 (29%)	6201 (59%)/4297 (41%)	
Not Stated	0	1 (<0.5%)	
Ethnicity			0.374
White/ Other/Not specified	13 (93%)/ 1 (7%)	8839 (84%)/ 1660 (16%)	
UKELD	55 ± 3	54 ± 6	0.69
MELD	16.5 ± 4.4	16.8 ±7.1	0.867
Urgent status	3 (21%)	1580 (15%)	0.50
Primary Liver Disease			0.999
Primary Sclerosing Cholangitis	2 (14%)	778 (7%)	
Hepatitis C liver cirrhosis	0	1350 (13%)	
Alcoholic Liver disease	2 (14%)	1837 (18%)	
Other/Not stated	10 (71%)	6534(62%)	
Cause of Graft failure			<0.001
Hepatic Artery thrombosis	1 (14%)	235 (8%)	
Chronic Rejection	1 (14%)	214 (7%)	
Biliary Complications	1 (14%)	91 (3%)	
Death with functioning graft	2 (28%)	1115 (38%)	
Primary Graft Failure	1 (14%)	181 (6.1%)	
TMAT	1 (14%)	0	
Cause of Death			<0.001
Haemorrhage from ruptured vascular aneurysm	1 (20%)	8 (<0.5%)	
Pulmonary Infection	2 (40%)	118 (4%)	
TMAT	1 (20%)	0	
Metabolic Brain Injury	1 (20%)	0	
Other	0	2425 (91%)	

Table 4.1. Clinical Characteristics of liver transplant recipients from deceased organ donors with Immune thrombocytopenia (ITP) and all deceased donors without ITP

1.26 Discussion

The analysis in this Chapter has described, for the first time, a national experience of using donors with ITP and has established that clinically significant TMAT is not a common occurrence in organ transplant recipients. Although donors with ITP make up a very small proportion of the total donor pool (0.15%), they made a significant contribution to organ transplantation with a total of 49 organ transplants, and because of the discrepancy between organ supply and demand it is imperative that organs from donors are not rejected unnecessarily (137).

The absence of TMAT in 31 kidney and 4 heart transplant recipients from the series is consistent with three previous TMAT cases following liver transplantation, in which recipients of other organs (5 kidneys and a heart) from the same donors with ITP did not develop TMAT (130,132). Passenger lymphocyte induced haemolysis is most frequent following haematopoietic stem cell transplantation and progressively less likely following heart and lung transplantation, then liver/small bowel/pancreas then kidney transplantation in proportion to the number of transplanted lymphocytes (138). A larger number of lymphocytes transmitted to the recipient in the donor graft may therefore explain why TMAT has occurred following liver but not kidney or heart transplantation.

With only one TMAT case in this series it is not possible to identify characteristics of donors with ITP that could distinguish those whose organs carry the greatest risk of TMAT. In this case series, and in all five previous TMAT cases, the donors all died of ICH and had platelets $<20 \times 10^9$/l prior to death. Of the five ITP donors with a reported clinical history three had been refractory to multiple therapies including splenectomy, but two died as result of ICH as part of their acute ITP presentation. Failure of the donor with ITP to respond to splenectomy suggests that their liver is a major site of platelet destruction by the reticuloendothelial system(75,76,77). In our series, one recipient of a liver from a donor with ITP who had required splenectomy developed TMAT and one did not. Extramedullary haematopoiesis in the donor liver represents a greater burden of transplanted haematopoetic tissue.

There were a limited number of time zero liver biopsies available, but the degree of extramedullary haematopoiesis and its significance in predicting TMAT could be explored in future studies.

The progressive thrombocytopenia at day zero and three in liver recipients was expected. The platelet count is usually reduced post orthotopic liver transplantation, typically falling to a nadir around post-operative day four, followed by a gradual recovery (139). This thrombocytopenia is thought to be caused by factors such as reduced thrombopoietin production, haemodilution and platelet sequestration in the reperfused liver graft. There may also be patient specific variables such as sepsis, bleeding or disseminated intravascular coagulation (increased platelet consumption), medication, viral infection or heparin induced thrombocytopenia (80). Hence other causes of thrombocytopenia must therefore be considered in cases of suspected TMAT. Furthermore, like ITP, TMAT remains a clinical diagnosis. Serological testing may be supportive if the same anti-platelet antibodies are found in recipient and donor. However, the significance of these antibodies is unclear since it is unknown whether they can be detected in liver recipients of donors with ITP unaffected by TMAT. Secondly, platelet-associated IgG can be elevated in non-immune thrombocytopenia and antibodies to specific platelet glycoproteins cannot always be detected in patients with ITP (81). Hence negative serological testing of donor and recipient does not exclude the presence of TMAT.

The natural history and optimal treatment of TMAT is unclear. In three cases the platelet counts had improved within 1-3 weeks with only IVIg ± steroids (130,132). In two cases refractory to multiple therapies including splenectomy, the platelets recovered following liver retransplantation day 11 for rejection in one case and following retransplantation day 43 for refractory TMAT in the other (131).

The kidney transplant recipient that developed ITP after 8 years post transplantation is not likely to be a donor derived TMAT since lymphocytes do not persist following solid organ transplantation (128). The incidence of ITP is approximately 4 per 100,000 person years but occurs more frequently on the background of immune dysregulation (136). In a series of 256 liver transplant

recipients, 8 (0.7%) cases of new ITP occurred at a median time from transplant of 53.5 months (range 1.9-173) (100).

There are some limitations to this analysis. The retrospective nature of the registry analysis may limit the accuracy and completeness of the donor and recipient data; the numbers presented in this analysis are likely an underestimate of the actual number of donors who had ITP as well as the impact of TMAT, as other than the single TMAT case there were no recipients with severe day three thrombocytopenia. However, we cannot exclude the possibility of milder episodes of TMAT that were not recognized as such by the treating teams.

The potential to increase organ donation from deceased organ donors with a history of increased risk behaviour for the transmission of blood-borne viral infection

Publications from this work: Trotter et al. Deceased organ donors with a history of increased risk behaviour for the transmission of blood-borne viral infection: The UK experience. Transplantation. 2017; 101(7):1679-1689.

1.27 Introduction

Unintended HCV, HBV, HIV and HTLV from deceased organ donors is a rare but serious complication of organ transplantation (113). This risk is minimised by performing relevant laboratory screening investigations in deceased donors prior to implantation of their organs. Currently available screening strategies cannot completely discount the presence of a recently acquired viral infection, and considerable importance is attached to the identification of donors with a history of increased risk behaviour (IRB) associated with the acquisition of HCV, HIV, HBV and HTLV (57,66,113,140). While the discard of organs from those with a history of IRB would minimize disease transmission, it would markedly reduce the number of transplants performed. Consequently, the risk of disease transmission from donors with IRB needs to be balanced against the potential benefits of organ transplantation.

Solid organ donors who have a history of prior or current intravenous drug use (IVDU), or of recent or historical imprisonment, and those who have a history of high-risk sexual behaviour are viewed at greatest risk of transmission of BBV (140,141). In the UK, current guidance from SaBTO and the European Directive on Organ Donation requires that detailed information on 'behavioural history that could have put the donor at an increased risk of blood borne viruses' be obtained (62) The information needed includes 'questions about risk behaviours such as recreational drug use, men who have sex with men (MSM), and risks such as accidental body fluid exposure' (123). UK guidance on donor assessment is consistent with that in the US where the need to assess behavioural risk factors for a donor to be at increased risk of transmitting HIV, HBV and HCV is highlighted (57). The donor history with respect to such IRB also provides an important context for the interpretation of

the results from microbiological screening for HIV, HCV, HBV and HTLV (123,140,142). Current screening tests for viral markers have limited sensitivity, and serological screening may result in an infective window period of up to 70 days following infection when antibodies to virus are undetectable (142).

In this chapter I analyse the UK experience of deceased organ donors, both potential and actual, with a history of IRB, highlighting the overall prevalence and types of IRB. My aim was to establish the impact of IRB on organ donation and utilization, as well as on their transplant recipient outcomes.

1.28 Methods

1.28.1 Identification of deceased organs donors with increased-risk behaviour

The UKTR was examined to identify all deceased organ donors between 1st January 2003 and 31st December 2015, who had a history of any one of the following IRB: IVDU, current or previous imprisonment, MSM, sex in exchange for money or drugs, and high risk sexual partner (defined as a sexual relationship with any of the previously mentioned increased risk groups). For the purposes of this study, “potential donors” were defined as deceased donors for whom consent/ authorization for organ donation had been obtained, “actual organ donors” as deceased donors who had one or more solid organs removed for transplantation on the basis that recipient centres had provisionally agreed to use them for transplantation, and “utilised organ donors” as actual organ donors whose organs were eventually transplanted. The decision as to whether or not a potential donor proceeds to organ donation is dependent on transplant clinicians at individual transplant centres indicating that they are willing to accept the organs for transplantation. There are no centralized clinical advisors involved in this decision.

In the UK, a donor transplant coordinator (designated in 2008 as a SNOD) is required to enquire from the next of kin, medical notes and the potential donor’s family doctor, whether there is a history of IRB and record these findings. Additional UK guidance published in 2000 highlighted the

requirement to screen potential organ donors for behaviour associated with BBV.

Free text entries of all potential donors were searched using the terms ‘intravenous drug use’, ‘sex worker’, ‘Men who have sex with men’ and ‘prison’. All common abbreviations, misspellings, synonymous terms and colloquialisms of the above search terms were also searched. Donors with a history of IVDU and imprisonment were sub-categorised based on whether or not they had been an IVDU or imprisoned during the preceding 12 months. Donors with a history of high-risk sexual behaviour were sub-categorised according to the type of behaviour into any one of ‘high risk partner’, ‘sex worker’, and ‘prior high risk partner’.

It is important to note that a number of patients did not fall into the category of potential donors because formal consent for donation was not sought for a variety of reasons that included a belief by the clinicians caring for the patient that the patient’s IRB would exclude organ and tissue donation. Information on the number of patients who did not progress to become potential donors for the entire study period (2003-2015) was not available but the PDA was interrogated to obtain information on patients excluded from the present analysis. Between 1st January 2009 and 31st December 2015 there were 12,040 potential donors which were included in the present analysis, and during the same period the PDA showed that 1,022 patients with an identified IRB (89% IVDU) did not get consented for organ donation for a variety of reasons that included IRB. For 86 patients excluded from the present analysis, IVDU was stated explicitly as a reason why the patient’s family was not approached for consent for organ donation.

1.28.2 Identification of recipients of organs from donors with increased-risk behaviour

The UKTR was examined to identify recipients of organs from donors with IRB and information on outcome (patient and graft survival) obtained. UK transplant centres are required to notify NHSBT of any potential donor-derived disease transmission and adverse events relating to the donation process.

Details of any donor transmitted infections were collected from a designated transplant incident reporting registry held by NHSBT.

1.28.3 Statistical Analysis

Univariate analysis comparing clinical characteristics between IRB and non-IRB potential donors, who were seronegative for BBV, was carried out using Student's t-test for approximately normal continuous data, and the Mann-Whitney U test for non-normal continuous data. Categorical comparisons were made using the χ^2–squared test.

Kaplan-Meier curves were used to show death-censored graft survival and patient survival and the univariate log-rank test was used to compare unadjusted survival rates.

Cox proportional hazards regression model and a logistic regression model were fitted in a stepwise selection method in order to control for potentially confounding factors. Donor related variables considered for inclusion in the multivariate model were donor age, donor type, ethnic group, sex, past medical history of diabetes and hypertension, liver disease, cardiac disease, smoking history and whether the donor had a history of IRB. Recipient factors included were age, ethnicity, sex, primary renal disease, HLA mismatch level and cold ischaemic time.

1.29 Results

One or more IRB was identified in 659 (3.8%) potential deceased donors, and 454 (3.6%) actual organ donors. Of the potential donors with a history of IRB, 47% had a history of IVDU, 33% a history of imprisonment, 10% were MSM, and 9.9% a history of high risk sexual behaviour. For actual donors with a history of IRB, 41% had a history of IVDU, 37% had a history of imprisonment, and 21% had a history of high risk sexual behaviour, and these proportions did not differ significantly from the behaviours in potential donors (p=0.147).

1.29.1 Organ donors who were seropositive for HIV, HCV, HBV and HTLV

Overall, 285 (1.7%) potential organ donors were found to be seropositive for BBV markers. 104 (36.5%) seropositive potential donors proceeded to organ donation; in contrast to the 78% conversion rate observed in seronegative potential donors ($p<0.001$). Organs from 81 (77.8%) of the seropositive organ donors were subsequently transplanted, compared to 95.7% of seronegative organ donors ($p<0.001$).

Half (50.5%) of potential donors who were seropositive for viral infection had a history of IRB, and in most (78.5%) this included IVDU. A history of imprisonment, MSM and high risk sexual behaviour was less common (16.7%, 2.7% and 2.1% respectively). The clinical characteristics of potential and actual seropositive donors are shown in Table 5.1. Positive serology for HCV was more common in donors with a history of IRB. In contrast, markers of HIV, HBV and HTLV were all more common in seropositive donors with no history of IRB (Table 5.1).

The types of organs from seropositive organ donors that were used for transplantation differed according to whether or not there was a history of IRB. The 62 organ donors with a history of IRB provided 48 livers and 11 kidneys that were used for transplantation, whereas the 42 donors with no history of IRB donated 25 livers and 32 kidneys that were transplanted ($p<0.001$).

	Potential donors with increased-risk behaviour (n=144)		Potential donors with no increased-risk behaviour (n=141)		p-value
	Non-proceeding (n= 82)	Proceeding (n= 62)	Non-Proceeding (n=99)	Proceeding (n=42)	
Age (y) (median and IQR)	45 (35-53)	36 (31-47)	52 (44-59)	47 (38-56)	<0.001
Male / Female (%)	66 (80.5%)/ 16 (19.5%)	38 (62%)/ 24 (38%)	60 (60.6%)/ 39 (39.4%)	26 (61.3%)/ 16 (38.7%)	0.044
White Ethnicity (%)	79 (96.3%)	56 (91.8%)	89 (89.9%)	36 (85.7%)	0.128
HIV antibody	3 (3.7%)	2 (3.2%)	8 (8.5%)	1 (2.4%)	0.420
HCV antibody	77 (93.9%)	59 (95.1%)	62 (62.6%)	27 (64.2%)	<0.001
HBsAg positive	3 (3.7%)	3 (4.8%)	13 (14.3%)	12 (28.6%)	<0.001
HTLV	1 (0.7%)	0	19 (17%)	2 (4%)	<0.001
Increased-risk behaviour- All	82	62			
High risk sexual behaviour	5 (6.1%)	2 (3.2%)			
IVDU	61 (74.3%)	52 (83.9%)			
Prison	16 (19.5%)	8 (12.9%)			
Organs Transplanted					<0.001
Liver		48		25	
Kidney		11		32	
Other organs		0		0	

Table 5.1. Clinical characteristics of potential and proceeding organ donors that were seropositive for HIV, HCV, HBsAg and HTLV

1.29.2 Increased-risk behaviour and organ donation in donors who were seronegative for viral infection

To examine the association between IRB and organ donation, all seropositive potential donors were excluded from subsequent analysis. After exclusion, there were 16,977 remaining potential donors of which 12,737 (75%) proceeded to organ donation (Figure 5.1). A history of IRB was identified in 515 (3%) of potential and 392 (3%) of actual organ donors, suggesting that overall, a history of IRB did not adversely influence the decision to proceed to organ donation. 25% of potential donors with no history of IRB and 24% of

those with a history of IRB did not proceed to donation (p=NS). Potential donors with a history of IRB were, when compared to those with no history of IRB, much younger, and significantly less likely to have hypertension, cardiac disease and diabetes (Table 5.2). Potential donors with IRB were more likely to be smokers and to have a history of alcohol abuse.

	Potential Donors with increased-risk behaviours (n= 515)	**Potential donors with no increased-risk behaviours (n= 16462)**	**p-value**
Age (y) (median, IQR)	40 (32-50)	53 (40-64)	<0.001
Male (%)	448 (87%)	8942 (54%)	<0.001
Female (%)	67 (13%)	7513 (46%)	
White ethnicity (%)	467 (91%)	15482 (94%)	0.002
DBD(%)	271 (53%)	8976 (55%)	0.393
DCD (%)	244 (47%)	7486 (45%)	
Past History of Alcohol Abuse			<0.001
Yes	241 (47%)	2301 (14%)	
No	256 (50%)	12926 (79%)	
Unknown/Not stated	18 (3%)	1235 (8%)	
Past History of Hypertension			<0.001
Yes	81 (16%)	4587 (28%)	
No	418 (81%)	10525 (64%)	
Unknown/ Unstated	16 (3%)	1350 (8%)	
Past History of Cardiac Disease			<0.001
Yes	44 (9%)	2003 (12%)	
No	447 (87%)	13065 (79%)	
Unknown/ Unstated	24 (5%)	1394 (8%)	
Past History of Diabetes			0.009
Yes	35 (7%)	1284 (8%)	
No	460 (89%)	14003 (85%)	
Unknown/ Unstated	20 (4%)	1175 (7%)	
Smoking History			<0.001
Yes	408 (79%)	6655 (40%)	
No	94 (18%)	8649 (53%)	
Unknown/Unstated	13 (3%)	1158 (7%)	

Table 5.2. Clinical Characteristics of seronegative potential donors with increased-risk behaviour compared with all other deceased organ donors.

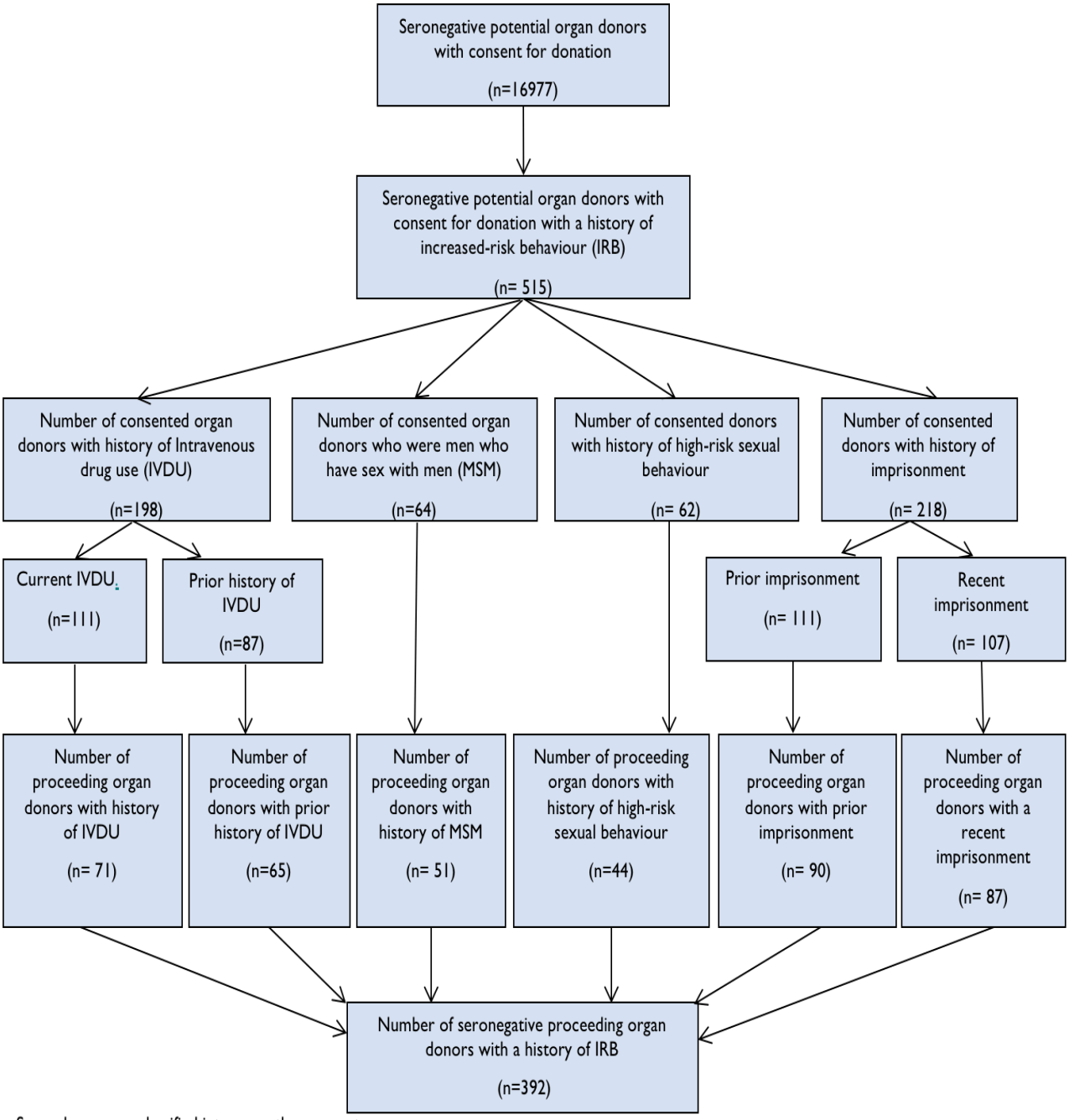


Figure 5.1. Flow diagram for seronegative organ donors identified with increased-risk behaviour

There were significant differences in the conversion rate from potential to actual donors according to the type of IRB (Figure 5.2). Potential donors with a history of IVDU were less likely to proceed to organ donation than donors with no history of IRB and this effect was most marked in potential donors with a history of recent rather than historical IVDU. Those with a history of high risk sexual behaviour alone were as likely to proceed to donation as those with no

history of high risk sexual behaviour (Figure 5.2). History of imprisonment alone (previous or current) was associated with an increased rate of proceeding to donation compared to donors with no history of IRB (Figure 5.2). However, when a logistic regression model was fitted to adjust for the significant differences in age and co-morbidity between donors with or without a history of IRB, IRB was associated with significantly fewer potential organ donors becoming actual organ donors (odds ratio=1.580 (95% CI 1.273-1.962, p<0.001).When the logistic regression model was fitted for the different types of IRB, IVDU (both recent and historical) was associated with significantly fewer potential organ donors becoming actual organ donors (Recent IVDU, odds ratio=3.552 (95% CI (2.373-5.315), p<0.001 and historical IVDU, odds ratio =1.984 (95% CI 1.205-3.268) p=0.007, respectively) (Table 5.3).

The number of potential donors with a history of IRB increased markedly over the 13-year study period and the percentage of donors proceeding to donation also rose in the latter part of the study period (Figure 5.3).

	Odds Ratio (95% Confidence Intervals)	**p-value**
Donor age (y)	1.035 (1.033 -1.038)	<0.001
Past medical history of hypertension vs. No past medical history of hypertension	1.192 (1.094-1.29)	<0.001
High-risk sexual behavior vs. No high-risk sexual behaviour	1.373 (0.900-2.094)	0.141
Imprisonment vs. No history of Imprisonment	0.859 (0.570-1.295)	0.468
Historical IVDU vs. No history of IVDU	1.984 (1.205-3.268)	0.007
Recent IVDU vs. No history of IVDU	3.551 (2.373-5.315)	<0.001

Table 5.3. The likelihood of potential donors not proceeding to become actual organ donors based on the presence of selected risk factors.

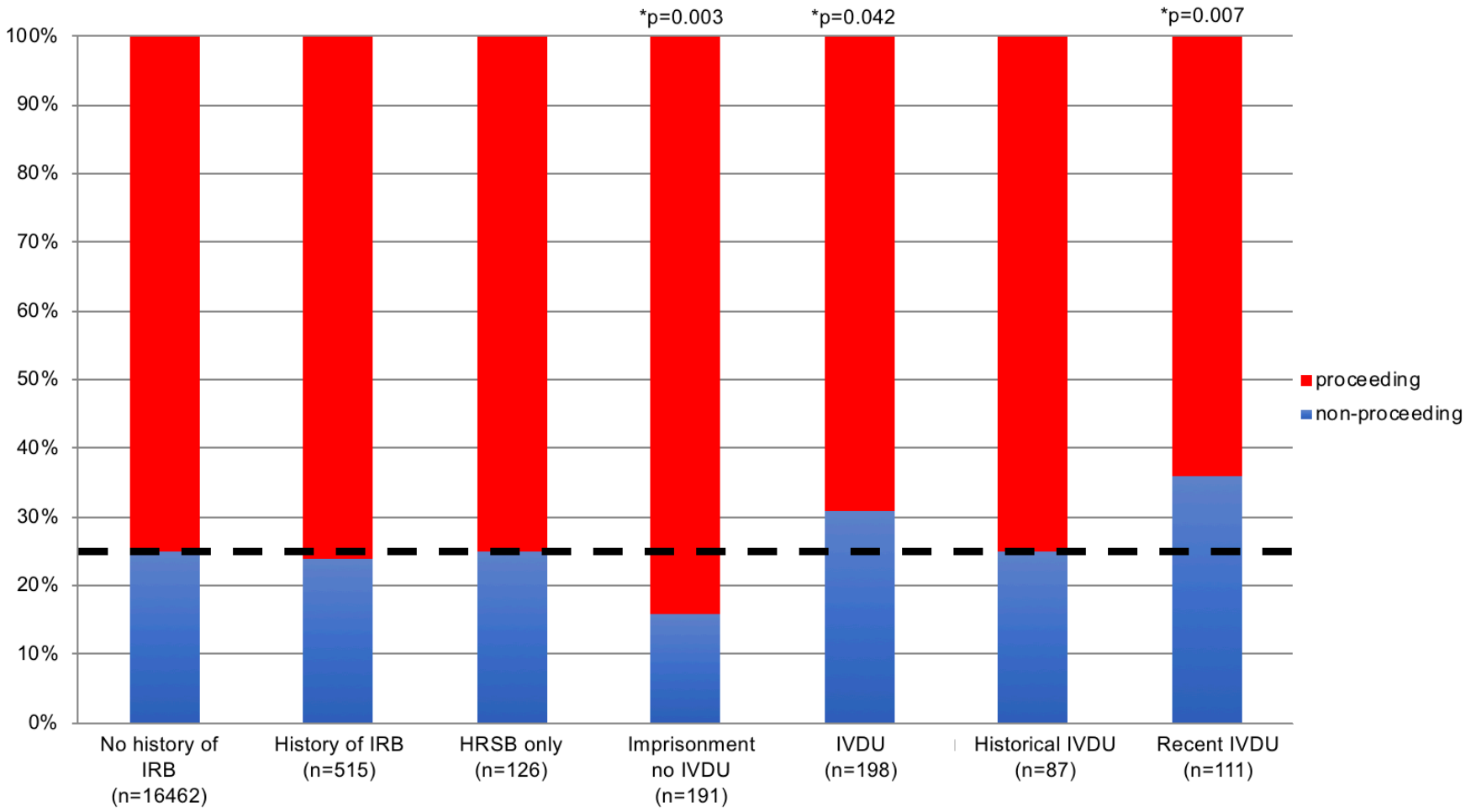


Figure 5.2. Proceeding and non-proceeding seronegative consented organ donors according to whether or not they had history increased-risk behaviour. **All p-values refer to category of IRB compared to all donors with no history of IRB.**

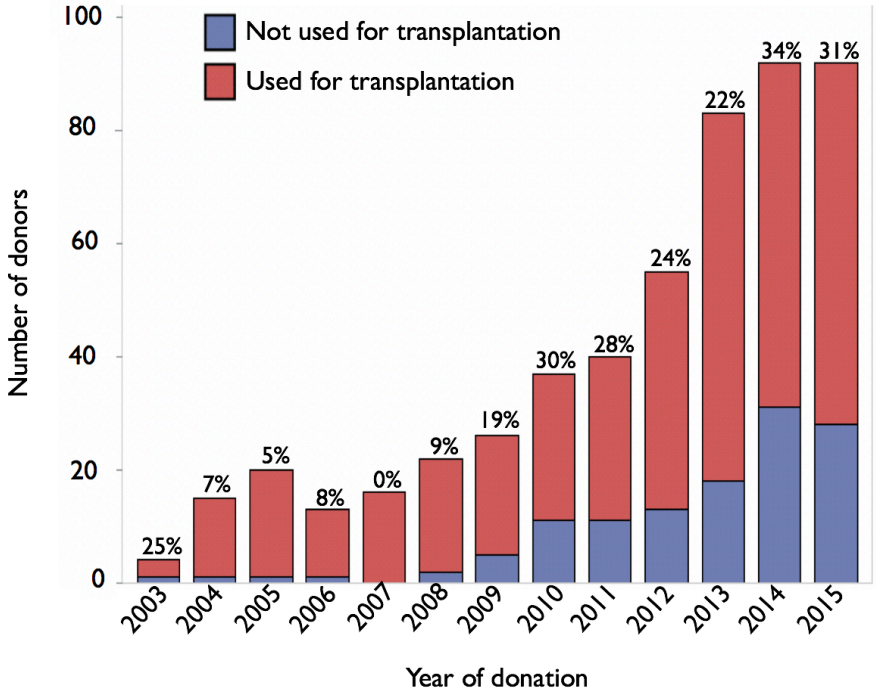


Figure 5.3. Number of seronegative potential donors with increased-risk behaviour whose organs were used for transplantation and those whose were not used for transplantation.

Proportion of potential organ donors with a history of increased risk behaviour who did not proceed to organ donation is shown above each column.

1.29.3 Clinical characteristics of actual organ donors with history increased-risk behaviours

Potential donors with a history of IRB, who proceeded to become actual organ donors were younger (39.8 ± 12.6 years vs. 44.3 ± 11.6 years, $p<0.001$) and more likely to be DBD than DCD donors (36.2% DCD vs. 82.9% DCD, $p<0.001$) than those potential donors with IRB who did not proceed to organ donation.

The clinical characteristics of the 392 actual organ donors with a history of IRB, along with the clinical characteristics of all other deceased organ donors are shown in table 5.4. Actual organ donors with a history of IRB were younger, more often males and more likely to be of an ethnic minority other than white. Organ donors with a history of IRB were more likely to have a history of smoking and of alcohol abuse (table 5.4).

	Proceeding donors with a history of increased-risk behaviour (n= 392)	All other deceased proceeding organ donors(n= 12345)	p-value
Age (y)	39 (30-48)	50 (38-61)	<0.001
Gender			<0.001
Male	341 (87.0%)	6492(52.6%)	
Female	51 (13.0%)	5849 (47.4%)	
Not stated	0	4 (<0.5%)	
DBD (%)	250(63.8%)	8476 (68.3%)	0.056
DCD (%)	142(36.2%)	3918(31.7%)	
White ethnicity (%)	352 (89.8%)	11540 (93.5%)	0.004
Non-White (%)	40 (10.2%)	805 (6.5%)	
Body Mass Index (BMI)	24.4 (22.0-27.5)	25.7 (22.9-29.0)	<0.001
Past History Alcohol Abuse			<0.001
Yes	165 (42.1%)	1611 (13.1%)	
No	218 (55.6%)	10294 (83.4%)	
Unknown/Not stated	9 (2.3%)	440 (3.6%)	
Smoking History			<0.001
Yes	311 (79.3%)	5327 (43.2%)	
No	77 (19.6%)	6651 (53.9%)	
Unknown/Unstated	4 (1.0%)	367 (3.0%)	
Past History of Cardiac disease			0.176
Yes	32 (8.2%)	1267 (10.3%)	
No	348 (88.8%)	10549 (85.5%)	
Unknown/Unstated	12 (3.1%)	529 (4.3%)	
Past History of Hypertension			<0.001
Yes	61 (15.6%)	3244 (26.3%)	
No	325 (82.9%)	8603 (69.7%)	
Unknown/Unstated	6 (1.5%)	498 (4%)	
Past History of Diabetes			0.568
Yes	22 (5.6%)	822 (6.7%)	
No	360 (91.8%)	11138 (90.2%)	
Unknown/Unstated	10 (2.6%)	385 (3.1%)	

Table 5.4. Clinical Characteristics of deceased seronegative proceeding organ donors with increased-risk behaviour compared with all other deceased organ donors.

1.29.4 Clinical characteristics of recipients receiving organs from donors with increased-risk behaviour

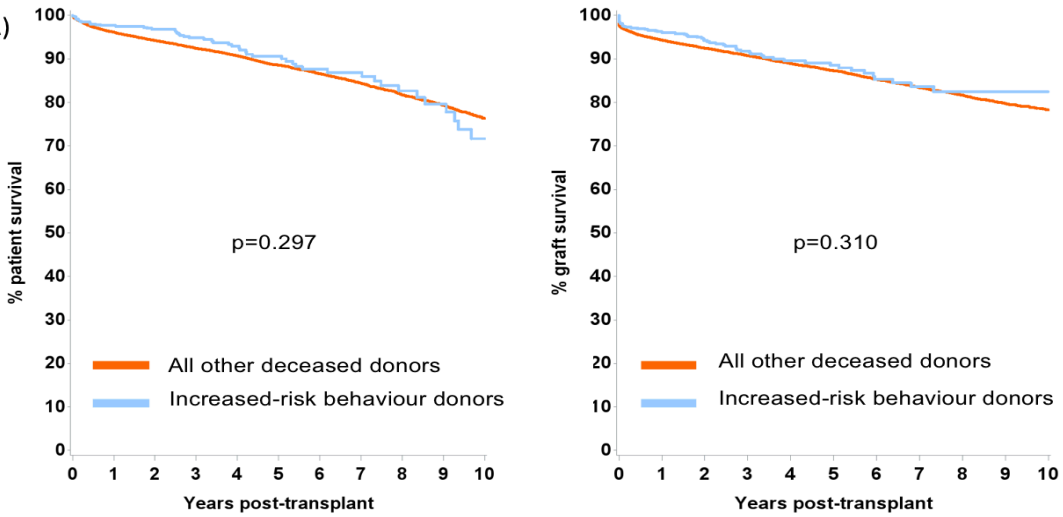
Over the 13-year study period, a total 1,091 transplants were carried out using organs from seronegative deceased donors with a history of IRB (624 kidney, 278 liver, 63 heart, 39 lung (including one lung pair), 2 heart and lung transplants, 84 pancreases, and 1 bowel transplant).

Recipients of kidneys from donors with a history of IRB were younger, more often of non-white ethnicity and less well matched for HLA than recipients of kidneys from donors with no IRB (Table 5.5). Recipients of kidneys from donors with IRB spent a similar amount of time on the transplant waiting list and had a similar duration of dialysis pre-transplant when compared to those who received kidneys from donors without IRB. Recipients of kidneys from donors with IRB had similar graft and patient survival to those who received kidneys from all other deceased donors (Figure 5.4a). When the recipients of the different types of IRB were compared to all other recipients, a donor history of recent IVDU did not adversely influence patient or graft survival (Figure 5.4b).

	Increased Risk Behaviour Donors (n= 624)	All other deceased donors (n= 18881)	P-value
Age (y)	48 (38-56)	50 (39-60)	<0.001
Gender			
Male/Female (%)	393 (63.1%)/ 230 (36.9%)	11788 (62.5%)/ 7083(37.5%)	0.552
Not stated	1 (<0.5%)	38 (<0.5%)	
Ethnicity			
White/Not white (%)	460 (73.8%)/ 163 (26.2%)	14663 (77.7%)/ 4208 (22.3%)	0.009
Not stated	1 (<0.5%)	38 (<0.5%)	
***cRF >85%**	63 (10.0%)	1800 (9.5%)	0.889
HLA Group			0.256
1	74 (11.9%)	2719 (14.4%)	
2	215 (34.5%)	6654 (35.3%)	
3	288 (46.2%)	8198 (43.4%)	
4	46 (7.4%)	1310 (7.0%)	
Missing/Not stated	1 (<0.5%)	29 (<0.5%)	
Primary Renal Disease			0.522
Diabetic Nephropathy	43 (6.9%)	1544 (7.6%)	
Glomerulonephritis	110 (17.6%)	3347 (17.7%)	
Pyelonephritis	50 (8.1%)	1437 (5.3%)	
Polycystic Kidney Disease	70 (11.2%)	2261 (12.0%)	
Other/ Not stated	351 (56.3%)	10292 (57.4%)	
Time on dialysis (days)	1295 (727-1994)	1252 (706-1955)	0.552
Waiting time (days)	827 (361-1370)	832 (354-1450)	0.489

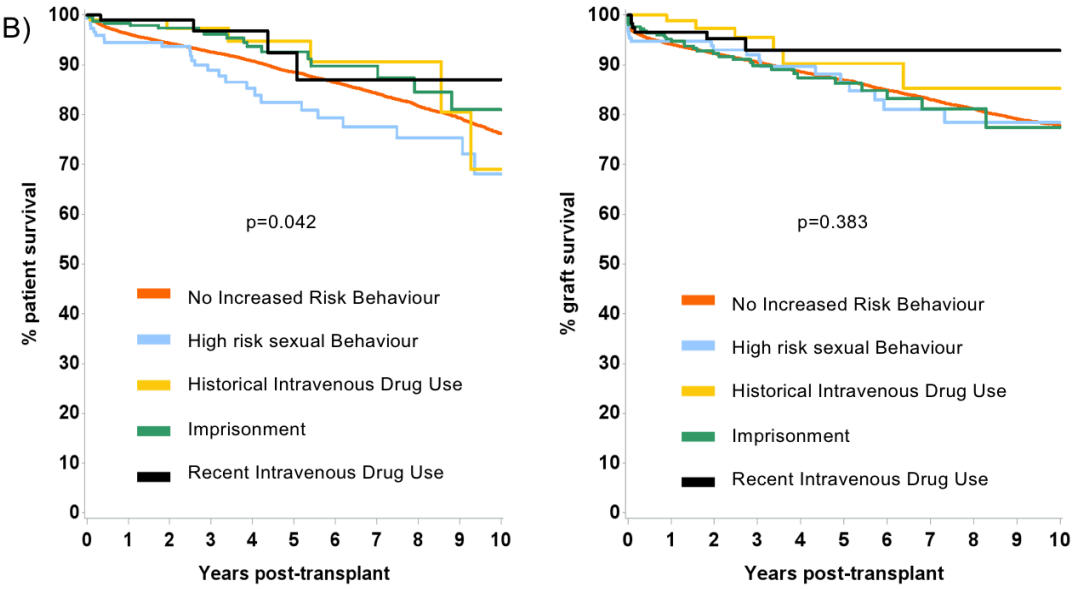
Table 5.5. Clinical characteristics of recipients of seronegative deceased donor kidneys according to whether or not the donor had a history of increased-risk behaviour.

A)



Donor Type	Total Number	5-year patient survival: Number ay risk	10-year patient survival: Number at risk
Increased risk behavior donor	624	177 (90.2%)	40 (75.6%)
All other deceased donor	18881	8031 (88.9%)	2268 (76.2%)

B)



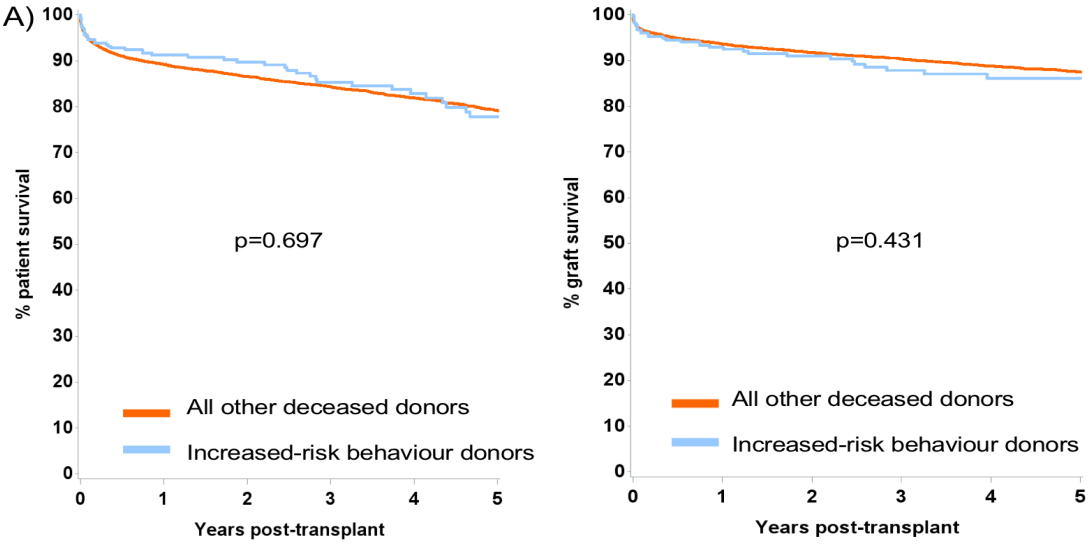
	Total Number	5 year patient survival: Number at risk	10 year atient survival :Number at risk
No Increased Risk Behaviour	18881	8342 (88.6%)	2490 (76.2%)
High Risk Sexual Behaviour	152	59 (82.5%)	17 (68.1%)
Historical Intravenous Drug Use	98	36 (94.8%)	6 (69.1%)
Imprisonment	256	63 (89.8%)	23 (80.1%)
Recent Intravenous Drug Use	118	21 (92.5%)	16 (87%.0%)

Figure 5.4a and b. Patient and death censored Graft survival of kidney transplant recipients from seronegative organ donors with increased-risk behaviour and from all other seronegative deceased organ donors**.** P-value corresponds to score test of the overall null hypothesis that there are no differences in survival curves for all groups i.e. comparing survival across all groups

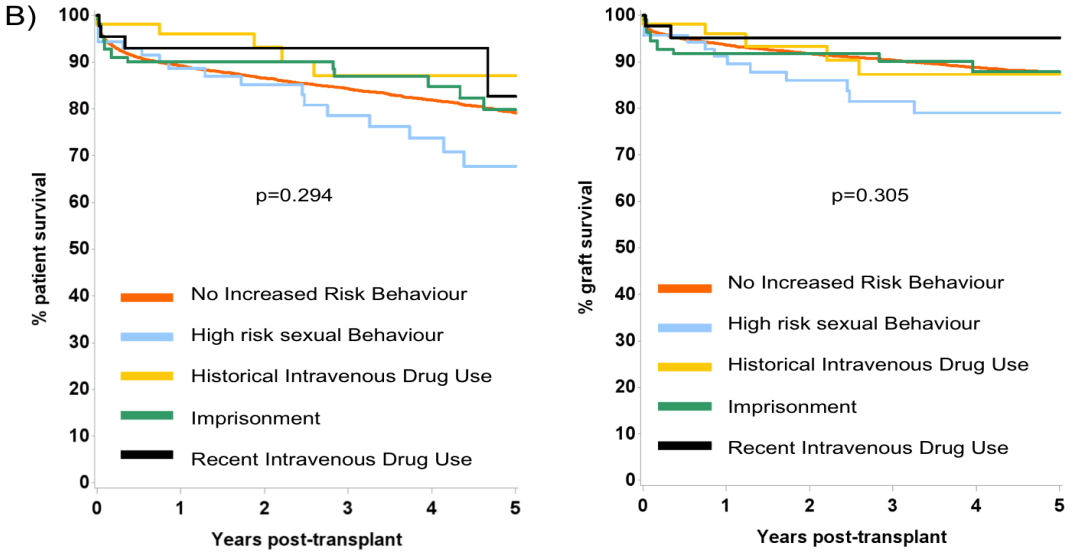
Recipients of livers from donors with a history of IRB were older, more often male, had a lower UKELD score, and more often HCV positive than recipients of livers from donors with no IRB (Table 5.6). Similarly, patient and graft survival following liver transplantation was comparable for recipients of livers from donors with and without IRB (Figure 5.5a and Figure 5.5b).

	Increased-risk behaviour Donors (n= 278)	**All other deceased donors (n= 8756)**	**p-value**
Age (y)	53 (43-59)	51 (37-59)	0.111
Gender			0.012
Male Female (%)	190 (68.4%) 88 (31.6%)	5205 (59.5%) 3546 (40.5%)	
Unknown/ Unstated	0	5(<0.5%)	
Ethnicity			0.148
White (%)	244 (87.8%)	7404 (84.6%)	
Non-White (%)	34 (12.2%)	1348 (15.4%)	
Unknown/Unstated		4 (<0.5%)	
Urgent Status	42 (15.1%)	1483 (16.9%)	0.421
UKELD score	53 (50-58)	55 (51-59)	0.016
Recipient HCV antibody positive	12 (4.3%)	484 (5.5%)	<0.001
Primary Liver Disease			0.012
HCV cirrhosis	38 (13.7%)	950 (10.7%)	
ALD	67 (24%)	1561 (17.7%)	
Other/Not stated	173 (62.2%)	6245 (71.3%)	

Table 5.6. Clinical characteristics of recipients of deceased donor livers according to whether or not the donor had a history of increased-risk behaviour



Donor Type	Total Number	3-year patient survival: Number at risk	5-year patient survival: Number at risk
Increased Risk Behaviour Donor	278	119 (85.6%)	67 (77.4%)
All other deceased donors	8756	4640 (84.3%)	3205 (79.0%)



Donor Type	Total Numbers	3 year patient survival number at risk	5 year patient survival number at risk
No Increased Risk Behaviour	8756	4768 (84.3%)	3320 (79.2%)
High risk sexual behaviour	71	35 (78.6%)	22 (67.7%)
Historical Intravenous Drug Use	52	29 (87.2%)	29 (87.2%)
Imprisonment	111	56 (87%)	32 (79.8%)
Recent Intravenous Drug Use	44	38 (93%)	8 (82.7%)

Figure 5.5a and b. Patient and death censored graft survival of liver transplant recipients from seronegative organ donors with increased-risk behaviour and all other seronegative deceased organ donors. P-value corresponds to score test of the overall null hypothesis that there are no differences in survival curves for all groups i.e. comparing survival across all groups

Because of the differences in donor and recipient demographics between recipients that received organs from donors with a history of IRB compared to those that did not, a Cox proportional hazards regression model was fitted to adjust for donor and recipient age, donor history of hypertension, HLA mismatch, cold ischaemic time and primary recipient disease. This showed that patient survival after kidney transplantation was not adversely affected by a donor history of IRB (Table 5.7). After assessing whether the different sub-types of IRB adversely impacted on transplant outcome, the multivariate analysis indicated recipients of kidneys from donors with high-risk sexual behaviour had significantly worse patient survival than those who received kidneys from donors with no history of high-risk sexual behaviour, even after adjusting for donor and recipient factors. Each of the high-risk sexual behaviours was assessed in turn, and this revealed that it was only those who received kidneys from donors with a high-risk sexual partner that had worse patient survival.

1.29.5 Disease transmission

From the 1,091 organ transplants from donors with IRB, one liver recipient and two renal recipients (all from the same organ donor) developed donor-derived HCV infection. The donor of the organs had a history of recent IVDU, and tested negative for HCV antibody at time of donation. Retrospective testing of the donor serum obtained at donation was positive for HCV Ribonucleic Acid. The liver recipient was known to be HCV positive at time of transplantation, but it was noted that the predominant HCV genotype changed from genotype 1 pre-transplant to donor genotype 3 after transplant. The two renal recipients were both HCV negative prior to transplantation. There were no reported unexpected HIV, HBV or HTLV transmissions from these IRB donors.

	Hazard Ratio	p-value
Donor Age (y)	1.009 (1.005-1.012)	<0.001
Recipient Age (y)	1.056	<0.001
DBD vs. DCD	1.151 (1.042-1.272)	0.006
Cold Ischaemic Time	1.009 (1.002-1.016)	0.012
HLA Mismatch		
1	0.840 (0.696-0.999)	0.0599
2	0.857 (0.729-1.001)	0.0573
3	0.883 (0.757-1.019)	0.1052
4	1.00	-
Male vs. Female	1.101 (1.010-1.200)	0.028
Primary renal disease		
All other causes	1.00	-
Glomerulonephritis	0.823 (0.731-0.927)	<0.001
Diabetic Neprhopathy	1.595 (1.409-1.805)	<0.001
Pyelonephritis	1.041 (0.896-1.221)	0.609
Polycystic kidney disease	0.661 (0.578-0.763)	<0.001
History of Hypertension		
No history of hypertension	1.00	-
Hypertension	1.186 (1.079-1.305)	<0.001
Unknown history of hypertension	1.243 (1.037-1.491)	0.02
Increased risk behaviour vs. No history of Increased risk behaviour	1.102 (0.833-1.457)	0.498
Sub-Types of Increased Risk Behaviour		
Recent IVDU	0.482 (0.136-1.713)	0.230
Historical IVDU	0.763 (0.326-1.787)	0.534
Imprisonment	0.804 (0.514-1.256)	0.338
High-risk sexual behaviour	1.897 (1.253-2.872)	0.003
Sub-types of High risk sexual behaviour		
High risk partner	3.004 (1.592-5.667)	<0.001
Men who have sex with men	1.376 (0.770-2.461)	0.281
Not specified	3.819 (0.944-15.450)	0.060
Prior high-risk partner	2.510 (0.351-17.930)	0.359

Table 5.7. Cox proportional hazards regression model for patient survival following renal transplantation

1.30 Discussion

Routine screening of all potential organ donors for a history of IRB to determine risk of transmission of BBV infection is routinely undertaken in most countries to help inform the decision on organ usage. The present analysis provides insight on the impact of this policy on organ donation and utilization in the UK, where the prevalence of blood borne viral infection is slightly lower than that in the USA and broadly similar to Western Europe (77,80,143).

Around 4% of all potential organ donors, for whom consent for donation was obtained, had a history of IRB and 22% of these (2% of all potential donors) were seropositive for blood borne viral infection (mostly HCV), at the time organ donation was being considered and over half had a history of IRB. This again is lower than that observed in the US, where an estimated 20% of deceased donors have an increased risk for BBV (144). Positive serology for blood borne viruses may indicate a very high risk of disease transmission during transplantation, and enables an informed decision on whether to proceed with organ donation, and if so, to allocate organs to appropriate potential recipients; in the majority of cases the recipients are likely to be selected on the basis that they already have infection corresponding to that identified in the donor.

In the present analysis, we were particularly interested in the extent to which IRB in seronegative potential donors impacted on organ donation and transplantation. Overall, around three quarters of all potential organ donors in the UK proceeded to become actual organ donors, on the basis that transplant implanting centres had provisionally accepted them for transplantation. A history of IRB (all types) was not associated with a reduction in the proportion of potential donors that proceeded to become organ donors. However, a history of IVDU accounted for nearly half of all IRB and was associated with a relatively small but significant reduction in the proportion of potential donors proceeding to donation, especially when the drug use may have been recent.

Potential donors with IRB were significantly younger and had less additional comorbidity than those with no IRB, and when these variables were taken into

account by logistic regression analysis, IVDU (both recent and historical) were associated with donors not proceeding to become actual organ donors. Our analysis of the PDA (a prospective registry of all patients aged <80 years who died in critical care units of acute UK hospitals, irrespective of their medical suitability to become organ donors) indicated that a large number of these identified registry patients did not get consented for organ donation because of their history of IRB (in particular IVDU).

The number of potential donors with IRB in the present analysis increased markedly over the 13-year study period. This likely reflects, for the most part, a true increase in the number of such donors over time, in line with the general trend towards increased consideration of organs from other types of high-risk donor (145). However, it is also likely that some of the increase in potential donors with IRB over time may be attributable to a bias in data capture, as clinical practice in organ donor screening by transplant coordinators and documentation became more standardised.

While the risk of disease transmission in seronegative donors with IRB is very low, not all transplant centres routinely assess recipients for graft-derived acquisition of blood borne viral disease and consequently the present analysis may provide an underestimate of disease transmission from donors with IRB. Although seronegative donors with a history of IRB represent a small proportion of the total donor population they made a significant contribution to organ transplantation in the UK over the 13-year study period, providing organs for over a thousand transplants.

There were three confirmed transmissions of HCV to two renal transplant recipients and one liver transplant recipient. All three episodes of disease transmission originated from the same donor, who was known to be an active IVDU at time of donation. Using standard serological testing the window period from infection with HCV to detection by antibody assays is around 70 days (142,146-148) and with NAT is 3-5 days (142,146,148). Both serological testing and NAT testing carry the risk of false positive results and hence the unnecessary discard of potentially infection free organs from potential donors. NAT testing is only currently available in selected UK centres and recent evidence suggests that NAT testing would improve utilization of organs from

IRB donors, but not from donors with no history of IRB (142). Hence even when NAT testing is available a thorough history regarding IRB is still important to aid interpretation of positive results.

As might be expected, recipients of organs from seronegative donors with IRB had transplant outcomes (patient and graft survival) comparable to recipients of organs from deceased donors with no history of IRB, even after adjustment for differences in donor and recipient demographics. However, those who received kidneys from donors with a high-risk sexual partner had worse patient survival than all other deceased donors. The exact cause of this remains unclear. When the causes of renal recipient death in this cohort were examined, no deaths (n=8) were attributable to disease transmission from the donor (2 post transplant proliferative disease, and one each of gastro-intestinal haemorrhage, haemorrhage from graft site, septicaemia, viral hepatitis, non-lymphoid malignant disease, and ischaemic heart disease). The case of viral hepatitis was fulminant liver failure secondary to HCV genotype 1b, which was already present in the recipient prior to transplantation. There was no significant difference in graft or patient survival in recipients of livers from donors with high-risk sexual behaviour and all other deceased donors.

The comparison of recipient characteristics according to whether or not they received a kidney from a donor with a history of IRB revealed that recipients of kidneys from donors with IRB were significantly younger and significantly more likely to be of non-white ethnicity. Donors with a history of IRB were also significantly younger and of non-white ethnicity than all other deceased donors, and kidney allocation and acceptance policies in terms of age, blood group and HLA matching would likely explain the differences observed in recipient demographics. In support, it was notable that for liver transplant recipients, where HLA-matching is not undertaken, there was no significant difference in the ethnicity of recipients according to whether or not they received a liver from a donor with IRB. Because kidney donors with IRB were significantly younger than other deceased kidney donors, and recipients of kidneys from younger donors have improved transplant outcomes, it might have been expected that transplant outcomes would have been better in recipients of kidneys from donors with IRB (145,149). The number of

recipients of kidneys from donors with IRB in the present analysis may not have been sufficient to demonstrate the advantage of younger donor age on transplant outcome.

The analysis is the first to report in detail on different categories of IRB in a national cohort of deceased organ donors, and provides important information on which to base future transplant policy for managing the risk of disease transmission. The numbers presented likely represent an underestimate of potential donors with IRB in the donor population, because of underreporting. This is evidenced by the small number of reported MSM in the registry (0.44%), whilst estimates from a recent US census analysis and meta-analysis estimated that around 3.9% of the US adult male populations are MSM, and in the UK it is estimated that 2.0-2.5% of the adult male population are MSM (150,151).

Research suggests that a patient would be willing to accept a kidney from a donor with IRB if the organ was deemed otherwise healthy (152): individuals are more concerned about the perceived poor quality of the organ and the risk of disease transmission rather than having a prejudice or concern about a particular type of increased risk behaviour per se (152).

While the present analysis indicates that a history of IRB, particularly IVDU, in seronegative potential donors is associated with a reduction in organs being accepted for transplantation, such donors represent a valuable source of organs for transplantation and the risk of disease transmission in the context of UK blood borne virus epidemiology is relatively small. Moreover, recent advances in the management of transmissible viruses particularly HCV, means that even if viral disease transmission occurs it can in many cases be successfully managed (2). It has also been suggested that kidneys from seronegative donors with a history of IRB may be a valuable source of organs for potential recipients with an increased likelihood of death whilst on the waiting list (82,153,154). When organs from donors with a history of IRB are used for transplantation it would be prudent for all centres to test recipients within an appropriate time period following transplantation in order to exclude donor derived infection.

Potential and actual deceased donors with HCV

Publications from this work: Trotter et al. Use of organs from hepatitis C virus positive donors for uninfected recipients: a potential cost-effective approach to save lives? Transplantation. 2018:102(4):664-672.

1.31 Background

Currently around 200,000 people in the UK are infected with HCV and with increasing demand for organs for transplantation selected HCVpos donors may represent an additional source of organs for transplantation (77,155).

At present, organs from HCVpos deceased donors are usually declined for transplantation because of the high probability of disease transmission, with an accelerated risk of cirrhosis and liver failure; even in recipients who are HCV positive there is often reluctance to use organs from HCVpos donors. In many cases HCV antibody positive recipients have received treatment and cleared the virus. National guidance in the US and UK cautions against the use of organs from HCVpos donors (55,62,64,141).

Until recently, treatment of HCV in allograft recipients was expensive, toxic and relatively ineffective (84). The advent of highly effective direct acting anti-viral agents (DAA) has greatly improved the outcome for HCV infected patients, with sustained virological response (SVR) rates in excess of 95% (84-86,156-159). Hence, a large number of patients who would have required transplantation secondary to the end organ liver and/or kidney damage associated with chronic HCV infection are now being treated effectively prior to the need for transplantation (159). This will result in greater consideration being given to the use of HCVpos donor organs for HCV negative recipients, as a large proportion of the HCVpos recipients, who could have previously received the HCVpos donor organs, is reduced due to successful treatment with DAA (159). The safety of using HCVpos donor organs varies depending on the organ being transplanted, with much of the current evidence demonstrating efficacy of DAA in the transplant population following donor transmission of HCV pertaining to kidney transplantation (50,160,161,162). There is concern regarding the use of livers from HCVpos donors because of the increased rate of progression to cholestatic hepatitis observed in liver

transplant candidates with HCV (163,164). However, there is evidence to suggest that DAA use in the liver cohort also achieves SVR and reversal of hepatic decompensation (164,165). It was hypothesised that there were a large number of non-proceeding HCVpos donors whose organs would otherwise have been considered of good quality for transplantation.

The aims of this analysis were to identify the seroprevalence of HCV in the UK deceased potential organ donor population, to determine the extent to which the presence of HCV impacted on their likelihood to proceed to organ donation, and to establish the quality of the donor organs that were not used for transplantation. I also aimed to estimate the impact that the use of organs from such donors would likely have in terms of additional transplants performed, transplant outcome, and specifically the cost benefit of using HCVpos donor kidneys for HCV negative recipients compared to a patient remaining on haemodialysis.

1.32 Methods

1.32.1 Identification of patients dying in UK critical care units who were not considered for donation because of the risk of HCV transmission

Many patients who die in critical care units and might be suitable organ donors are not considered for organ donation because the team caring for the patient do not consider donation as an option. To determine the number of patients who died in critical care and could have potentially donated organs but were not considered eligible as donors because of the presence of HCV or of increased risk behaviour posing an increased risk for HCV transmission (such as IVDU), the UK PDA was examined. A potential eligible donor is defined as a patient with no absolute contra-indications to organ donation who met the requirements for brain-stem death testing or if death is thought likely to occur within 4 hours of withdrawal of treatment (166).The PDA was searched to identify deaths occurring from 1st October 2009 (when information in the PDA was made more comprehensive) to 1st January 2016. Patients with HCV were identified in the PDA by searching through the free text entries using the search terms *'hepatitis', 'hepatitis C', 'HCV' and 'HepC'.* All common

abbreviations and misspellings of these search terms were also searched. Patients with a history of intravenous drug use (IVDU) were identified from the free text entries in the PDA using the search terms *'intravenous drug use', 'IVDU', 'Needle', 'Heroin', 'Overdose', 'Injected', 'IVDA'*. All common abbreviations, misspellings, synonymous terms and colloquialisms of the above search terms were also searched.

1.32.2 Identification of consented potential and proceeding organ donors in the UK who were hepatitis C positive

The UKTR includes information on all deceased potential donors for whom consent for organ donation had been obtained irrespective of whether or not they proceeded to donate organs for transplantation. The UKTR was examined to identify HCVpos potential and actual deceased donors in the UK between 1st January 2000 and 1st January 2016. HCVpos donors were identified by the presence of anti-HCV antibody in the serum at time of referral for organ donation; only a minority of the donor cohort had reported HCV RNA status in the UKTR as part of donor characterisation. Consented potential donors were categorised as "non-proceeding organ donors" when, for whatever reason, organ donation did not occur, as "proceeding organ donors" when one or more of their solid organs were retrieved for transplantation irrespective of whether they were subsequently used for transplantation, and "actual organ donors" when one or more of their organs were used for transplantation.

1.32.3 Identifying recipients of organs from hepatitis C positive donors

The UKTR was used to identify all recipients of organs from deceased HCVpos donors, and to obtain data on recipient survival, death censored graft survival and recipient HCV status.

1.32.4 Estimation of non-proceeding donor organ quality

The quality of non-proceeding donor organs, in terms of their suitability for transplantation was assessed by eGFR calculated using the MDRD equation, liver tests (LT), the UKKDRI and the UK DLI (104,105,107).

1.32.5 Cost analysis of haemodialysis versus kidney transplantation from a HCVpos donor together with antiviral therapy

To assess whether kidney transplantation along with the use of DAA to treat transmitted HCV would be cost effective compared to haemodialysis, a cost analysis was carried out using the current estimated costs of renal transplantation in the UK (£53,288 first year plus £8,526 for each additional year), haemodialysis (£29,841) and a 12-week course of DAA therapy (sofosbuvir and ledipasvir +/- ribavirin depending on the HCV genotype, £38,980) (167,168). This combination of anti-viral agents was selected based on the National Institute for Health and Care Excellence (NICE) recommendations published in 2015. While the present analysis used only the combination of sofosbuvir and ledipasvir in the cost analysis, it is important to note that many more therapies have subsequently been approved by NICE (168-170).

1.32.6 Statistical analysis

Continuous parametric variables were compared using Student's t-test and continuous non-parametric variables were compared using Mann-Whitney U test. Categorical variables were compared using Chi-squared test. Survival analysis was assessed using Kaplan-Meier tables. All analyses were performed using SAS.

1.33 Results

1.33.1 Patients dying in UK critical care units who were not considered for donation because of the risk of HCV transmission

Between 2009 and 2016, 274,600 patients who died in UK critical care units and were not considered for organ donation for a variety of reasons were identified from the PDA, of which 780 (0·3%) patients were reported to have HCV infection and 882 (0.3%) had a history of IVDU. Of the 780 patients reported to have HCV, 277 (35.5%) also had a history of IVDU. Compared to all other patients not considered for donation in the PDA, those with reported HCV infection were younger (median 48 years IQR 41-57 vs. median 68 years

IQR 56-76, p<0·001), were more likely to be male (69·5% male vs. 59·3% male, p<0.001), and were more likely to be of Asian descent compared to all other patients (7·3% vs. 4·4%, p<0·001) (Table 6.1).

Of the 780 patients with reported HCV infection, 370 had no other primary contraindication to organ donation, and met the requirements for brain stem death testing or could have been considered as a DCD donor. In 120 of the 370 patients, it was stated explicitly in free text entries of the PDA that the risk of HCV transmission was the reason that donation was considered not appropriate.

Clinical Characteristics	**Non- proceeding potential donors with HCV (n = 780)**	**Non-proceeding potential donors without HCV (n=274241)**	**p-value**
Age (y)	48 (41-57)	67 (55-76)	<0.001
Male/Female (%)	542 (69.5%)/ 237 (30.4%)	162676 (59.3%)/ 111402 (40.62%)	<0.001
Ethnicity (%)			<0.001
White	598 (76.7%)	207035 (75.5%)	
Asian and Asian-British	57 (7.3%)	11662 (4.5%)	
Other	125 (16.0%)	55544 (20.3%)	
Cause of Death			<0.001
Multi-Organ Failure	302 (38.7%)	39714 (14.5%)	
Cardiac Arrest	78 (10.0%)	96968 (35.4%)	
Intracerebral Haemorrhage	63 (8.1%)	18048 (6.6%)	
Hypoxic Brain Damage	60(7.7%)	11885 (4.3%)	
Liver failure	54 (6.9%)	2357 (0.9%)	
All other causes and unstated	223 (28.6%)	105,269 (38.4%)	
Primary Contraindication			<0.001
Malignancy	23 (2.9%)	10,189 (3.7%)	
HIV or HIV related disease	19 (2.4%)	231 (<0.5%)	
Multi-Organ Failure	95 (12.2%)	10,341 (3.8%)	
Other medical contraindication	25 (3.2%)	1675 (0.6%)	
Donor specific contraindication	24 (3.1%)	2639 (1.0%)	
Other/ Not stated/Unknown	583 (74.7%)	249,166 (90.9%)	

Table 6.1. Clinical Characteristics of non-proceeding potential organ donors identified as being HCV positive and all other non-proceeding potential donors

1.33.2 Proceeding and non-proceeding organ donors who were hepatitis C virus seropositive

Analysis of the UKTR for the period 2000-2015, identified 19,692 deceased potential organ donors. Of these, 244 (1·2%) were identified as anti-HCV antibody positive. Whereas only 98 (40·2%) of the HCVpos potential donors proceeded to become actual donors, 15,068 (76·5%) of the HCV seronegative (HCVneg) donors proceeded to donate one or more organs for transplantation (p<0.001). Organs from 76 (77·6%) of the 98 HCVpos proceeding organ donors were used for transplantation, whereas organs from 14,458 (95·9%) of HCVneg donors were subsequently transplanted (p<0·001). The number of potential HCVpos deceased donors increased over the study period, but the percentage proceeding to donate organs did not show any clear trend (Figure 6.1).

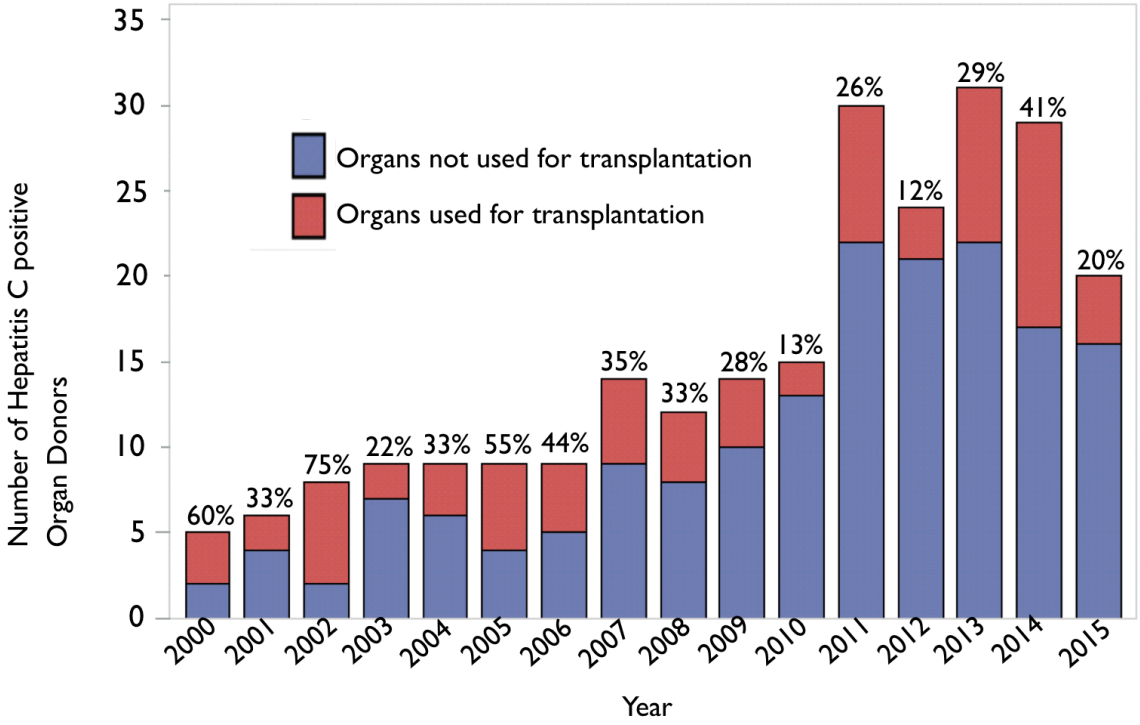


Figure 6.1. Total number of Hepatitis C positive donors whose organs were used for transplantation and those that were not. Proportion of Hepatitis C positive donors whose organs were used for transplantation shown above each column

Over half (60·4%) of the 244 HCVpos potential organ donors had a history of increased-risk behaviour for blood borne viral disease. Only 6 (2·5%)

consented HCVpos donors were co-infected with other blood borne viruses (Human Immunodeficiency Virus (n=2), Hepatitis B Virus (n=2) or Human T cell Lymphotropic virus (n=2)).

The clinical characteristics of proceeding HCVpos donors were compared to those of non-proceeding HCVpos donors and to all proceeding HCVneg donors (Table 6.2). Proceeding HCVpos donors were significantly younger than non-proceeding HCVpos donors and all other proceeding HCVneg negative donors (median age 41.5 years (IQR 32-51) vs. 48.5 years (39-54) and 49.0 years (37-60), respectively, p=0.010). Both proceeding and non-proceeding HCVpos donors were less likely to have a medical history of hypertension compared to all proceeding HCVneg donors (12 (12.2%), 24(16.4%) and 3717 (24.7%), respectively, p=0.004). However, both proceeding and non-proceeding HCVpos had significantly higher reported rates of alcohol abuse, drug abuse, liver disease and smoking history compared to proceeding HCVneg donors (Table 6.2).

	Proceeding HCVpos donor (n=98)	**Non-proceeding HCVpos donors (n=146)**	**Proceeding HCVneg donors (n=15068)**	**p-value**
Age (years)	41·5 (32-51)	48·5 (39-54)	49·0 (37-60)	0·010
DBD **DCD (%)**	82 (83·7%) 16 (16·3%)	74 (50·7%) 72 (49·3%)	10883 (72·2%) 4185 (27·8%)	0·012
Male **Female (%)** Missing/Unknown	57 (58·2%) 41 (41·8%) 0	108 (74·0%) 38 (26·0%) 0	8079 (53·6%) 6985 (46·4%) 4(<0.5%)	0·370
White ethnicity	95 (96·9%)	136 (93·2%)	14431 (95·8%)	0·248
BMI	25·0 (21·9-27·4)	25·0 (22·6-28·3)	25·4 (22·7-28·7)	0·077
Diabetes				0·111
Yes	1 (1·0%)	10 (6·8%)	908 (6·0%)	
No	93 (94·9%)	111 (76·0%)	13707 (91·0%)	
Missing/Unknown	4(4·1%)	25 (17·1%)	449 (3·0%)	

	Proceeding HCVpos donor (n=98)	Non-proceeding HCVpos donors (n=146)	Proceeding HCVneg donors (n=15068)	p-value
Hypertension				0·004
Yes	12 (12·2%)	24 (16·4%)	3717 (24·7%)	
No	86 (87·8%)	122 (83·6%)	11347 (75·3%)	
Missing/Unknown	0	0	0	
Cardiac Disease				0·618
Yes	8 (8·2%)	13 (8·9%)	1410 (9·4%)	
No	84 (79·3%)	110 (75·3%)	13047 (86·6%)	
Missing/unknown	6 (11·1%)	25 (17·1%)	606 (4·0%)	
Liver disease				<0·001
Yes	22 (26·7%)	45 (30·8%)	418 (2·8%)	
No	68 (60·0%)	73 (50·0%)	13944 (92·5%)	
Missing/unknown	8 (25·2%)	28 (19·2%)	702 (4·7%)	
Alcohol Abuse				<0·001
Yes	30 (43·0%)	72 (55·4%)	1975 (13·1%)	
No	60 (61·2%)	57 (43·9%)	12546 (83·3%)	
Missing/Unknown	8 (7·4%)	16 (7·4%)	547 (3·6%)	
Drug abuse				<0·001
Yes	63 (44·4%)	85 (66·9%)	790 (5·2%)	
No	32 (45·2%)	42 (33·1%)	13686 (90·8%)	
Missing/Unknown	3 (10·4%)	19 (10·4%)	6 (<0.5%)	
Smoking history				<0·001
Yes	77 (78·6%)	107 (73·3%)	6622 (43·9%)	
No	15 (15·3%)	21 (14·4%)	7960 (52·8%)	
Unknown/Missing	6 (6·3%)	18 (12·3%)	486 (3·2%)	

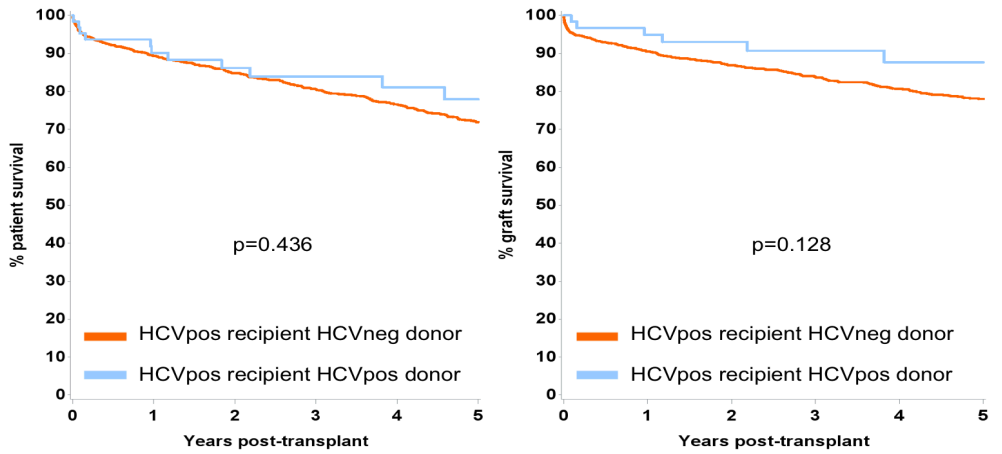
Table 6.2. Clinical characteristics of HCV seropositive (HCVpos) organ donors compared to those of HCV seronegative (HCVneg) organ donors

1.33.3 Outcomes of recipients of HCVpos donor organs

Of the 98 HCVpos proceeding organ donors, organs were used from 76 donors and this resulted in a total of 92 solid organ transplants (63 liver, 27

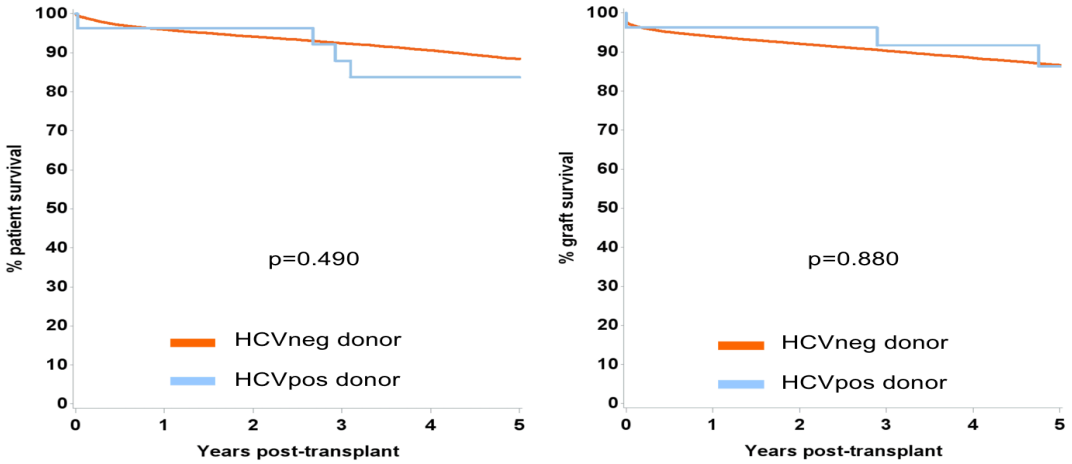
kidneys, 2 heart). Patient and graft survival in recipients of livers and kidneys from HCVpos donors was no different to that observed in recipients of such organs from HCVneg deceased donors (Figure 6.2 and Figure 6.3). One of the heart transplant recipients died 7years 7 months after transplantation secondary to coronary occlusive disease, whilst the other heart transplant recipient is alive with a functioning graft (4 years 8 months).

Of the liver transplant recipients, 96.8% (n=61) were known to be or have been HCVpos. The 2 liver transplant recipients that were not known to have HCV required a liver transplant urgently. Of the 27 kidney transplant recipients, 8 (29.6%) were reported to be HCV antibody positive, 11 (40.7%) HCVneg, and 8 (29.6%) of unknown status. Of the heart transplant recipients both recipients were recorded as being HCVneg. One of the heart transplant recipients fulfilled the criteria for super-urgent listing.



Donor type	Total Number	1-year patient survival: Number at risk	2-year patient survival: Number at risk	3-year patient survival: Number at risk	4-year patient survival: Number at risk	5-year patient survival: Number at risk
HCVneg donor	1668	1335 (89.4%)	1123 (84.9%)	899 (80.5%)	799 (76.7%)	617 (71.9%)
HCVpos donor	63	51 (90.0%)	43 (86.3%)	38 (83.9%)	29 (81.4%)	26 (78.4%)

Figure 6.2. Patient survival and death censored graft survival of recipients who received livers from hepatitis C virus seronegative (HCVneg) donors compared to those who received livers from HCV seropositive (HCVpos) donors



Donor Type	Total Number	1 Year Patient survival: Number at risk	3-year Patient survival: Number at risk	5-year Patient survival: Number at risk
HCVneg donor	23602	21577 (95.7%)	16936 (92.4%)	12904 (88.4%)
HCVpos donor	27	26 (96.3%)	21 (87.9%)	20 (83.7%)

Figure 6.3. Patient survival and death censored graft survival of recipients of kidneys from hepatitis C negative donors compared to those who received kidneys from hepatitis C positive donors

1.33.4 Estimation of non-proceeding donor organ quality

The most common reason given for consented HCVpos donors not proceeding to become actual organ donors was the presence of positive donor virology (76·0%); only 15 (8·9%) of such donors were declined because of poor organ function (Table 6.3).

The quality of organs in non-proceeding HCVpos consented donors was similar to that of HCVneg proceeding donors (Table 6.3). Of the non-proceeding HCVpos potential donors, 42% had an eGFR>90mls/min and a similar proportion had liver tests within normal range. UKKDRI calculated for non-proceeding HCVpos donors showed that half (49·9%) of the donors were in the best two UKKDRI quartiles. The DLI scores calculated indicated that 42 (28·7%) livers were in the two best DLI quartiles (Table 6.3).

Reported Reason for Decline	
Donor Unsuitable-Virology	120 (71·4%)
Donor Unsuitable-History	77 (45·6%)
Non-Heart Beating donor	62 (36·9%)
Family refusal	23 (13·6%)
Poor function	15 (8·9%)
Other/Not Stated	92 (54·7%)
UK Kidney Donor Risk Index	
≤ 0.87	34(23·3%)
0.871-1.02	38(26·0%)
1.021-1.34	40(27·4%)
≥1.341	26 (17·8%)
Missing	8(5·5%)
eGFR (ml/min)	103·0 (70·5-144.5)
Creatinine at time of donation	67·5 (51-101)
Bilirubin (µmol/L)	13·0(8-22)
Alanine Transferase (IU/l)	53(29-111)
Alkaline Phosphatase (IU/l)	92·5 (70-133)
UK Donor Liver Index	
<0.96	25 (17·1%)
0.96<LRI ≤1.11	17 (11·6%)
1.11<LRI ≤1.32	21 (14·4%)
LRI >1.32	83 (56·9%)

Table 6.3. Estimation of organ quality of HCVpos deceased donors who did not proceed to organ donation

1.33.5 Cost analysis

We assessed if kidney transplantation and routine treatment with DAA would be cost effective compared to haemodialysis. As expected kidney transplantation from a HCVneg donor was cost effective compared to haemodialysis (Figure 6.4). While the use of routine anti-viral therapy in recipients of kidneys from HCVpos donors increased the cumulative cost of transplantation at 5 years by £38,979 per patient transplantation remained cost effective compared to haemodialysis at 5 years (Figure 6.4).

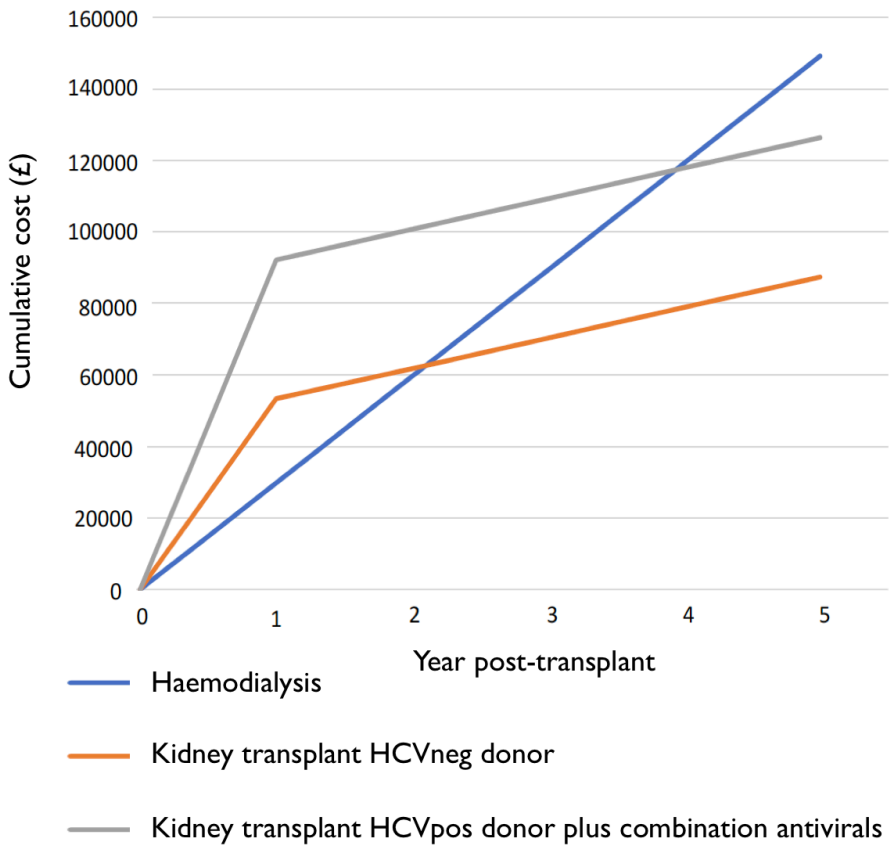


Figure 6.4. Cumulative cost analysis of haemodialysis compared to receiving either a kidney from a HCVneg donor or receiving a kidney from a HCVpos donor and receiving combination sofosbuvir and ledipasvir for 12 weeks.

1.34 Discussion

This chapter explored the opportunities for increasing organ donation and transplantation in the UK through the use of organs from HCVpos donors by analysing the entire organ donation pathway from patients dying in critical care units who were not considered for donation through to donors whose organs were removed but subsequently declined for transplantation. Our findings confirm that many patients dying in UK critical care units are not considered as potential donors because of a history of HCV, and the majority of consented, deceased potential donors with HCV do not proceed to organ donation because of the high risk of disease transmission.

The rationale for undertaking the present analysis was that the availability of DAA now provides a treatment that allows for safe transplantation of organs from HCVpos donors(162,171,172). DAA are small-molecule inhibitors of the

HCV viral replication cycle that target non-structural viral proteins(85,173,174). Genotypic coverage varies among the agents, but combination therapy permits the use of highly effective interferon-free regimens achieving SVR at 12 weeks in more than 95% of infected individuals. Several studies have shown successful HCV clearance using a variety of interferon-free, DAA-based regimens in genotype 1 and 2 infected kidney and liver transplant recipients with preserved allograft function, and the DAAs were safe, effective, and well tolerated (85,86,171-174). A recent open label, single group, pilot trial also demonstrated the feasibility of using HCVpos kidneys for HCVneg recipients (175). Studies are underway assessing the use of liver grafts from HCV viraemic donors for HCVneg recipients but there are no published findings as yet. Several studies have demonstrated high rates of SVR in both cirrhotic and non-cirrhotic liver transplant recipients with DAA, suggesting that if HCV was transmitted with the graft, treatment with combination DAA would likely achieve SVR also (85,164,165,176).

An important consideration in the proposition to use organs from donors with HCV for HCV naïve recipients is the possible legal implications of intentionally transmitting an infection. In the UK, the use of HCV infected organs is not prohibited, although guidance stipulates that recipients must give fully informed and specific consent and antiviral treatment must be made freely available. Similarly, in the US, federal law does not prohibit the use of HCV infected organs for transplantation (177).

The present analysis of the PDA identified 370 patients with a history of HCV over an 8-year period that were eligible to donate organs but where consent for donation was not sought. In 120 of these, infection by HCV was stated explicitly as the reason for the patient not proceeding to become a potential donor. The patients identified from the PDA with a history of HCV/IVDU were significantly younger and a greater proportion were of non-white ethnicity compared to all other patients identified in the PDA. These results are consistent with those reported by other studies investigating the clinical characteristics of deceased donors with HCV or a history of increased risk

behaviour for the transmission of blood borne viral disease(15,82,140,159,178).

The present analysis showed that for patients for whom consent for organ donation had been obtained, the presence of anti-HCV antibody was associated with a high likelihood (69%) that their organs would be declined for transplantation because of concern about disease transmission. In other respects, the declined HCVpos donors would have been considered satisfactory organ donors. They were of similar age to all other proceeding deceased donors and a significantly smaller proportion had a past medical history of hypertension. However, it is important to note that non-proceeding HCVpos donors were significantly more likely to be smokers, abuse alcohol, and have diabetes, all of which can detrimentally impact allograft survival. Nevertheless, the use of organs from donors with such conditions is accepted in current transplant practice.

It should also be noted that there is a possibility of co-infection of other blood borne viral infections in HCVpos donors. In this cohort of non-proceeding deceased HCVpos donors, 6 (2.5%) were co-infected with HIV, HBV or HTLV. Although this represents a small proportion of the total, it is important to consider that if increased numbers of donors with HCV were to be consented and then used for transplantation the risk of missing a recent HIV or HBV infection may possibly increase, although with current organ donor screening practice this risk is likely to be small (141).

Declined HCVpos donors often had good renal and liver function and based on validated UK Donor Risk Indices, 77% of kidneys and 80% of livers from the non-proceeding HCVpos donors would be predicted to be functioning at 5 years if they had been transplanted.

The majority of implanted HCVpos organs were livers and most of the liver recipients (96.8%) were known to already have had HCV infection prior to transplantation. Only a small minority of kidneys were used from proceeding HCVpos donors, yet were it not for the presence of HCV they would generally be considered good quality kidney donors: compared to HCVneg donors, proceeding HCVpos donors were younger and a smaller proportion had a

history of hypertension. Although the number of transplant recipients of organs from HCVpos donors was small, their outcomes in terms of patient and graft survival were comparable to those in recipients of organs from HCVneg donors.

While the routine use of HCVpos donors for transplantation would represent a major change in clinical practice, there are already precedents in the case of CMV and EBV, where it is accepted that transplantation may result in the transmission of viral disease and protocols are in place to mitigate their impact by prophylactic or pre-emptive therapy (69,72). With the use of DAA, acquisition of HCV through the transplanted graft, may become viewed in a similar light (179).

The use of antiviral therapy in recipients of kidneys from HCVpos donors would add considerably to the cost of renal transplantation in the first 12 months. However, the cost analysis performed in the present analysis demonstrated that despite the high costs of combination sofosbuvir and ledispavir, their use to clear transmitted HCV from the renal allograft recipient would be cost effective compared to dialysis at 5 years. Similarly, a recent US publication described the costs of haemodialysis being between $40,000 and $73,000 and the cost of a combination of elbasvir/grazoprevir being $63,000 indicating that similar cost benefit from transplanting HCVpos kidneys would be seen in the US (172,180). It is likely that the costs of DAA therapy will fall so the cost benefit may become greater in the future. Based on the last year of data in this analysis, and if the use of organs from HCVpos donors became part of UK practice, we could expect an additional 21 deceased donors with HCV. If each of these donors donated on average 2.3 organs for transplantation, like other UK deceased donors, we would expect 48 transplants of which 2-3 may be expected to fail treatment with current DAA therapy. However, it is important to note that many salvage therapies are in practice or in development, meaning that even those who do not clear the virus with first line treatment will still likely achieve SVR (181).

SaBTO, has suggested that the use of organs from such donors in some circumstances be permitted, and this advice has been accepted. National

clinical guidelines have been drawn up by a consortium of interested professional bodies.

There are limitations to the present analysis. The first concerns determination of the HCV status of potential donors. Because the identification of HCVpos patients dying in critical care units through the PDA is based on entry of free text in the audit rather than a requirement to state the outcome of viral tests, it is likely that the number of patients classified as HCVpos is an underestimate. In the case of the UKTR of all consented potential donors, the presence of HCV infection was based on the results of serology and not on the presence of HCV RNA. In the UK, deceased donors who test positive for anti-HCV antibodies will be subsequently tested for HCV RNA with the result available after donation and transplantation. However, it is important to note that an increasing number of deceased organ donors who test positive for anti-HCV will be HCV RNA negative secondary to increased use of DAA. Although, centres in the UK may still not be able to test deceased donors for HCV RNA pre-transplant, it is important to consider that a proportion of anti-HCV antibody positive donors will not transmit HCV to the recipient.

Data from the UK blood donor service, where both HCV serology and NAT testing are performed on all blood donors, indicates that approximately 20% of the potential organ donors who are seropositive for HCV are likely to be RNA negative and therefore unlikely to transmit infection (155) . The second limitation concerns the cost analysis of routine anti-viral therapy in recipients of kidneys from HCVpos donors. The cost analysis performed was based on current costing by NICE using only the DAA currently recommended in their guidance, but in this rapidly moving field many such treatments have now been approved (168-170). However, there are now a number of novel DAA and these may be more or less cost effective in transplantation. Also, it has not been possible to comment on the expected extra costs associated with routine testing of transplant recipients for the presence of HCV. Thirdly, there is currently no information regarding the distribution of HCV genomes in the UK organ donor population as genotype determination is not part of routine organ donation screening. However, currently approved treatments include combinations that are active across all genotypes, with variable but usually

high SVR of >95%. Data from the UK general population can be used to infer the expected proportion of different genotypes in the UK organ donor population. In the UK, 90% of infected strains belong to genotype 1 or 3 with the latter being more common than the former (155). This analysis cannot assess the likelihood of consent for transplantation in those potential donors where there was no attempt to determine their wishes. A further limitation of this analysis is not knowing the HCV status of all renal transplant recipients. However, given the time period that these transplants were performed over it is unlikely that these kidneys would have been transplanted into HCVneg recipients without confirmation of either recipient HCV status or further testing (not available in the UKTR) to confirm that the donor did not have HCV RNA.

Transplantation of organs from deceased organ donors who died following ligature asphyxiation.

Publications from this work: Trotter et al. Transplantation of kidneys from DCD and DBD donors who died after ligature asphyxiation: the UK experience.
American Journal of Transplantation. June 2018. Epub ahead of print.

1.35 Introduction

Kidneys from deceased donors who have undergone ligature asphyxiation are often used for transplantation, although there is little information on whether this mode of death influences transplant outcomes. Ligature asphyxiation is usually the result of attempted suicide by hanging and is one of the most common methods of suicide. Moreover, suicide remains a common cause of death worldwide, especially in the younger population (97,182,183). In situations where attempted resuscitation and hospitalization has occurred following ligature asphyxiation, individuals may become potential DBD or DCD organ donors. However, ligature asphyxiation in these circumstances is associated with a period of global tissue hypoxia, often of an unknown duration, which may cause warm ischaemic injury of the transplantable organs (94,95,184). During ligature asphyxiation there is compression of the carotid arteries, jugular veins and the trachea, resulting in raised intracranial pressure, cerebral oedema and catastrophic brain injury (98). In addition to the above, the victims of ligature asphyxiation may also develop pulmonary oedema and multi-organ failure secondary to global tissue hypoxia (98). While hypoxic tissue injury following ligature asphyxiation is a concern in DBD donors, it may have an even greater impact on organs from DCD donors where the organs are also subjected to a second period of warm ischaemic injury between cardiac arrest and cold perfusion of the organs (29). However, many potential donors who die following ligature asphyxiation are relatively young and previously healthy and therefore might be a source of good quality kidneys that can be used safely for transplantation (185).

The evidence on which to base decisions regarding the use of organs from deceased donors following ligature asphyxiation is limited and comprises case

reports and single centre experiences (94,95,184). Moreover, the published experience relates almost exclusively to DBD donors, with little or no published evidence for DCD donors who are becoming an increasingly important source of organs for transplantation (94,95,184).

To improve the evidence base and aid decision making on the use of organs from donors who die following ligature asphyxiation, I undertook a retrospective national UK cohort analysis of all kidney transplants performed using organs from DBD and DCD donors.

1.36 Methods

1.36.1 Identification of recipients who received organs from donors who died from ligature asphyxiation

The UKTR was examined to identify the recipients of kidneys (both single and dual kidney transplant recipients) from donors who died secondary to ligature asphyxiation in the UK between 1st January 2003 and 31st December 2016 and information on death-censored graft survival and patient survival was collected. In recipients of renal allografts, 1 year eGFR was calculated (107).

All-cause graft failure was taken as time from transplantation to graft nephrectomy or return to permanent dialysis, whichever was earlier, or to death of the patient with a functioning graft. Survival of the patient was defined as time from transplantation until death. We defined PNF as failure of a graft to ever function. DGF was defined as the need for dialysis within the first 7 days after transplantation (excluding recipients with PNF). Graft survival was censored at 5 years. Warm ischaemic time was defined as the time from circulatory arrest to cold perfusion of the kidneys. Downtime was defined as either time from discovery of cardiac arrest until return of circulation following resuscitation or when the free text entries in the registry referred to the time as downtime.

1.36.2 Statistical analysis

Univariate analysis was carried out using the Student's t-test for parametric continuous data and the Mann–Whitney U test for non-parametric continuous

data. Comparisons between groups were made using the χ^2 test for categorical data. Kaplan–Meier tables were used to compare death-censored graft survival and patient survival. The univariate log-rank test was used to test differences in survival.

Cox proportional hazards regression model was fitted with factors known to impact on patient and graft survival. Patient and graft survival were censored at 1 year to determine factors associated with 1 year survival and at 5 years to determine the factors associated with 5-year survival. This was performed as a large proportion of donors who died following ligature asphyxiation had kidneys used for transplantation in the last 3 years. Patients without graft or patient follow-up (n=79 (0.4%)) were not included in the analysis. Log cumulative hazard plots were drawn and proportionality of hazards was checked using log–log plots.

Multivariable linear regression modelling was carried out to assess the impact that donor cause of death from ligature asphyxiation had on 1 year eGFR and creatinine. Logistic regression analysis was performed to assess the impact of donor cause of death by ligature asphyxiation on potential donors proceeding to kidney donation and the impact of this cause of death on DGF and PNF rates.

Multiple imputation was used to account for missing donor and recipient variables. There were no missing data for donor type, ethnicity and whether or not cause of death was by ligature asphyxiation. Missing information about past medical history of hypertension and/or diabetes was 7.1%. For past medical history of cardiac disease and smoking there were 0.98% and 2.3% missing data respectively. In terms of recipient characteristics, there were <1% missing data for recipient gender, HLA mismatch level, ethnicity and recipient sex, <2% for CIT and 37% for warm ischaemic time in DCD donors. Missing data were assumed to be missing at random and the missing variables had an arbitrary missing pattern. The imputed variables were all independent variables. Missing data were estimated by a discriminant function approach for categorical variables, a logistic regression approach for ordinal variables and linear models for cumulative variables. The FCS method was used to impute missing values of both continuous and class variables in the

dataset with an arbitrary missing pattern. For each analysis requiring multiple imputation, 20 imputed datasets were created.

Donor-related variables considered for inclusion in the multivariable models were donor age, donor type, ethnic group, sex, cause of death, past medical history of diabetes, hypertension and cardiac disease, previous drug abuse and smoking history, and blood group. Recipient factors included were recipient age, ethnicity, sex, sensitization, primary renal disease (five categories), blood group (O, A, B, AB), HLA mismatch and CIT. Other factors considered for inclusion were renal transplant unit, which was included as a random effect, and year of transplant (as an ordinal variable).

An addition to the above multivariable analyses, a case-control propensity score matched analysis was also performed to examine transplant outcomes in recipients of kidneys from donors who died following ligature asphyxiation. Propensity scores were calculated using logistic regression on the probability of a recipient receiving a kidney from a donor who died following ligature asphyxiation. The scores were then used to match recipients of kidneys from donors who died following ligature asphyxiation to recipients of kidneys from all other deceased donors with similar propensity scores. This was accomplished with 1:1 matching. The following covariates were included in the estimation of propensity scores since they have been shown in previous analyses of the UK dataset to impact on transplant outcomes: donor age, recipient age, donor past medical history of hypertension, primary renal disease, HLA mismatch grade, cold ischaemic time, donor weight, donor type (DBD and DCD) and transplant year (149,186).

1.37 Results

1.37.1 Potential and proceeding kidney donors who died secondary to ligature asphyxiation

Over the 14-year study period (1st January 2003 to 31st December 2016), 2.7% (n=521) of all potential UK organ donors died secondary to ligature asphyxiation. Nearly all (98.7%) were a result of attempted suicide, but a small proportion (1.3%) were accidental. From this pool of potential donors,

409 (78.5%) subsequently proceeded to donate one or more kidneys for transplantation. By comparison, only 69.9% of potential donors who died from all causes other than ligature asphyxiation proceeded to donate kidneys for transplantation (p<0.001). Of the potential donors who died from ligature asphyxiation and proceeded to kidney donation, 192 (46.9%) were DBD donors and 217 (53.1%) were controlled DCD donors.

The proportion of potential DBD donors who died after ligature asphyxiation and proceeded to donate kidneys was similar to that for all other types of potential DBD donors (91.4% vs 87.6% respectively, p=0.092). Compared to potential DBD donors, a lower proportion of all potential DCD donors proceeded to kidney donation, irrespective of whether the cause of death was from ligature asphyxiation (50.1% vs 87.7%, p<0.001). However, more potential DCD donors proceeded to donate organs after ligature asphyxiation than after causes of death other than ligature asphyxiation (69.8% vs 49.4%, p<0.001).

Relatively little information was available in the transplant registry regarding the physiological events occurring around the time of ligature asphyxiation. A total of 203 (39.0%) potential donors who died following ligature asphyxiation were reported to have had a cardiac arrest at the time of ligature asphyxiation and had a recorded 'downtime' (i.e. the length of time following cardiac arrest until return of circulation at the time of resuscitation). Of these, 73.8% proceeded to donate kidneys for transplantation compared to 80.7% of potential donors with no stated downtime (p=0.125). The median recorded downtime was 25 minutes (IQR 15–40 minutes). Of donors who died from ligature asphyxiation, DCD donors had significantly shorter recorded downtimes compared to DBD donors (median 22 minutes (IQR 15–34.5) vs median 33 minutes (IQR 19–45.5), p=0.0151).

1.37.2 Factors associated with potential deceased donors proceeding to donate kidneys for transplantation

A multivariable analysis was undertaken on all potential donors (n=19,310) to determine whether death from ligature asphyxiation was independently associated with a potential donor proceeding to donate one or more kidneys

for transplantation. As shown in Table 7.1a, the following donor factors were associated with proceeding to donate kidneys: donor age; DBD donor type; no past medical history of diabetes, hypertension or cardiac disease; and white ethnicity. Following adjustment for the above donor variables, ligature asphyxiation in potential donors remained strongly associated with an increased likelihood of kidney donation for transplantation (odds ratio 1.211 (95% confidence interval 1.080–1.357), p<0.001). A further multivariable analysis was performed to assess what factors influenced donors who died following ligature asphyxiation to proceed to kidney donation. Table 7.1b, demonstrates that younger donor age, DBD donor type, no history of smoking or liver disease, no history of intravenous drug use, and having been imprisoned were all independently associated with a donor who died following ligature asphyxiation proceeding to donate a kidney for transplantation.

1.37.3 Clinical characteristics of proceeding kidney donors (DBD and DCD) who died from ligature asphyxiation

The clinical characteristics of proceeding kidney donors who died after ligature asphyxiation and those who died from all other causes are shown in Table 7.2; the data are shown separately for DBD and DCD. Both DBD and DCD kidney donors who died from ligature asphyxiation were significantly younger and a greater proportion were male than those DBD and DCD donors who died from other causes. Four (<0.5%) DBD donors who died from causes other than ligature asphyxiation did not have gender known.

Donors who died following ligature asphyxiation (both DBD and DCD donors) had a markedly lower incidence of hypertension and cardiac disease than donors who died from causes other than ligature asphyxiation. The proportion of kidney donors who died following ligature asphyxiation who had diabetes mellitus was numerically lower than that of donors who died from all other causes, but the difference was only significant in the case of DCD donors. More kidney donors (both DBD and DCD) who died following ligature asphyxiation had a history of smoking compared to all other deceased donors. DBD and DCD donors who died following ligature asphyxiation had significantly higher pre-donation serum creatinine levels.

Donor characteristics (n=19,310)	***Odds Ratio (95% Confidence Interval)***	***p-value***
Donor Age	0.983 (0.981-0.986)	<0.001
Donor ethnicity		
White	1.00	-
Non-white	0.794 (0.731- 0.863)	<0.001
Donor Type		
DCD	1.00	-
DBD	2.536 (2.444-2.631)	<0.001
Past medical history of diabetes		
No	1.00	-
Yes	0.753 (0.707- 0.803)	<0.001
Past medical history of hypertension		
No	1.00	-
Yes	0.902 (0.863-0.942)	<0.001
Past medical history of cardiac disease		
No	1.00	-
Yes	0.863 (0.819-0.908)	<0.001
Past medical history of smoking		
No	1.00	-
Yes	0.970 (0.933-1.01)	0.115
Donor cause of death		
No ligature asphyxiation	1.00	-
Ligature asphyxiation	1.211 (1.080-1.357)	0.001

Table 7.1a. Factors associated with potential deceased donors proceeding to donate one or more kidneys for transplantation. 19, 310 potential deceased donors were analysed by logistic regression.

Donor characteristics (n=521)	***Odds Ratio (95% Confidence Interval)***	***p-value***
Donor Age (years)	0.975 (0.965-0.985)	<0.001
Donor ethnicity		
White	1.00	-
Non-white	1.259 (0.829-1.911)	0.279
Donor Type		
DCD	1.00	-
DBD	1.973 (1.664-2.340)	<0.001
Past medical history of diabetes		
No	1.00	-
Yes	0.951 (0.630-1.436)	0.811
Past medical history of hypertension		
No	1.00	-
Yes	1.223 (0.850-1.758)	0.278
Past medical history of cardiac disease		
No	1.00	-
Yes	0.901 (0.514-1.580)	0.716
Past medical history of smoking		
No	1.00	-
Yes	0.829 (0.706-0.973)	0.022
History of IVDU		
No	1.00	-
Yes	0.543 (0.412-0.715)	<0.001
History of imprisonment		
No	1.00	
Yes	1.438 (1.055-1.961)	0.022
History of liver disease		
No	1.00	
Yes	0.479 (0.324-0.709)	<0.001
Downtime (minutes)	1.005 (0.994-1.016)	0.387
Pre-donation creatinine (umol/l)	1.000 (0.999-1.002)	0.911

Table 7.1b. Factors associated with potential donors who died following ligature asphyxiation proceeding to donate one or more kidneys for transplantation

	DBD donors who died following ligature asphyxiation (n=192)	DBD donors who died from all other causes(n=8846)	p-value	DCD donors who died following ligature asphyxiation (n=217)	DCD donors who died from all other causes (n=4291)	p-value
Age (y)	32 (22-43)	49 (37-59)	<0.001	34 (24-47)	54 (43-65)	<0.001
Male/Female (%)	113 (58.9%)/79 (41.1%)	4448 (50.3%)/ 4394(49.7%)	0.074	160 (73.7%)/57 (26.3%)	2583 (60.2%)/1708 (39.8%)	<0.001
White ethnicity	181 (94.3%)	8404 (95.0%)	0.658	208(95.9%)	4145 (96.6%)	0.557
History of Hypertension Yes/No	5 (2.6%)/ 187 (97.4%)	2172 (24.6%)/ 6480 (73.3%)	<0.001	14 (6.5%) 197 (90.8%)	1222 (28.5%) 2780 (64.8%)	<0.001
Unknown/Unstated	0	194 (2.2%)		6 (2.8%)	289 (6.7%)	
History of Cardiac disease Yes/ No	1 (0.5%) 189 (98.4%)	746 (8.4%) 7900(89.3%)	<0.001	5 (2.3%) 199 (91.7%)	598 (13.9%) 3359 (78.3%)	<0.001
Unknown/Unstated	2 (1.0%)	200 (2.3%)		13 (5.9%)	334 (7.8%)	
History of Diabetes Yes/No	8 (4.2%)/ 183 (95.3%)	480 (5.4%)/ 8272(93.5%)	0.565	5 (2.3%)/ 201 (92.6%)	325 (7.6%)/ 3696 (86.1%)	0.007
Unknown/Unstated	1 (0.5%)	94 (1.1%)		11 (4.9%)	270 (6.3%)	
Smoking History Yes/ No	125 (65.1%)/ 65(33.9%)	4231 (47.8%)/ 4522 (51.1%)	<0.001	140 (64.5%)/ 74 (34.1%)	1802 (42.0%)/ 2233 (52.1%)	<0.001
Unknown/Unstated	2 (1.0%)	93 (1.1%)		3 (1.4%)	256 (6.0%)	
Pre-donation serum creatinine (umol/l)	121 (93-162)	84 (67-107)	<0.001	101 (80-129)	84 (65-108)	<0.001
Missing	0	9 (<0.5%)		3 (1.4%)	223 (5.2%)	

Table 7.2. Clinical Characteristics of proceeding kidney donors who died from ligature asphyxiation compared to all other deceased donors.

1.37.4 Clinical characteristics of recipients of kidneys from donors who died following ligature asphyxiation

Donors who died following ligature asphyxiation provided kidneys for 650 kidney only transplants. The clinical characteristics of recipients of kidneys from DBD and DCD donors who died following ligature asphyxiation and those who died from all other causes are shown in Table 7.3. Recipients of kidneys from donors who died following ligature asphyxiation were significantly younger than those receiving kidneys from donors who died from other causes, but were of similar gender and ethnicity. There was no difference in the crf or HLA mismatch between recipients of kidneys from deceased donors who died following ligature asphyxiation and those who died from all other causes. The primary renal disease in recipients of kidneys from DBD and DCD donors who died following ligature asphyxiation was broadly similar to that for recipients of kidneys from other DBD and DCD donors. The CITs of kidneys from DBD donors who died following ligature asphyxiation were significantly shorter than those for kidneys from all other DBD donors. CITs were similar for kidneys from DCD donors who died following ligature asphyxiation and all other DCD donors.

Over the 14-year study period there was a marked increase in the number of deceased donor kidney transplants performed in the UK, predominantly because of an increase in transplants using kidneys from DCD donors (Figure 7.1a). The number of kidney transplants performed from both DBD and DCD donors who died following ligature asphyxiation increased progressively over the study period (Figure 7.1b), such that half of the transplants using kidneys from such donors were performed in the last 4 of the 14-year study period.

	DBD donors following ligature asphyxiation(n=294)	All other DBD donors (n=14382)	p-value	DCD donors following ligature asphyxiation(n=356)	All other DCD donors (n=6662)	p-value
Age (y)	43 (29-53)	48 (37-58)	<0.001	47 (38-57)	55 (46-63)	<0.001
MaleFemale (%)	182 (61.9%)/ 112(38.1%)	8774 (61.0%)/ 5599 (39.0%)	0.879	211 (59.3%)/ 143(40.2%)	4406 (66.2%)/ 2250 (33.8%)	0.001
White ethnicity (%)	203 (69.1%)	11006 (76.5%)	0.003	284 (79.8%)	5167 (77.6%)	0.396
Dual kidney transplant (%)	0 (0)	101(0.7%)	0.352	3 (0.8%)	318 (4.7%)	0.01
cRF >85%	44 (15.0%)	1805 (12.6%)	0.217	20 (5.6%)	293 (4.4%)	0.304
HLA Mismatch Grade			0.638			0.168
1	58 (19.7%)	2728 (19.0%)		9 (2.5%)	226 (3.4%)	
2	124 (42.2%)	5841 (40.6%)		96 (26.7%)	1581 (23.7%)	
3	106 (36.1%)	5327 (37.1%)		216 (59.8%)	3889 (58.4%)	
4	6 (2.0%)	481 (3.3%)		40 (11.0%)	965 (14.5%)	
CIT			<0.001			0.248
<12hours	78 (27.1%)	2662 (18.5%)		110 (31.3%)	1977 (30.0%)	
12 to 18 hours	129 (44.8%)	6820 (47.5%)		162 (46.4%)	2973 (45.1%)	
18 to 24 hours	65 (22.6%)	3354 (23.3%)		68 (19.5%)	1320 (20.0%)	
>24 hours	16 (5.6%)	1395 (9.7%)		9 (2.6%)	322 (4.9%)	
WIT (min)	-	-		7 (6-10)	8 (6-10)	0.796
Primary Renal Disease			0.040			0.192
Diabetic Nephropathy	19 (6.4%)	1004 (7.0%)		26 (7.5%)	637 (9.5%)	
Glomerulonephritis	38 (12.8%)	2497 (17.4%)		73 (20.8%)	1256 (18.8%)	
Pyelonephritis	19 (6.4%)	1218 (8.5%)		24 (6.7%)	462 (7.0%)	
Polycystic Kidney Disease	25 (8.5%)	1515 (10.5%)		42 (11.6%)	1011 (15.2%)	
Other	193 (65.7%)	8147 (56.6%)		191 (53.5%)	3295 (49.5%)	

Table 7.3. Clinical Characteristics of renal transplant recipients from organ donors who died from ligature asphyxiation compared to those who died of all other causes. *Missing data was <1% gender and HLA Mismatch level ethnicity and recipient sex and <2% for cold ischaemic time, 37% for warm ischaemic time.

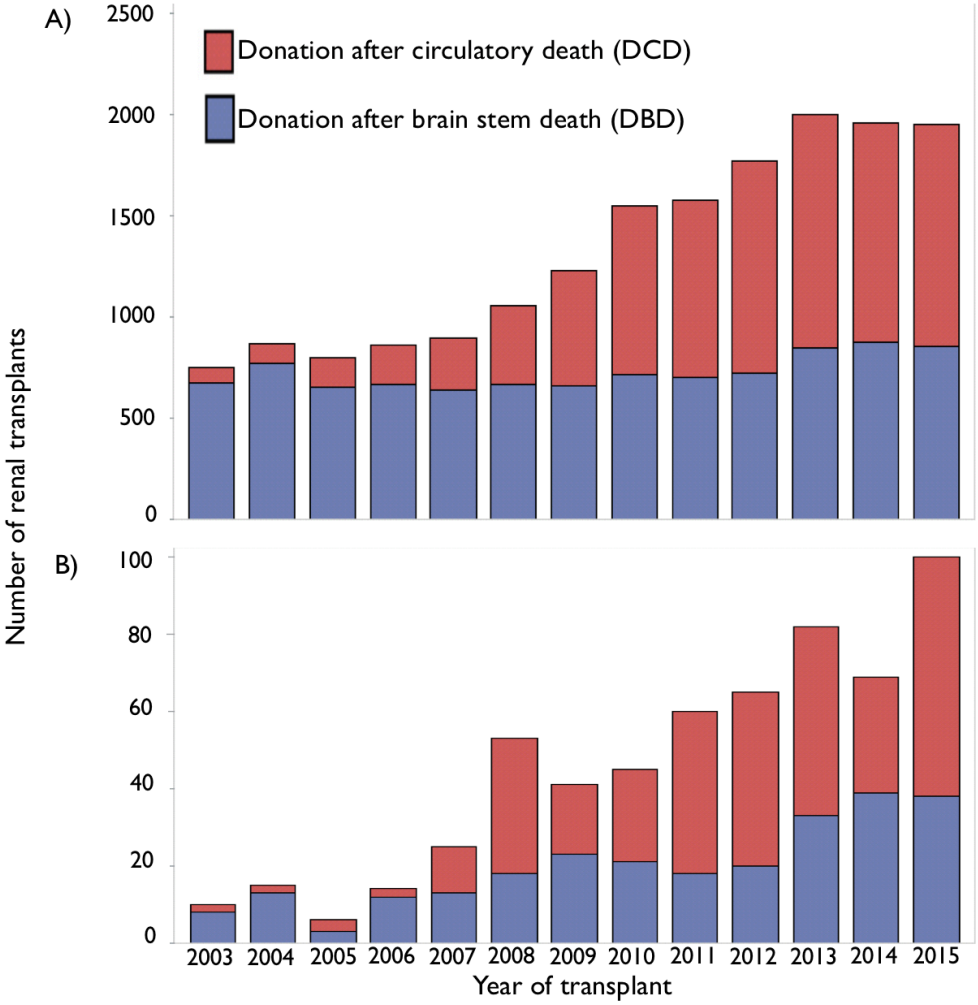


Figure 7.1. Number of renal transplants carried out from 2003-2015 from
A) all deceased donors by donor type (DBD and DCD) and
B) Donors who died following ligature asphyxiation and donor type (DBD and DCD)

1.37.5 Outcomes in recipients of kidneys from donors who died following ligature asphyxiation

The results of analyses of patient and graft survival are shown in Figures 7.2–7.5. For these and the multivariable analyses the median follow-up of kidney transplant recipients was 48 months (IQR 24–96 months). For kidney transplant recipients transplanted in 2016, the median follow-up was 96 days (IQR 88–356 days).

For transplant outcomes when comparing recipients of kidneys from donors who died following ligature asphyxiation with those who did not I chose to analyse recipients of kidneys from DBD and DCD donors separately. For

recipients of kidneys from DBD donors, graft survival was superior for those who received kidneys from donors who died following ligature asphyxiation, but there was no difference in patient survival (Figure 7.2). For recipients of kidneys from DCD donors, both patient and graft survival were better for those who received kidneys from donors who died following ligature asphyxiation (Figure 7.3). A comparison of recipients of kidneys from DBD and DCD donors who died following ligature asphyxiation showed similar patient and graft survival (Figure 7.4). Finally, a comparison of recipients of kidneys from all kidney donors (DBD and DCD) who died following ligature asphyxiation and those who received kidneys from all other deceased kidney donors demonstrated better patient and graft survival for those who received kidneys from donors who died following ligature asphyxiation (Figure 7.5).

As already shown, significant differences were identified in donor and recipient demographics between recipients of kidneys from donors who died following ligature asphyxiation and all other deceased kidney donors. The factors considered in the analyses included donor and recipient age, CIT, donor type (DBD or DCD), HLA mismatch level, recipient primary renal disease and donor comorbid diseases.

The results for the multivariable analyses (both unadjusted and adjusted) are shown in Table 7.4. Numerically, 1 year and 5-year patient and graft survival were superior when the donor cause of death was by ligature asphyxiation than by other causes, both before and after confounder adjustment (Table 7.4). DGF and PNF rates were comparable between recipients of kidneys from donors who died of ligature asphyxiation and those who received kidneys from all other deceased donors after adjustment for donor and recipient characteristics.

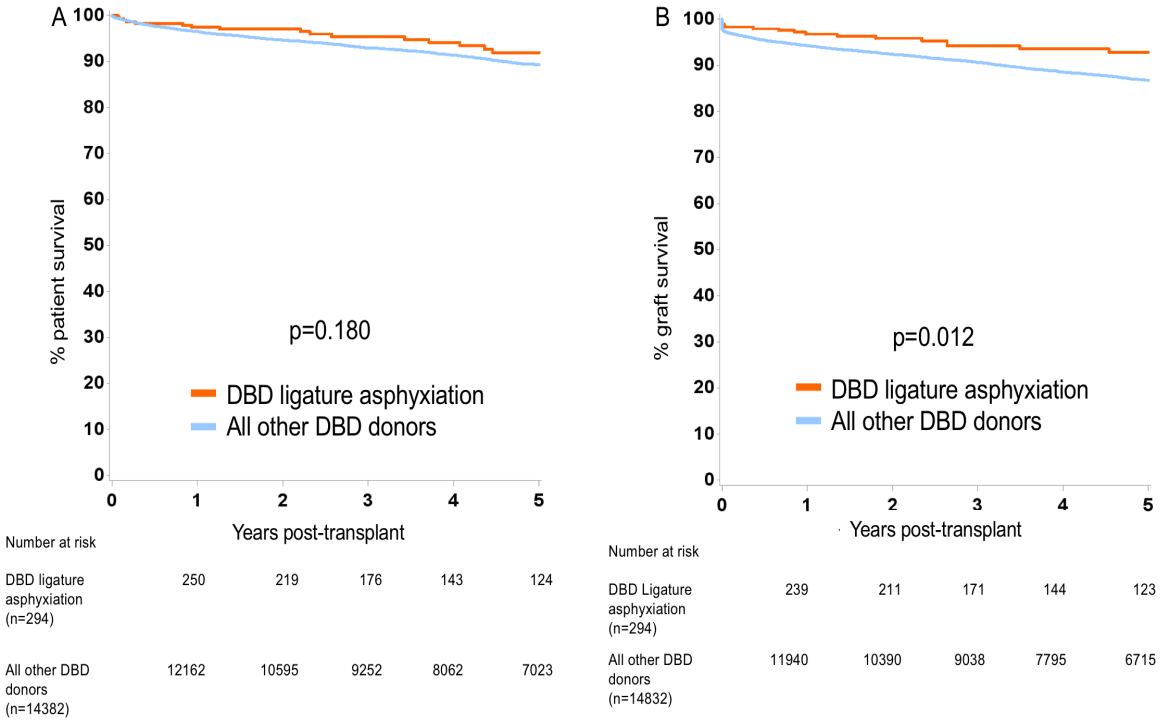


Figure 7.2. Kaplan-Meier estimates of A) Patient survival from renal transplantation from DBD donors who died following ligature asphyxiation and all other DBD donors and B) Death censored graft survival from renal transplantation from DBD donors who died following ligature asphyxiation and all other DBD donors

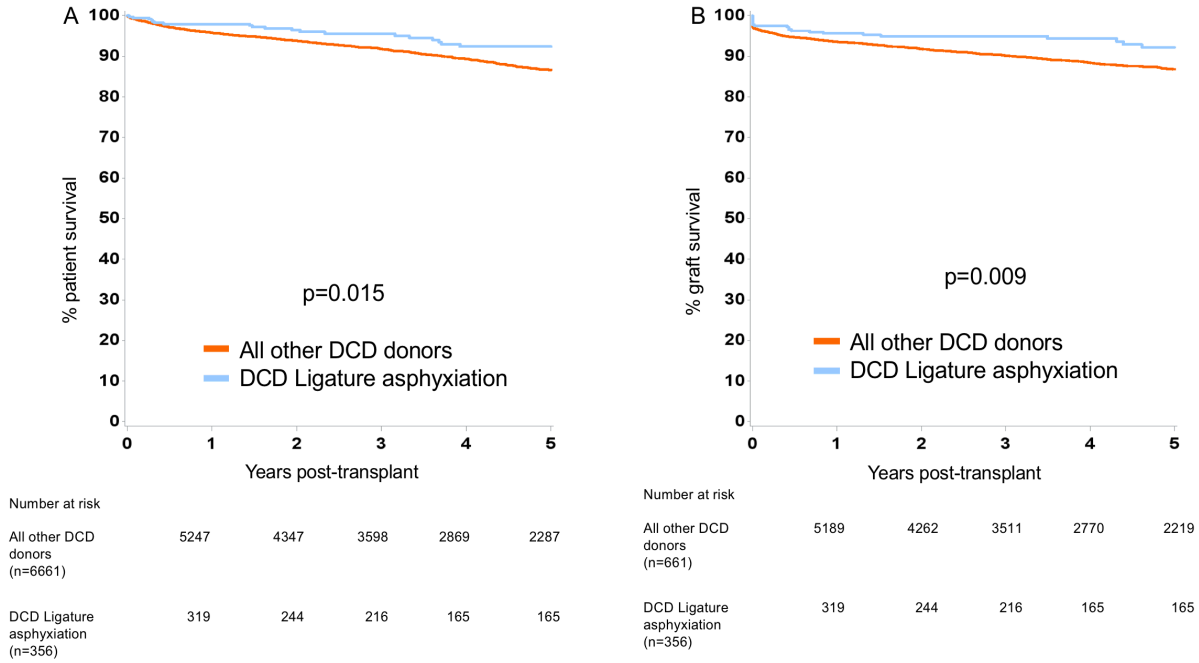


Figure 7.3. Kaplan-Meier estimates of A) Patient survival from renal transplantation from DCD donors who died following ligature asphyxiation and all other DCD donors and B) Death censored graft survival from renal transplantation from DCD donors who died following ligature asphyxiation and all other DCD donors

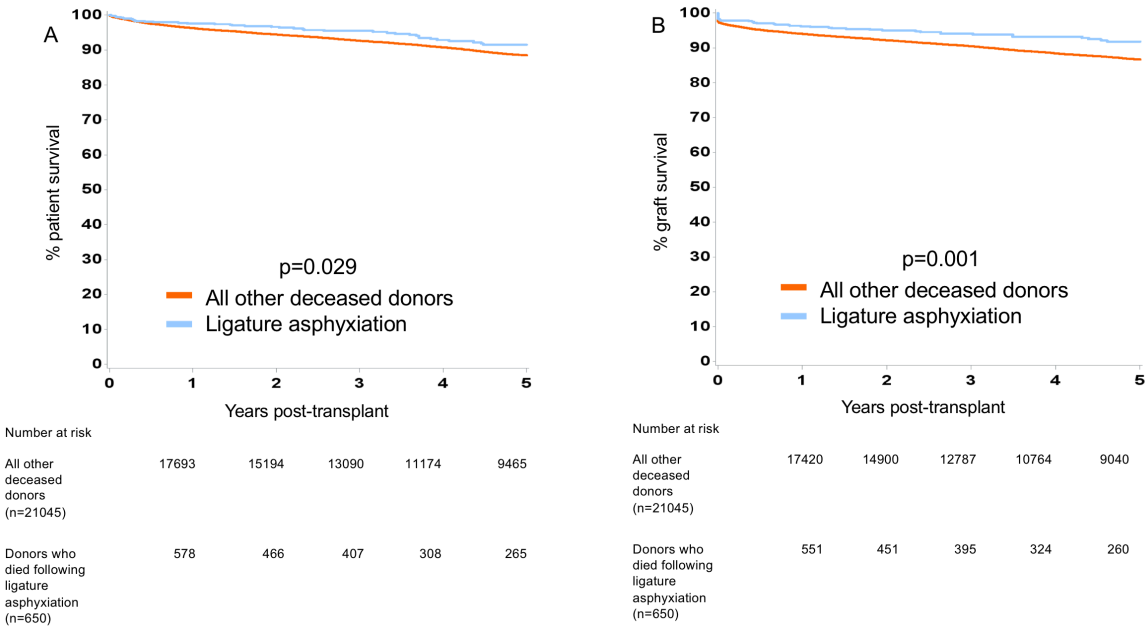


Figure 7.4. Kaplan-Meier estimates of A) Patient survival from renal transplantation from donors who died following ligature asphyxiation (both DBD and DCD) and all other deceased donors and B) Death censored graft survival from renal transplantation from donors who died following ligature asphyxiation (both DBD and DCD) and all other deceased donors

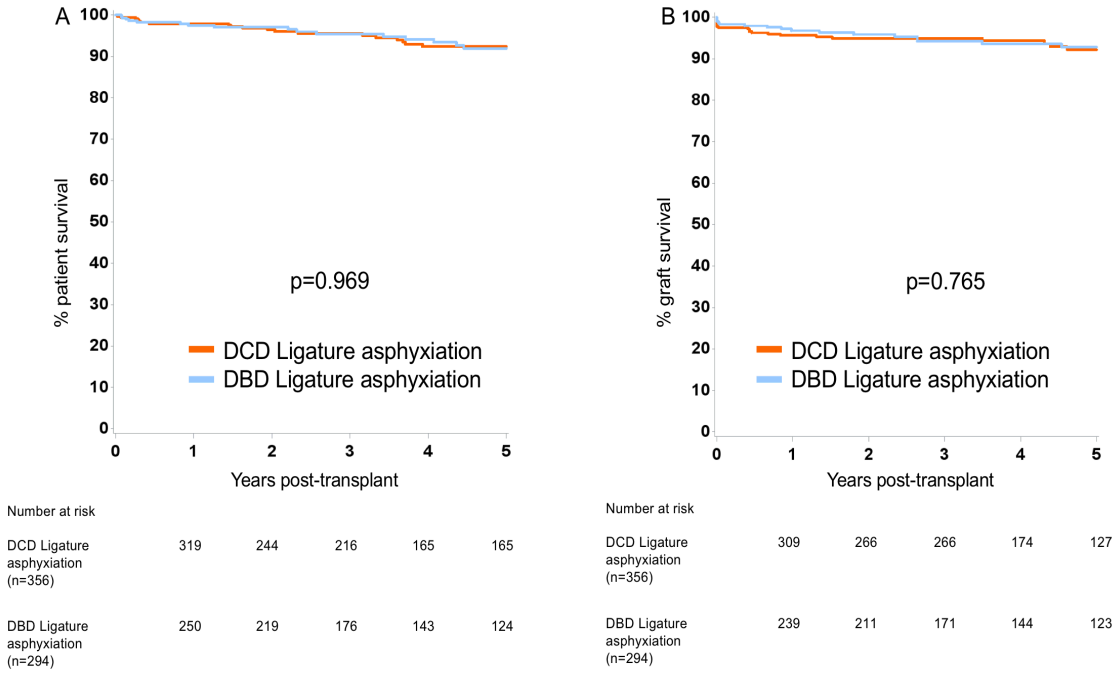


Figure 7.5. Kaplan-Meier estimates of A) Patient survival from renal transplantation from DCD and DBD donors who died following ligature asphyxiation and B) Death censored graft survival from renal transplantation from DCD and DBD donors who died following ligature asphyxiation

Of the 21,682 deceased donor kidney transplants performed, 18,059 (83.4%) were first-time kidney transplant recipients. In a sensitivity analysis of first kidney only transplants, patient and graft survival were similar for those who received their first kidney transplant from donors who died following ligature asphyxiation and for those who received kidneys from all other deceased donors.

Of the 21,682 deceased donor kidney only transplant recipients, 18,258 (82.3%) had 12 month post-transplant serum creatinine recorded and, of these, data were available to calculate eGFR for 18,216. Twelve month eGFR was significantly higher for those who received kidneys from donors who died from ligature asphyxiation (both DCD and DBD) (Figure 7.6).

To examine the impact that donor death by ligature asphyxiation had on 12-month post-transplant eGFR, a multivariable linear regression model was fitted. Following adjustment for donor and recipient factors, death by ligature asphyxiation was not an independent predictor of 12 month eGFR (p=0.452).

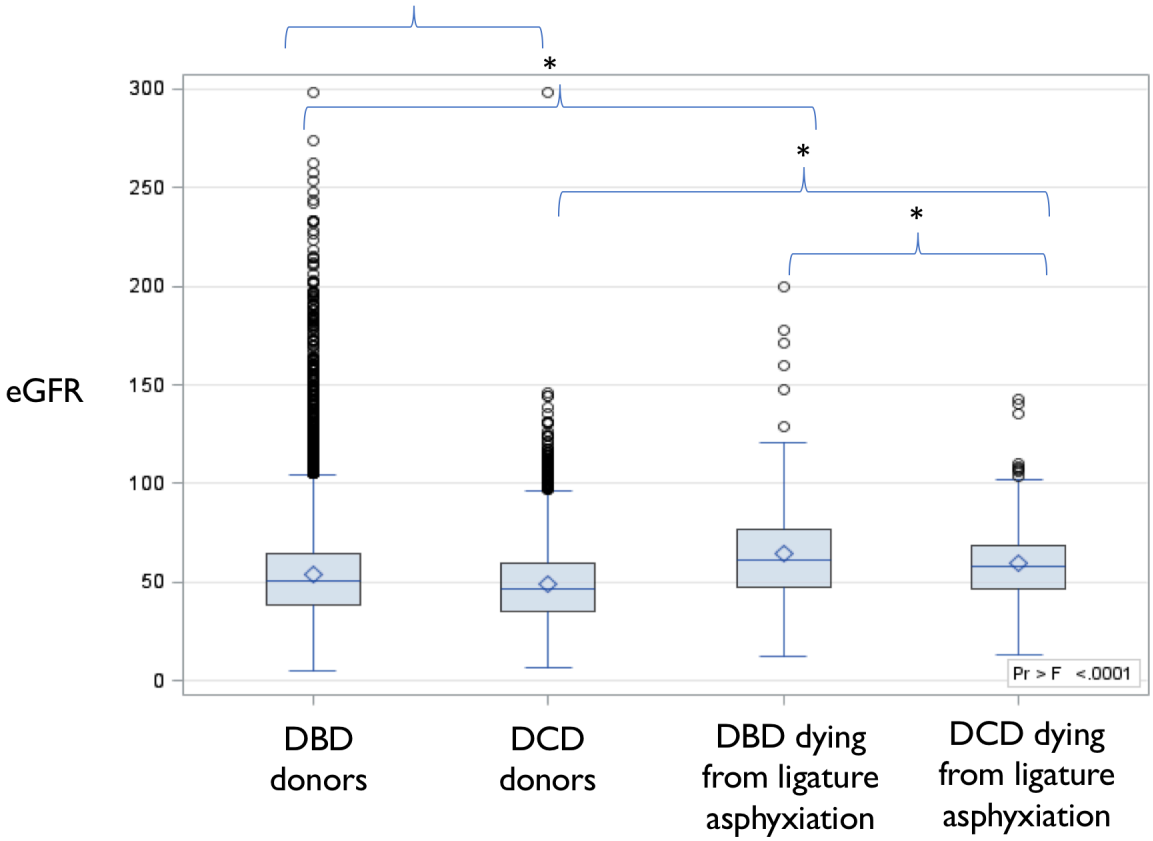


Figure 7.6. 12 month eGFR by donor type and whether the donor died secondary to ligature asphyxiation. *p<0.05

	DBD donors following ligature asphyxiation (n=294)	All other DBD donors (n=14382)	DCD donors following ligature asphyxiation(n=356)	All other DCD donors (n=6661)	Unadjusted Ratio (95% CI) Ligature asphyxiation vs. non-ligature asphyxiation	Adjusted ratio (95% CI) Ligature asphyxiation vs. non-ligature asphyxiation	Adjusted p-value
Primary-non-function	1/262 (0.4%)	275 /12741 (2.2%)	8/320 (2.5%)	157/5899 (2.7%)	OR 0.694 (0.357-1.351)	OR 0.989 (0.704-1.388)	0.948
Delayed graft function	40/262 (15.2%)	2778/12741 (21.8%)	116/320 (36.3%)	2377/5899 (40.3%)	OR 0.946 (0.783-1.142)	OR 1.050 (0.952-1.160)	0.325
1-year death censored graft survival	96.8%	94.3%	95.6%	93.6%	HR 0.638 (0.426-0.955)	HR 0.851 (0.565-1.283)	0.442
5-year death censored graft survival	92.8%	86.8%	92.2%	86.8%	HR 0.557 (0.403-0.771)	HR 0.775 (0.564-1.06)	0.115
1-year patient survival from transplantation	97.5%	96.5%	97.9%	95.8%	HR 0.613 (0.361-1.041)	HR 0.984 (0.585-1.655)	0.951
5-year patient survival from transplantation	91.9%	89.3%	92.4%	86.6%	HR 0.667 (0.478-0.932)	HR 1.05 (0.757-1.456)	0.772
1-year first kidney death censored graft survival (n=18059)	97.8%	96.5%	98.0%	95.7%	HR 0.619 (0.388-0.987)	HR 0.814 (0.506 1.307)	0.269
5-year first kidney death censored graft survival (n=18059)	95.2%	88.4%	93.5%	87.3%	HR 0.506 (0.343-0.745)	HR 0.705 (0483-1.03)	0.070
12-month eGFR (n= 17846)	61.4 (46.7- 76.6) (n=238)	50.4 (38.3-64.8) (n=11953)	57.9 (46.2- 68.7) (n=299)	46.6 (34.9-59.6) (n=5350)	PE 9.525 (7.482-11.567)	PE 0.686 (-1.103- 2.476)	0.452

Table 7.4. Comparison of kidney transplant outcomes by donor type (DBD and DCD) and donor death secondary to ligature asphyxiation. OR= Odds Ratio. HR= Hazard Ratio. PE=Parameter estimate.

To assess whether the additional warm ischaemic insult from ligature asphyxiation in DCD donors impacted on transplant outcomes, a separate multivariable analysis of such donors was performed. This revealed that even after adjusting for warm ischaemic time in DCD donors there was no difference between transplant outcomes for recipients of kidneys from DCD donors who died following ligature asphyxiation and all other DCD donors (Table 7.5).

Renal transplant recipients from DCD donors	**Unadjusted ratio (95% CI) Ligature asphyxiation vs. non-ligature asphyxiation**	**Adjusted ratio (95% CI) Ligature asphyxiation vs. non-ligature asphyxiation**	**Adjusted p-value**
Primary-non-function	OR 0.972 (0.473- 1.996)	OR 1.196 (0.823-1.739)	0.348
Delayed graft function	OR 0.849 (0.670- 1.074)	OR 0.988 (0.887-1.101)	0.827
1-year death censored graft survival	HR 0.666 (0.383-1.158)	HR 0.890 (0.505-1.570)	0.688
5-year death censored graft survival	HR 0.608 (0.389-0.948)	HR 0.827 (0.524-1.305)	0.413
1-year patient survival from transplantation	HR 0.463 (0.206-1.04)	HR 0.821 (0.831-1.878)	0.640
5-year patient survival from transplantation	HR 0.564 (0.353-0.902)	HR 0.961 (0.593-1.556)	0.871
1-year first kidney death censored graft survival	HR 0.666 (0.383-1.158)	HR 0.890 (0.505-.1.568)	0.688
5-year first kidney death censored graft survival	HR 0.608 (0.389-0.948)	HR 0.827 (0.524-1.305)	0.413
12-month eGFR	PE 11.185 (8.798-13.572)	PE 1.858 (-0.426- 4.141)	0.111

Table 7.5. Comparison of DCD kidney transplant outcomes by donor death secondary to ligature asphyxiation.

To reduce the impact of potential bias from confounding variables, a case-control propensity score matched analysis was also performed. Recipients of kidneys from donors who died following ligature asphyxiation (n=622) were

matched to controls based on propensity scores generated using selected donor and recipient variables (see methods). This analysis showed all transplant outcomes of recipients of kidneys from donors who died following ligature asphyxiation were similar to those in the matched control group (Table 7.6). An additional case-control propensity score matched analysis was performed comparing outcomes in recipients of kidneys from DCD donors who died following ligature asphyxiation and controls who received DCD donor kidneys. This also confirmed that kidneys from donors who died following ligature asphyxiation had similar outcomes to matched controls.

	Recipients of kidneys from donors dying after ligature asphyxiation (n=622) Median Propensity score (0.059 (0.031-0.108)	Matched control recipients (n=622) Median Propensity score (0.060 (0.030- 0.105)	Propensity score matched ligature asphyxiation vs. non-ligature asphyxiation	p-value
PNF	9/570 (1.6%)	11 /580 (1.9%)	OR 1.083 (0.456-2.569)	0.897
DGF	152/570 (26.7%)	132/580(22.8%)	OR 0.810 (0.619-1.060)	0.687
1-year death censored graft survival	96.1%	96.3%	HR 1.051 (0.593-1.862)	0.865
5-year death censored graft survival	91.3%	89.2%	HR 0.805 (0.537-1.208)	0.295
1-year patient survival from transplantation	97.5%	97.8%	HR 0.664 (0.347-1.273)	0.218
5-year patient survival from transplantation	90.7%	92.5%	HR 0.985 (0.640-1.515)	0.945
1-year first kidney, death censored graft survival (n=1077)	96.6%	96.8%	HR 1.06 (0.544-2.046)	0.875
5-year first kidney, death censored graft survival (n=1077)	92.9%	90.9%	HR 0.800 (0.499-1.282)	0.353
12-month eGFR (n=1104)	61 (47-74)(n=535)	59 (47-74)(n=557)	PE 1.575 (-3.392-2.788)	0.848

Table 7.6. Transplant outcomes in a 1-1 case-control propensity score matched analysis of recipients of kidneys from donors who died following ligature asphyxiation and their matched controls

1.38 Discussion

Organ donors who die following ligature asphyxiation represent a relatively small but important proportion of the overall deceased donor population (~3% in the present analysis). Most of these deaths result from attempted suicide by hanging and tragically the incidence of this continues to increase, predominantly among younger males where suicide is the second most common cause of death (185,187). The mode of death following ligature asphyxiation results in global tissue hypoxia and the effect that this has on end-organ function following kidney transplantation has never been fully assessed. The results of the present national cohort analysis clearly demonstrate that the outcomes for recipients of kidneys from both DBD and DCD donors who have died following ligature asphyxiation are comparable to those for recipients of kidneys from donors who have died from all other causes.

In the present analysis, approximately half of the donors who died following ligature asphyxiation were DBD donors. Recipients of kidneys from such donors had similar patient survival and significantly better graft survival up to 5 years to those of recipients of kidneys from all other DBD donors. Moreover, DGF and 12 month eGFR were significantly better in recipients of kidneys from DBD donors who died following ligature asphyxiation. The superior outcomes seen in recipients of kidneys from DBD donors who died following ligature asphyxiation is likely attributable to the fact that such donors were younger and had less comorbid disease than all other DBD donors. Indeed, after case-mix adjustment in a multivariable analysis, 12 month eGFR outcomes were similar. The case controlled propensity score matched analysis also confirmed that transplant outcomes were comparable in recipients of kidneys from donors dying from ligature asphyxiation and their matched controls.

It is now widely accepted that while recipients of kidneys from DCD donors have increased rates of PNF and DGF, the long-term clinical outcomes are comparable to those observed in recipients of kidneys from DBD donors (149,187). As observed with DBD donors who died following ligature

asphyxiation, recipients of kidneys from DCD donors who died following ligature asphyxiation had superior transplant outcomes compared to those seen in recipients of kidneys from all other DCD donors. The additional warm ischaemic insult from ligature asphyxiation was not associated with an increase in either PNF or DGF. The additional analyses of DCD donors who died following ligature asphyxiation demonstrated that even after adjustment for warm ischaemic time, kidneys from such donors were not associated with poorer transplant outcomes than recipients of kidneys from all other DCD donors. This conclusion was confirmed by a case-control propensity score matched analysis of recipients of kidneys from DCD donors who died following ligature asphyxiation and their matched controls.

There is little information in the literature concerning the outcome following transplantation with kidneys from either DBD or DCD donors who died following ligature asphyxiation. A major strength of the present registry analysis is that it provides the first comprehensive analysis of transplant outcome in recipients of kidneys from donors who died following ligature asphyxiation. The analysis included a relatively large national cohort of kidney donors who died following ligature asphyxiation with a large proportion of DCD donors.

As for all retrospective transplant registry analyses, some degree of caution is required in the interpretation of the results because residual confounding factors not included in the analysis may have influenced the findings, such as significant recipient comorbidity. In the present analysis, some degree of selection bias is likely to have occurred. For example, it is possible that only kidneys from younger previously healthy donors who died following ligature asphyxiation were selected for transplantation, thereby limiting the general applicability of the present findings. If the selection criteria for use of kidneys from potential donors following ligature asphyxiation were to be made less stringent, it cannot be assumed that the clinical outcomes would be equally favourable. Interestingly, the present analysis showed that potential organ donors who died following ligature asphyxiation were more likely to donate one or more kidneys for transplantation than all other potential deceased donors, even after adjustment for key favourable donor factors including

donor age. For those donors who died following ligature asphyxiation who had a cardiac arrest and an estimated ‘downtime’ before restoration of circulation, the data available suggested that this did not influence whether or not a potential donor proceeded to kidney donation. Donors who died following ligature asphyxiation were more likely to proceed to kidney donation if they had a history of imprisonment (7.4% of such donors had a history of imprisonment). This may be because donors who died by hanging whilst incarcerated had a shorter time to resuscitation but this is speculation.

Another potential weakness of the analysis is that donor cause of death from ligature asphyxiation was not one of the 65 reportable causes of death recorded in the transplant registry and so identification of such donors relied on manual review of the free text entries for all deceased organ donors using specific search term variables. It is unlikely that a significant number of donors who died following ligature asphyxiation were not identified, but it is possible that the numbers presented represent an underestimate of potential donors who died following ligature asphyxiation. The dataset used in the present analysis had very little missing data for most of the key variables. However, a further limitation of the analysis is that for some variables missing data may impact on the results and their interpretation. There were very few missing data on graft and patient survival (<0.5% overall and 0% for recipients of kidneys from donors who died from ligature asphyxiation). In the case of 12 month eGFR, data were missing in 17.8% of the entire study cohort, but this was distributed equally between recipients who received kidneys from donors who died following ligature asphyxiation and those who did not, making bias less likely.

Variations in risk appetite between UK kidney transplant centres and their impact on patient and graft outcomes

1.39 Introduction

Over the last 10 years there have been marked changes in deceased donor kidney transplant practice, with an increasing number of deceased donors with co-morbid diseases such as hypertension and diabetes, higher risk scores (as calculated by validated donor risk score indices) and around 30% of the UK deceased donor population are aged greater than 60 years old (30,188).

It has been apparent that there is variation between kidney transplant centres in the UK demonstrated through the wide variations in first offer decline rates and median time on the transplant waiting list (149,189). Hence, it is evident that different centres may be utilising different approaches to the changes in the deceased donor populations. These variations have also been observed in the US, where the impact of variation in centre risk appetite and its impact on liver and kidney transplant survival has been assessed (190,191). The extent to which a transplant centre's risk appetite impacts on patients' outcomes has never been fully assessed in a UK population. To address this, we need to know how we assess risk appetite. Risk is currently assessed through using validated donor risk indices (186,192,193). These risk scores do not encompass all aspects of donor risk, where the use of an organ may not necessarily impact on graft survival but may carry the risk of disease transmission or have a perceived risk of disease transmission (15,145,194,195).

The aims of this analysis were to develop a broader metric of risk, reflecting clinicians' concerns about both donor-related and organ-related risks. Then to use this metric to identify centres that accept kidneys from higher risk donors, and to describe changes in centre risk-taking behaviour over time and then determine if centre 'risk appetite' impacts on clinically relevant graft and patient outcomes.

1.40 Methods

1.40.1 Determining risk attitudes of centres over time

In 2006, a new allocation scheme (NKAS) for DBD kidneys was developed in the UK in order to address inequalities in access to transplantation. This NKAS improved access to transplantation generally however it was accepted that geographical variation and inequality to access would take several years to address (38,196). There are 23 adult kidney transplant centres in the UK, and in order to assess their appetites with regards to risk, ten donor and transplant factors were selected and analysed from 1st January 2006 to 31st December 2015. These factors were selected based on factors known to impact on graft survival but also to reflect putative factors and factors known to impact on offer acceptance. The factors selected were: Donor age ≥70 years, DCD donors, UKKDRI score ≥1.60, presence of donor malignancy (both past and present), increased infectious risk behaviour (IIRB), meningitis and encephalitis (ME) (both known and unknown causes), diabetes mellitus (DM), hypertension, Acute Kidney Injury Network (AKIN) score 2 and 3. A final factor of dual adult kidney transplantation (DAKT) was selected to reflect the surgical/clinical decision that the kidneys from these donors should be implanted as a dual in place of a single kidney. The proportion of renal transplants carried out from donors with these factors or that were implanted as DAKT were determined for all 23 adult kidney transplant centres in the UK over the 10-year study period. For each factor, for the whole 10-year study period, and the two 5-year time periods (2006-2010, 2011-2015), a median and interquartile range (IQR) of the percentage of renal transplants performed at each centre were calculated, and centres were attributed a score from 1 to 4 based on the quartile in which they sat (4 representing highest proportion of use). For example, figure 8.1 demonstrates the total number of deceased donor kidney transplants that were performed by UK renal transplant centres from 2006-2015 from donors with DM, with the median and centre separation shown by the dotted lines.

A single scoring system was developed called Score A. Score A was calculated based on the quartile each centre was in for each factor and these

scores were added to together for all 10 factors giving an overall score (maximum 40, minimum 10). From score A centres were again separated into quartiles around a median score, and analysed as a group (i.e. high risk centres for higher quartiles and low-risk centres for lower quartiles).

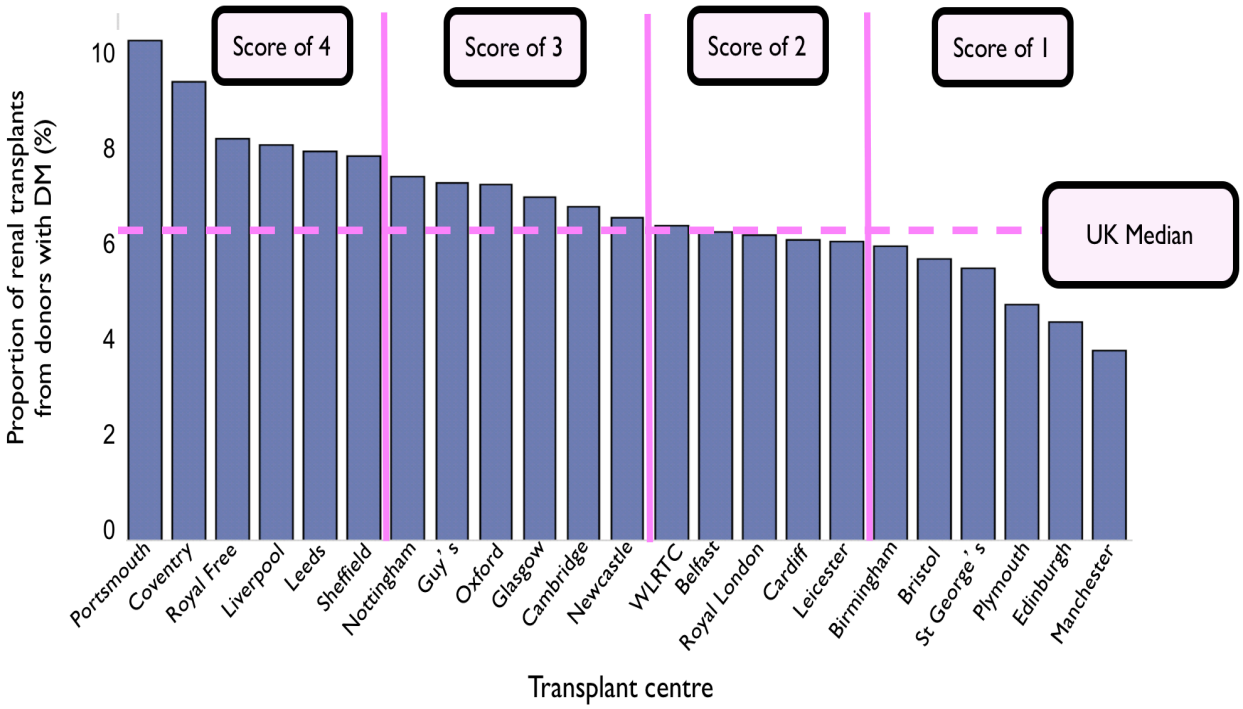


Figure 8.1. Proportion of renal transplants carried out from deceased donors with diabetes mellitus in the UK from January 1st 2000 to 31st December 2015

1.40.2 Identifying deceased kidney donors from the UK transplant registry

The UKTR was used to identify all recipients of kidneys from deceased organ donors from 1st January 2006 to 31st December 2015. Paediatric donors (age<10 years) and paediatric recipients (<18 years) were excluded from the analysis. Information on the donor's past-medical history of hypertension, DM (type 1, type 2 and unspecified), presence of malignancy (both past and present), donor type (DCD and DBD), and donor age were collected. Information on the deceased donors' change in serum creatinine and urine output was collected and used to calculate the donor's acute kidney injury network (AKIN) score as per methods described in Boffa et al (197). The UKKDRI was calculated for the deceased donors (198). Information on patient survival from transplantation and death censored graft survival was collected.

Recipients without graft or patient survival data were excluded from the analysis (n =12 (0. 08%)). Graft function was assessed via eGFR, calculated with 3-month and 12-month recipient serum creatinine by 4 variable MDRD equation (107).

1.40.3 Identifying deceased kidney donors with a history of increased risk behaviour and meningitis/ encephalitis

To identify deceased kidney donors with a reported history of IIRB (defined as: IVDU; imprisonment; donors who were MSM; and those with other high-risk sexual behaviours) and donors who died from ME the UKTR was examined. The free text entries of all identified deceased donors were searched using the terms 'intravenous drug use', 'sex worker', 'Men who have sex with men' and 'prison'. All common abbreviations, misspellings, synonymous terms and colloquialisms of the above search terms were also searched. All UK deceased donors whose cause of death was coded in the UKTR as 'meningitis' were readily identified. However, the designated codes for cause of death in the UKTR are limited to any one of 65 possible causes and there is no code for encephalitis in the registry. Deceased kidney donors who died secondary to ME were also identified through searching of free text entries using the search terms 'meningitis', 'encephalitis', and 'meningoencephalitis' as previously described in chapters 3 and 5.

1.40.4 Determining patient survival from listing

Information on adult patients listed for a kidney only transplant in the UK, who either subsequently received a kidney transplant, were removed from the list or died whilst on the list were collected from 1st January 2006 to 31st December 2015. Patients who were listed for a kidney transplant who received a living kidney transplant were excluded from this analysis.

If a patient was removed from the list with no information on outcome they were censored at time of suspension or removal. Information on patient mortality was collected from the UKTR and the Office of National Statistics to achieve maximum capture of mortality following listing for kidney transplantation.

1.40.5 Imputation

Missing observations were observed in kidney transplant recipient serum creatinine follow-up at 3 and 12 months. The proportion of data missing was 9.8% and 8% for 3-month and 12-month serum creatinine respectively. Multiple imputation based on chained equations was used to impute for missing values in 20 copies of the original first kidney transplant dataset. Linear models were used to estimate for this missing continuous data. Both 3-month and 12-month recipient creatinine were log transformed to account for skewness and to ensure no negative imputed values. Stepwise variable selection process was performed on the imputed datasets and variables selected for inclusion in the final linear regression model had a significance level <0.05. The results of outcomes of the linear regression of the 20 imputed datasets were then combined to account for any variation between the datasets.

1.40.6 Statistical Analysis

Principal univariate analysis was carried out using Student's t-test for parametric continuous data and Wilcoxon sums rank test for non-parametric continuous data. Categorical data was analysed using χ^2 test.

Multivariate analysis was carried out using logistic regression for determining likelihood of receiving a kidney transplant, and Cox proportional hazards regression was carried out to determine the effects of variables on death censored graft survival and patient survival from transplantation and from listing.

Cox proportional hazards regression model, logistic regression model and the linear regression model were fitted in a stepwise selection method to control for potentially confounding factors. Many donor factors known to impact on transplant outcome could not be adjusted for in our multivariate analysis as they were used to determine the risk scores for each centre (e.g. donor age and donor past medical history of hypertension). Hence, donor related variables considered for inclusion not already being adjusted for in our newly developed centre risk score were ethnic group, sex, past medical history liver

disease, cardiac disease, and smoking history. Recipient factors considered for inclusion were age, ethnicity, sex, primary renal disease, HLA mismatch level and cold ischaemic time. Similarly, recipient factors considered for analysis in our survival from listing analysis included the above plus receiving a transplant, time on the waiting list, and ABO blood group. If the factor was significant on step-wise selection method ($p<0.05$) the factor was included in the model.

1.40.7 Results

From 1st January 2006 to 31st December 2015 there were 8,888 deceased donors who donated at least one kidney for transplantation. These donors resulted in 15,024 kidney transplants (single kidneys and DAKT), of which 12,654 were recipients receiving their first kidney transplant.

The clinical characteristics of the deceased kidney donors and the kidney transplant recipients are shown in table 8.1.

	Number of deceased kidney donors (n= 8,888)
Age (y) (median + IQR)	52 (41-62)
Ethnicity	
White/ Other	8035 (93%)/597 (7%)
Donor Type	
DBD/ DCD	5515 (64%)/3117 (36%)
BMI (median + IQR)	26 (23-29)
Past Medical History of Diabetes	
Yes	546 (6%)
No	7854 (92%)
Unknown/ Not stated	114 (1%)
Missing	118 (1%)
Past Medical History of Hypertension	
Yes	2178 (27%)
No	5855 (71%)
Unknown/ Unstated	195 (2%)
Missing	118 (1%)
Past Medical History of Cancer	
Intracranial	148 (2%)
Cancer-not intracranial	178 (2%)
No cancer	8306 (96%)
Known Increased risk behaviour	
Yes/ No	315 (4%)/8317 (96%)
Diagnosis of Meningitis/ Encephalitis	
Known Cause	139 (2%)
Unknown Cause	42 (<0.5%)

Cause of death	
Cerebrovascular accident	2180 (25%)
Intracranial Haemorrhage	4829 (56%)
Trauma	719 (8%)
Other	904 (37%)
CMV status	
Positive	4268 (50%)
Negative	4251 (49%)
Unknown/ Not stated	38 (<0.5%)
Missing	75(<0.5%)
Acute Kidney Injury Network Score	
1	816 (9.2%)
2	461 (5.2%)
3	212 (2.4%)
Missing	591(6.6%)
UKDRI (median + (IQR)	1.06 (0.97-1.48)
KDRI (median + IQR)	1.34 (1.07-1.74)
	Number of deceased donor kidney transplant recipients (n=15024)
Age (y) (median + IQR)	52 (42-62)
Ethnicity	
White	11175 (76%)
Other	3444(24%)
HLA Mismatch level	
1	2028(14%)
2	4484 (31%)
3	7095 (49%)
4	1011(7%)
Crf>85%	1502 (10%)
Double Kidney Transplants (%)	341 (2%)
Cold Ischaemic Time (hours) (median + IQR)	15.0 (12.0- 18.4)
Cold Ischaemic Time DBD	15.3 (12.4-18.8)
Cold Ischaemic Time DCD	14.3 (11.3-17.8)
BMI (median + IQR)	26 (23-29.5)
Primary Renal Disease	
Glomerulonephritis	2604 (18%)
Diabetic Nephropathy	1217 (8%)
Polycystic Kidney Disease	1868 (13%)
Pyelonephritis	1111 (8%)
Other	7819 (53%)

Table 8.1. Clinical characteristics of Adult Deceased Organ Donors and their recipients in the UK from January 1st 2006 to December 31st 2015

Overall, there was a proportional increase in the number of deceased donor kidney transplants being performed from donors with risk attributes, however variation over time was noted (Figure 8.2a-8.2j).

Over the 10-year period there were marked changes in individual centre deceased donor kidney transplant practice (Figure 8.3a). Overall, there was a trend towards an increasing proportion of renal transplants being performed from donors with the selected risk attributes (Figure 8.3a-8.3i). However, when each risk attribute was assessed over the 5-year time periods some centres appeared to reduce their risk appetite for selected factors. As an example, Guy's and St Thomas' hospital, in the first 5-year time-period was in either the second lowest or lowest risk quartile for all 10 donor risk attributes, but in the later 5-year time-period they had dramatically changed practice and are now in the highest risk quartiles for over half of the selected risk attributes (Figure 8.4a, 8.4b, 8.4c).

From the information generated, risk score A was calculated (Table 8.2). From these scores, the UK median Risk Score A was calculated (median 25 (IQR 20-32). Centres were then separated into their respective quartiles and analysed as a group based on these quartiles.

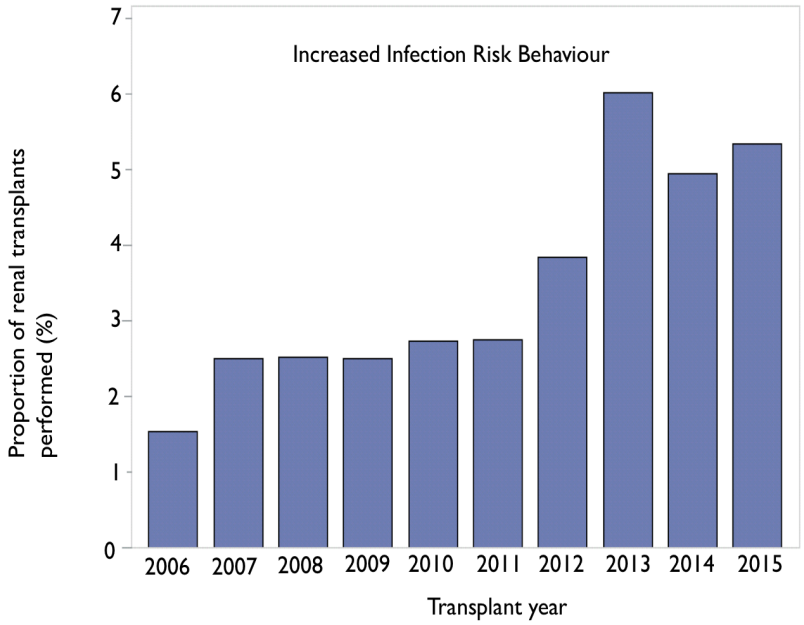


Figure 8.2a. Proportion of adult renal transplants carried out from deceased donors with increased infection risk behaviour from 1st January 2006 to 31st December 2015.

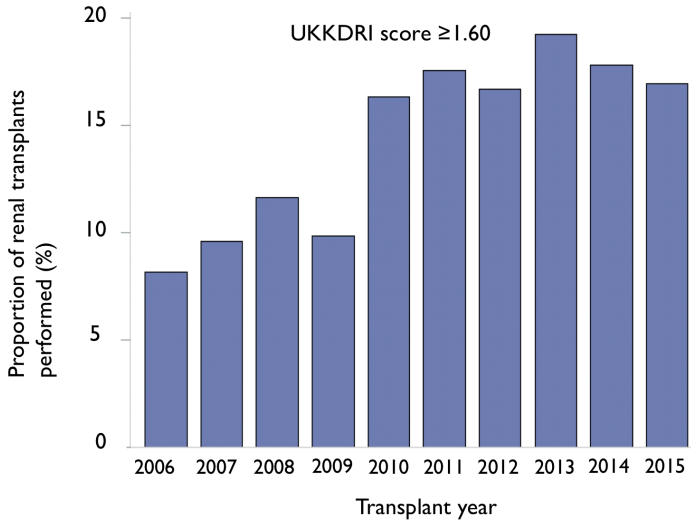


Figure 8.2b. Proportion of adult renal transplants carried out from deceased donors with a UKKDRI score ≥1.60 behaviour from 1st January 2006 to 31st December 2015.

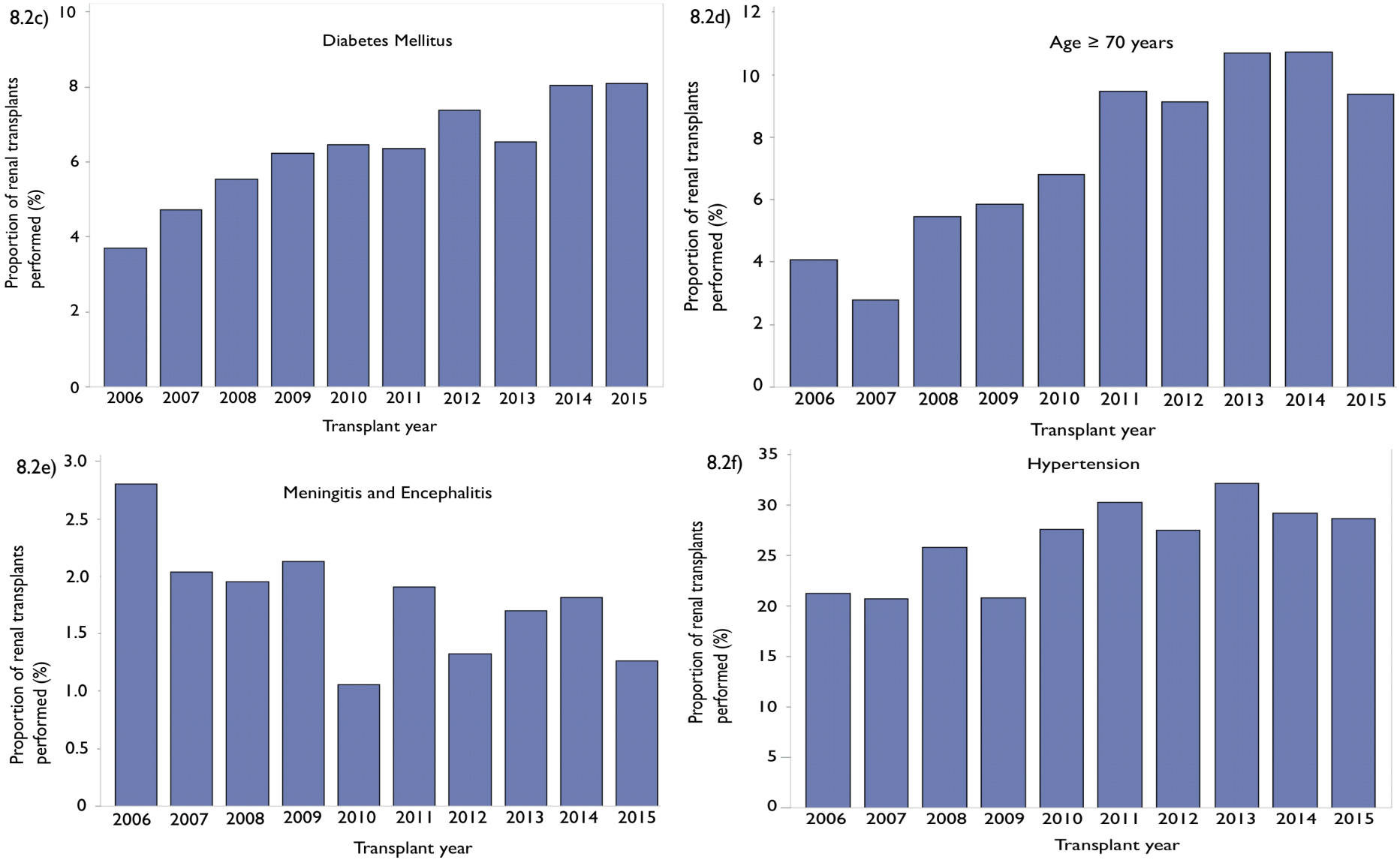


Figure 8.2c-8.2f. Proportion of adult renal transplants carried out from deceased donors with Diabetes Mellitus, 8.2d) Age ≥70, 8.2e)Meningitis/encephalitis, 8.2f)hypertension from 1st January 2006 to 31st December 2015.

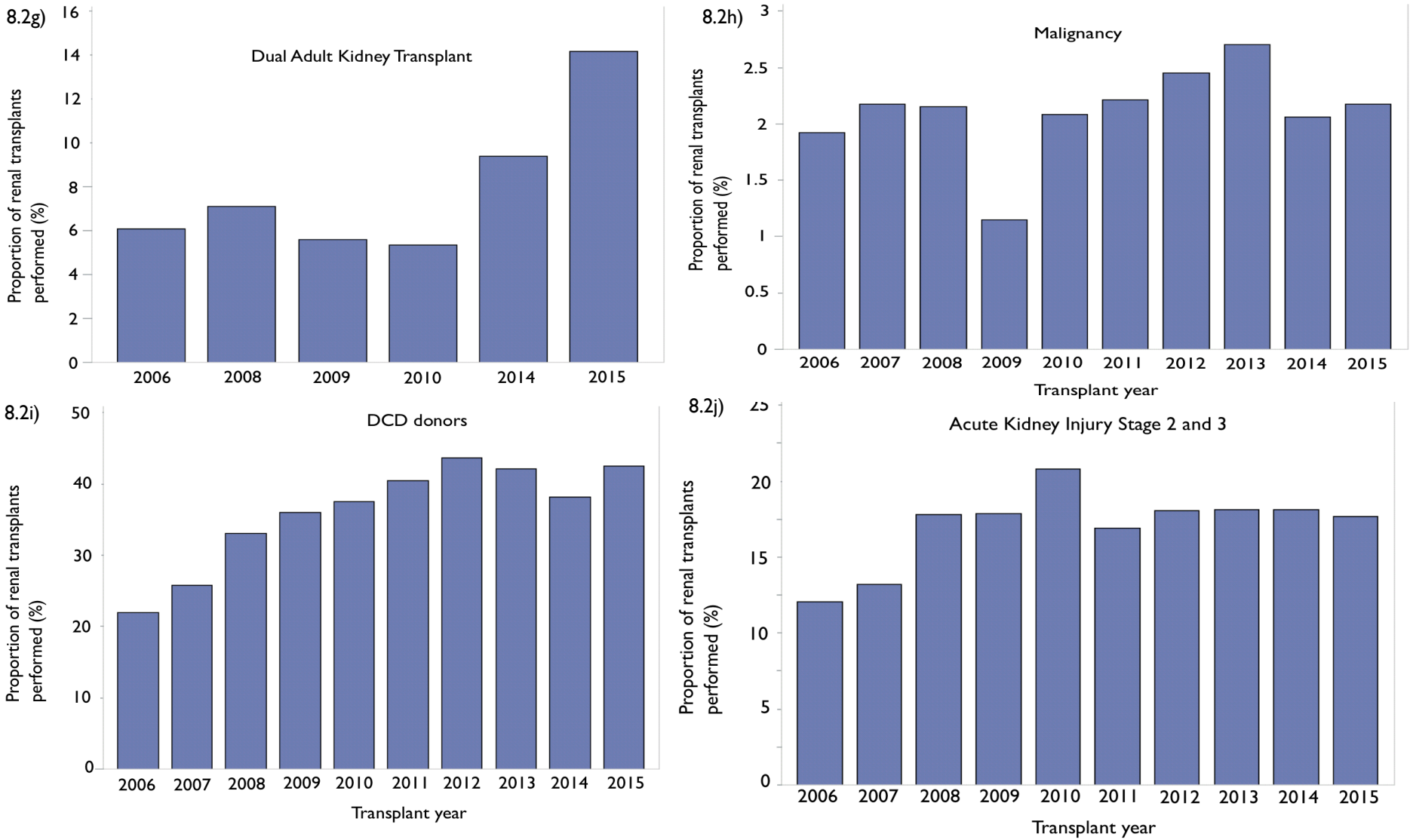


Figure 8.2g-8.2j) Proportion of adult renal transplants carried out from deceased donors that were 8.2g) DAKT, from donors with a 8.2h) Malignancy, 8.2i) DCD donors, and donors with 8.2j) AKIN stage 2 and 3 from 1st January 2006 to 31st December 2015

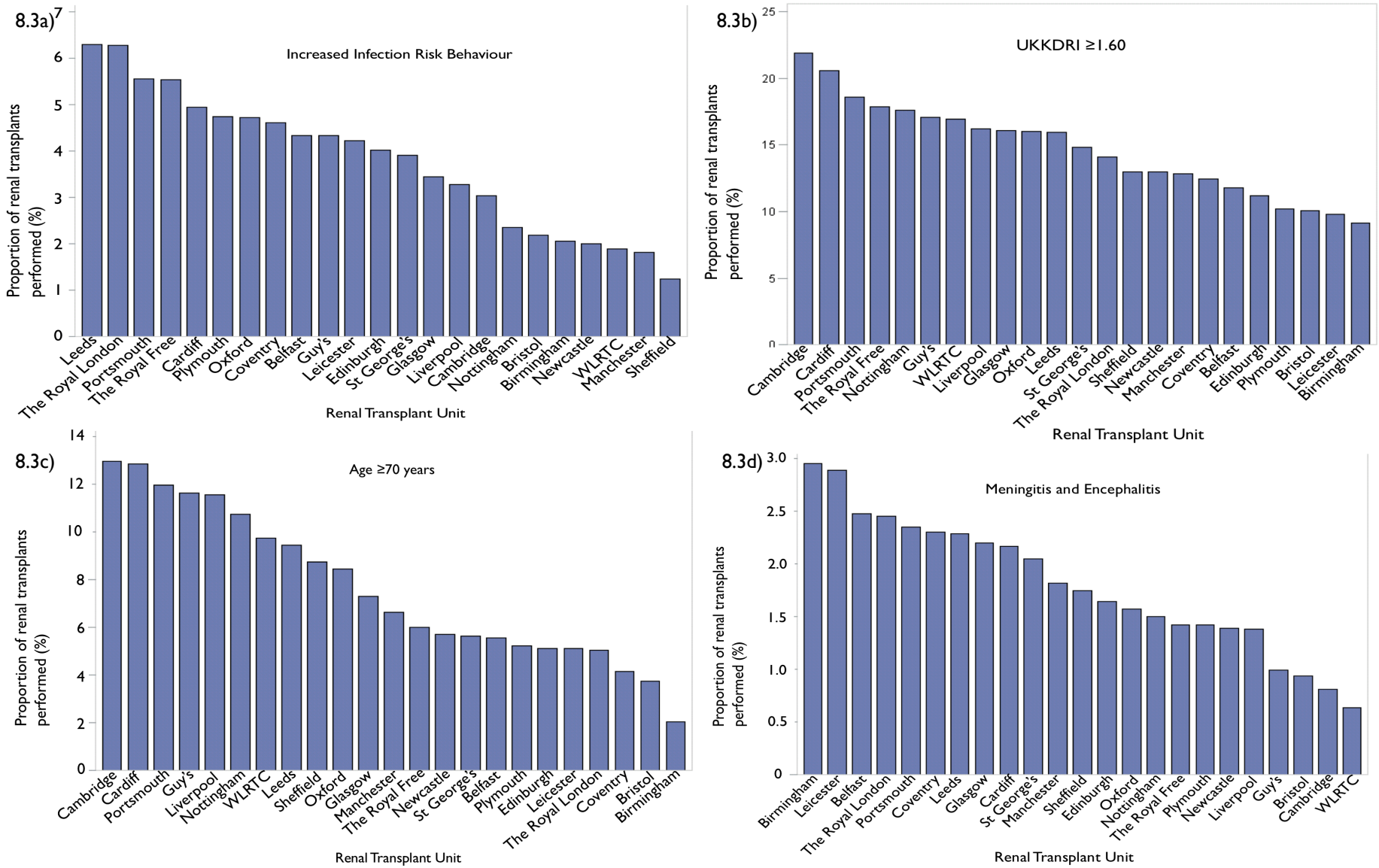


Figure 8.3a-8.3d. Proportion renal transplants carried out from deceased organ donors with IIRB, 8.3b) UKKDRI ≥1.60 , 8.3c) Age ≥70, 8.3d) ME in the UK by transplant centre from 01/01/2006 to 31/12/2015

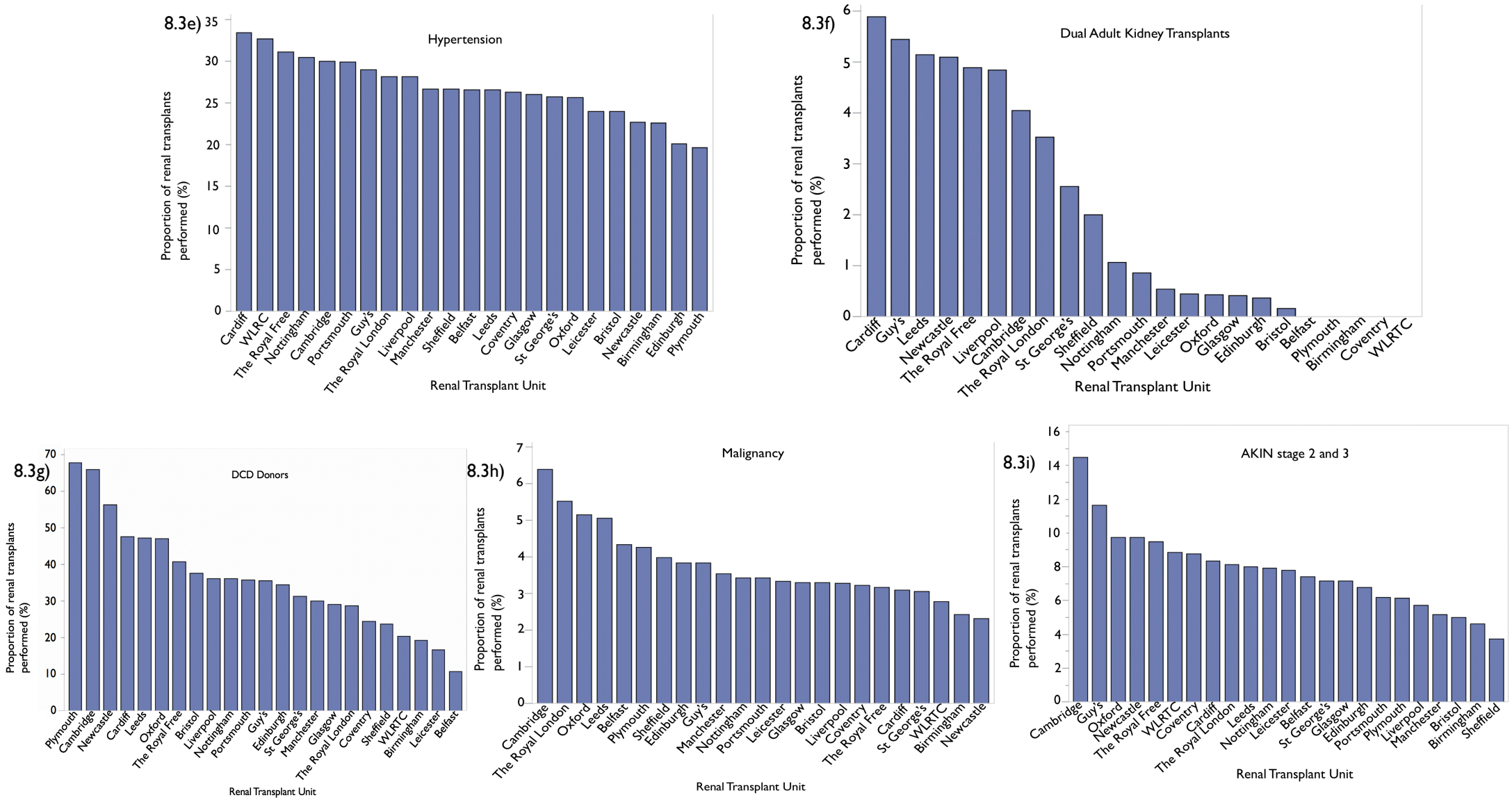


Figure 8.3e-8.3i. Proportion renal transplants carried out from deceased organ donors with hypertension, 8.3f) that were DAKT, 8.3g) who were DCD donors, 8.3h) with malignancy, 8.3i) AKIN stage 2 and 3 UK by transplant centre from 01/01/2006 to 31/12/2015

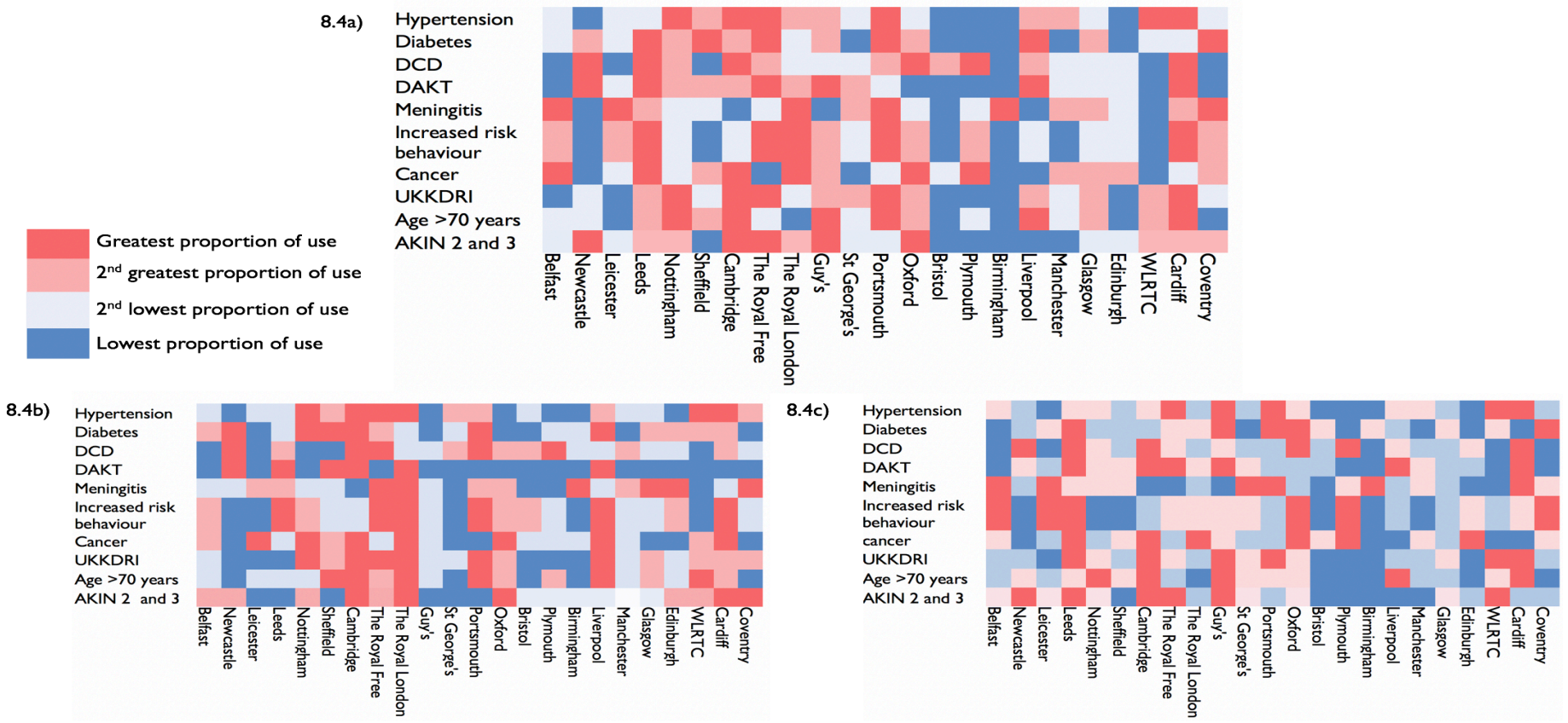


Figure 8.4a-c. Heat map of UK Renal transplant units by the quartile of the proportion of deceased donor renal transplants carried out from donors with risk behaviours or attributes from A)1st January 2006 to 31st December 2015, B) 1st January 2006 to 31st December 2010, and C) 1st January 2011 to 31st December 2015.

Renal transplant centre	Risk score A
Cardiff	34
Leeds	34
Portsmouth	33
Cambridge	33
Royal Free	32
Guy's	30
Nottingham	30
Oxford	29
Royal London	28
Liverpool	26
Glasgow	25
Coventry	24
Sheffield	23
Newcastle	23
Belfast	22
Plymouth	21
St George's	21
Manchester	20
Leicester	20
WLRTC	20
Edinburgh	17
Birmingham	13
Bristol	13

Table 8.2. UK adult renal transplant centre risk score A

1.40.8 Impact of centre risk appetite on transplant outcome

In order to establish what effect centre risk appetite was having on transplant outcomes, the risk scores were used to stratify first kidney transplant death censored graft survival for the whole-time period and the two 5-year time periods for the 12654 recipients of a first kidney only transplant. Analysis of the two 5-year time periods indicated that there was no significant difference in 5-year death graft survival between those recipients transplanted in the first-time period compared to the second (88.4% graft survival (95% CI 87.5-89.3%) vs. 86.9% graft survival (95% CI 85.5-88.1%) respectively, p =0.330).

Each transplant centre was analysed depending on the quartile of risk score A that they were in. This demonstrated that there was no significant difference

over the 10-year study period in death censored graft survival based on centre risk score (Figure 8.5). Following adjustment for recipient age, CIT, primary renal disease, HLA-mismatch level and year of transplant, centre risk score A was not an independent predictor of death censored graft survival (Table 8.3). Three month and 12-month eGFR was noted to be marginally poorer at centres with higher risk scores following adjustment for CIT, HLA mismatch level, recipient age, donor and recipient ethnicity and primary renal disease (Table 8.3).

DGF rates were noted to be higher at centres with higher risk scores before and after adjustment for recipient factors (Table 8.3).

Patient survival from transplantation was assessed and demonstrated no significant difference in outcome based on centre risk score (p= 0.301) (Figure 8.6) Following adjustment for recipient age, CIT, primary renal disease, HLA mismatch level, and year of transplant, it demonstrated that patient survival from transplantation was significantly worse if you received a kidney transplant at centres in the 3rd highest risk score group (1.188 (1.050-1.345), p=0.006). The exact explanation for this could not be elicited, and investigation of individual centres within this cohort did not demonstrate significantly worse outcomes at these centres.

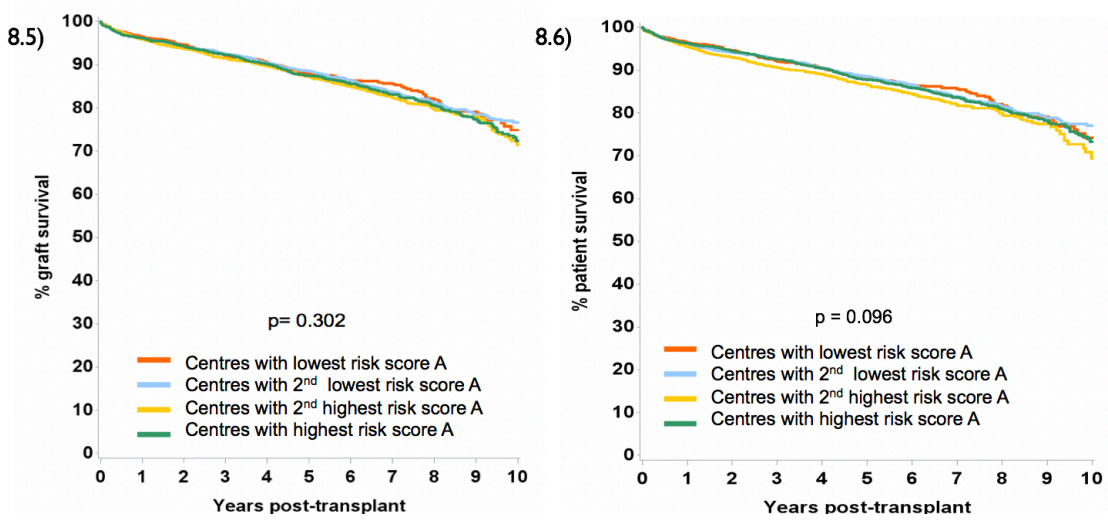


Figure 8.5 and 8.6. 10-year death censored first kidney transplant graft survival and patient survival from transplantation by centre risk appetite score A. P-value corresponds to score test of the overall null hypothesis that there are no differences in survival curves for all groups i.e. comparing survival across all groups

		Unadjusted ratio (95% CI)	Unadjusted p-value	Adjusted ratio (95% CI)	Adjusted p-value
10-year death censored graft survival$^{\delta}$	**Cohort size (n=12654)**				
	Risk score group 1 vs 2	HR 1.037 (0. 882-1.219)	0.662	1.080 (0.917-1.271	0.3030
	Risk score group 3 vs 2	HR 0.983 (0.860-1.124)	0.806	1.010 (0.881-1.157)	0.3576
	Risk score group 4 vs 2	HR 0.980 (0.858-1.119)	0.858	0.966 (0.842-1.107_	0.8439
Delayed Graft Function (DGF)*	**Cohort size (n=12654)**				
	Risk score group 1 vs 2	OR 0.678 (0.586-0.785)	<0.001	0.692 (0.597-0.803)	<0.001
	Risk score group 3 vs 2	OR 1.339 (1.207-1.486)	<0.001	1.350 (1.215-1.501)	<0.001
	Risk score group 4 vs 2	OR 1.784 (1.611-1.975)	<0.001	1.682 (1.514-1.867)	<0.001
10-year patient survival from transplantation$^{\delta}$	**Cohort size (n=15024)**				
	Risk score group 1 vs 2	HR 0.985 (0.845-1.150)	0.853	1.123 (0.961-1.312)	0.146
	Risk score group 3 vs 2	HR 1.108 (0.981-1.251)	0.0981	1.188 (1.050-1.345)	0.006
	Risk score group 4 vs 2	HR 1.063 (0.941-1.201)	0.325	1.017 (0.897-1.153)	0.794
3 month eGFR (mls/minutes per 1.73m^2)$^{\gamma}$	**Cohort size (n= 12654)**				
	Risk score group 1 vs. 2	PE 0.046 (0.019- 0.072)	0.001	PE 0.032 (0.007 - 0.058)	0.012
	Risk score group 3 vs 2	PE -0.028 (-0.051--0.006)	0.015	PE -0.039 (-0.061--0.017)	0.001
	Risk score group 4 vs 2	PE -0.050 (-0.069--0.031)	<0.001	PE -0.045 (-0.065--0.026)	<0.001
12 month eGFR (mls/minutes per 1.73m^2) $^{\gamma}$	**Cohort size (n=12654)**				
	Risk score group 1 vs 2	PE-0.003 (- 0.028-0.022)	0.798	PE -0.015 (-0.040-0.009)	0.2117
	Risk score group 3 vs 2	PE -0.03 (-0.054--0.009)	0.005	PE -0.041 (-0.063--0.019)	<0.001
	Risk score group 4 vs 2	PE -0.047 (-0.065--0.028)	<0.001	PE -0.041 (-0.05- -0.023)	<0.001

Table 8.3. Comparison of transplant outcomes by centre risk appetite score

1.40.9 Likelihood of receiving a kidney transplant

Information on the 22,801 people who were listed for a kidney transplant from 1st January 2006 to 31st December 2015 was collected and analysed in order to determine the impact that centre risk appetite had on the likelihood of patients listed at these centres of receiving a kidney transplant. Logistic regression analysis demonstrated, in comparison to risk score quartile 2, that centres with risk scores in the 1st quartile were significantly less likely to receive a kidney transplant (OR 0.920 (95% CI 0.849-0.998 p<0.001), and centres with risk scores in quartile 3 and 4 were significantly more likely to receive a kidney transplant (OR 1.367 (95% CI 1.266-1.476), p<0.001 and OR1.578 (95% CI 1.478-1.684), p<0.001 respectively). Following adjustment for recipient blood group, recipient ethnicity, primary renal disease at time of listing, recipient age of registration, centre risk score remained an independent predictor of receiving a kidney transplant (Table 8.4).

Cohort size (n=22801)	Unadjusted ratio (95% confidence interval)	Unadjusted p-value	Adjusted ratio (95% confidence intervals)	Adjusted p-value
Risk score group 1 vs 2	0.920 (0.849- 0.998)	<0.001	0.811 (0.745-0.884)	<0.001
Risk score group 3 vs 2	1.367 (1.266-1.476)	<0.001	1.310 (1.204-1.414)	<0.001
Risk score group 4 vs 2	1.578 (1.478-1.684)	<0.001	1.532 (1.430-1.641)	<0.001

Table 8.4. Logistic regression analysis of patients listed for a kidney only transplant in the UK's likelihood of receiving a kidney transplant following adjustment for recipient factors

As expected, analysis demonstrated that patients listed for a kidney transplant at lower risk score centres spent significantly longer on the transplant waiting list compared to those listed at centres with higher risk scores. Patients listed

for a kidney transplant at lowest risk scored centres 1 and 2 spend significantly longer on the kidney transplant waiting list compared those listed for a kidney transplant at risk score centres in 3 or 4 (risk score A quartile 1 (median 786 days (IQR 410-1232), risk score A quartile 2 (median 662 days (IQR 335-1077), risk score quartile 3 (median 627 (IQR 307-1027), and risk score quartile 4 (median 560 (IQR 261-932), p<0.0001).

1.40.10 Patient survival from listing

To determine the impact that a centre's risk appetite has on a patient's survival following listing for a renal only transplant, information on mortality of all patients listed for a kidney only transplant in the UK was analysed. This demonstrated that patients listed for a kidney transplant at centres with a lower risk score had similar patient survival from listing compared to those listed at centres with higher risk scores (Figure 8.7). Following adjustment for time on the waiting list, recipient age, recipient blood group, primary renal disease, and centre risk score, a centres risk appetite was not an independent predictor of patient survival from listing (Table 8.5).

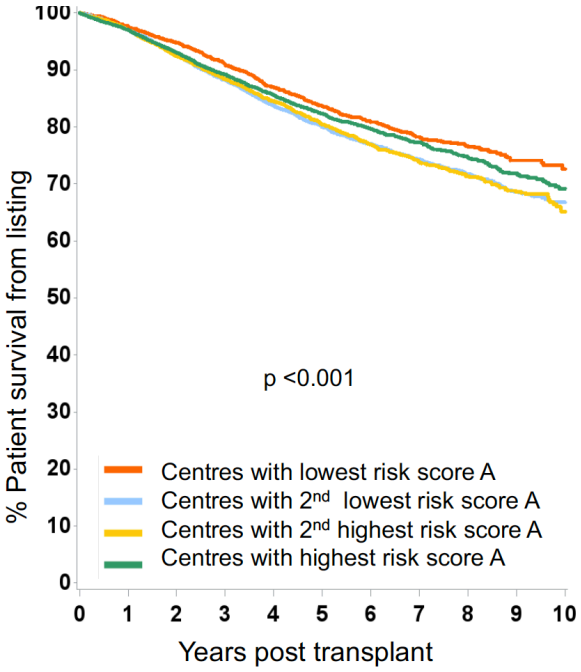


Figure 8.7. 10-year patient survival from listing by centre risk score A. P-value corresponds to score test of the overall null hypothesis that there are no differences in survival curves for all groups i.e. comparing survival across all groups

Cohort size (n=22801)	Unadjusted ratio (95% confidence interval)	Unadjusted p-value	Adjusted ratio (95% confidence intervals)	Adjusted p-value
Risk score group 1 vs 2	0.788 (0.712- 0.873)	<0.001	0.913 (0.824- 1.011)	0.808
Risk score group 3 vs 2	0.997 (0.916- 1.086)	0.952	1.075 (0.987- 1.171)	0.098
Risk score group 4 vs 2	0.894 (0.828- 0.965)	0.004	1.011 (0.937-1.092)	0.772

Table 8.5. Unadjusted and adjusted 10 year patient survival from listing based on centre risk score A quartile

1.41 Discussion

This chapter has described the changing nature of deceased donor kidney transplant practice in the UK over the last 10 years and has described the impact that these changes have had on transplant outcome for recipients across the UK. Firstly, it has importantly demonstrated that despite the increasing use of kidneys from more marginal donors, with factors that are known to negatively impact transplant outcome, kidney recipient graft and patient survival has remained good (30,188). This suggests that educated approaches to using kidneys from donors with risk factors, and careful recipient selection and management allow for successful transplantation of seemingly marginal organs. Secondly, it has also demonstrated that there is marked variation between UK adult kidney transplant centres with regards to their risk appetite for donor and organ related factors. Despite this variation, centres with greater appetites for risk have comparable transplant outcomes, and result in quicker transplantation for patients listed at those centres.

Over the last 10 years there have been marked changes in the clinical characteristics of deceased kidney donors in the UK. Firstly, we have seen a marked increase over time in the number of deceased kidney donors who are DCD donors, have a past medical history of hypertension, diabetes, or a

reported history of IIRB (15,149). These changes in transplant practice have resulted in wide variations in the proportion of organs used from these donors between centres. Variations in risk appetite have anecdotally been apparent in UK kidney transplant practice, as demonstrated in the variations in time spent on the waiting list between centres (188,189) However, it remained to be seen whether or not avoiding donor risk factors and accepting only the highest quality organs was the optimum strategy for your patients. This analysis has demonstrated that there may be benefits in adopting a pro-risk strategy, but that the benefits of this strategy may be influenced by individual centre characteristics which we are unable to fully comment on. This analysis has demonstrated that centres with higher risk appetites had similar risk adjusted 10-year death censored graft survival and patient survival from transplantation and had clinically similar 3-month and 12 month eGFR post kidney transplantation, despite these centres using organs from donors with characteristics that are known to negatively impact on graft function following transplantation.

An important outcome measure in transplantation is patient survival from listing, as this allows us to reflect not only on the survival of patients following transplantation, but that of all of those who need a kidney transplant. The analysis in this paper demonstrated that centres using higher risk strategies had similar patient survival from listing to those centres using lower-risk strategies. The analysis also importantly demonstrated that patients listed at higher risk centres were more likely to receive a kidney transplant and spend significantly less time on the transplant waiting list. Hence, variations in centre risk appetite are impacting on a patient's likelihood of receiving a kidney transplant, and therefore importantly the patients time spend on renal replacement therapy. Research has demonstrated the quality of life benefit, along with health economic benefit of kidney transplantation over renal replacement therapy in patients with end stage renal failure (199)(200,201).

This current research has limitations. Firstly, we are unable to comment on specific changes made at each centre over this study period. These specific changes, potentially in staffing or management, may elucidate further the variation we are observing the deceased donor kidney transplant practice

between centres. Secondly, there are many aspects of transplant practice not accurately captured in a registry analysis which again may explain the variations in transplant outcomes observed in this analysis.

Development of the UK aide memoire

1.42 Background

The decision to use an organ from a donor with a transmissible or potential transmissible infection, as described before, can be incredibly complex. The previous chapters of this thesis have demonstrated not only the complexities in accepting organs from donors with risk attributes and the potential dangers involved in this, but also that marked variations exist in this practice across the different UK transplant centres. The reasons why accepting an organ from a 'higher risk' donor can be difficult is that offers of organs from such donors may occur out of normal working hours, and given the scarcity of some of the donor attributes (e.g. ITP (0.7%) of the total donor population) no one accepting clinician or centre will have enough experience to confidently decide one way or another. The current SaBTO guidance published in 2018, is very thorough and contains guidance on several transmissible microbiological diseases. However, reading and interpreting this document can be difficult, and as the prior analysis has shown results in marked variations in decision making across the UK. In response to this and to summarise some of the main findings from this body of work the UK aide memoire was developed. The aide memoire aims to assist clinician decision making. The aide memoire summarises guidance on the use of organs from donors with infection, malignancy, autoimmune conditions and other donor attributes believed to confer risk to the recipients into a single easy to use online tool.

1.43 Aim

Produce a simple guide for clinicians to encourage appropriate matching of a donor organ to recipient, increase transplant rates with consequent benefit to recipients and donor families as well as reassure clinicians that they are working within national guidance.

1.44 Methods

1.44.1 Content

All available guidance from NHSBT, SaBTO and BTS on the use of organs from donors with infection (bacterial, viral, fungal, etc), malignancy, autoimmune disease/metabolic disease and donor risk attributes, such as cause of death or increased risk behaviour prior to donation were collated. Where guidance was not in place in the UK but present in Europe or the United States their guidance was used as a reference.

Original research articles assessing the risk of disease transmission from donors with meningitis/encephalitis, increased risk behaviour, immune thrombocytopaenia and donor death secondary to ligature asphyxiation were used to inform guidance on these conditions.

The document of collated guidance was then circulated round the chairs of the advisory committee, medical team at ODT and NHSBT Consultant Virologist and Microbiologist (figure 9.1).

1.44.2 Matching organ to recipient

In order to ensure that appropriate risks are being taken in the use of organs from donors with potential transmissible diseases, or conditions that will adversely impact organ quality, the aide memoire sought to classify organ transplant recipients into categories that reflected their overall risk of morbidity and mortality from not receiving a transplant. The categories were as follows:

- **Exceptional** - implies death without a transplant in 7 days;
- **Urgent** - implies death without a transplant within 1month. Examples include renal candidate with very limited vascular access; Patient with primary liver cell cancer approaching exclusion criteria; hepatic artery thrombosis with intra-hepatic sepsis; a highly sensitised kidney candidate; a long waiting heart or lung candidate with the option of a well-matched donor organ or a candidate under major psychological stress awaiting a graft.
- **Routine** implied all other candidates.

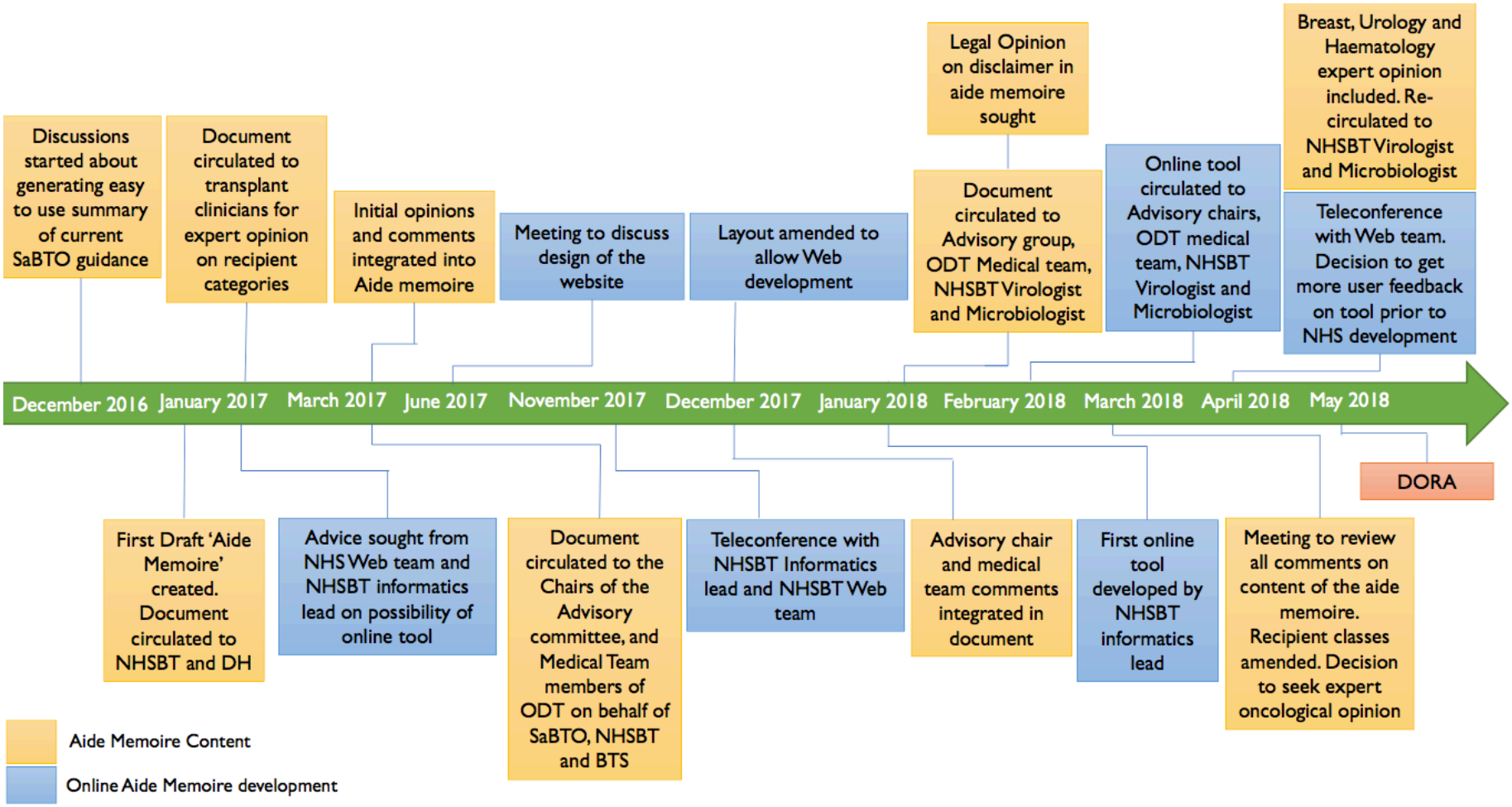


Figure 9.1. Timeline of development of the aide memoire

Each class of recipient for each donor disease/attribute was then attributed a symbol based on whether the organ should be used for transplantation for this recipient. The first, indicated the organ should not be used at all for transplantation. The second indicates that the transplanting clinician should think about using this organ for this recipient, and the final symbol indicates that in most situations this organ should be used for transplantation for this recipient.

The document was then separated into sections based on the broad groups of donor diseases/attributes. The sections are:
Infection:

- Viral infections
- Bacterial infections
- Protozoal infections
- Mycobacterium
- Fungi
- Other infectious agents
- Neurological conditions including Meningitis, Encephalitis and Meningoencephalitis.
- Malignancy
- Increased risk behaviours
- Autoimmune diseases
- Metabolic diseases.

1.44.3 NHS Online tool development:

- Work with NHS Web development team and NHSBT Clinical Informatics Lead
- Prototype online tool developed: http://www.txtools.net/sabto/.
- User feedback required by NHSBT Web team before they will start work on the tool (Figure 9.1).

1.45 Discussion

The development of a UK aide memoire will help streamline decision making in organ transplantation and will allow for greater use of organs from donors with risk attributes that currently are unnecessarily discarded. The aide

memoire will also help prevent the transmission of diseases that may result in significant patient morbidity or even mortality. This aide memoire is the first of its kind in transplantation in the UK.

The creation of this aide memoire will also allow NHSBT to audit the use of organs from donors with risk attributes covered by the aide memoire and see whether any improvements/changes have been made in response to its publication.

The aide memoire will also have a feature allowing transplant clinicians across the UK to report donor diseases/conditions that there is currently no guidance for, alerting NHSBT to the need to carry out research into these conditions and asses their safety in organ donation and transplantation.

A major limitation of this piece of work is the large number of diseases / conditions identified in the deceased donor population; in particular donor malignancies currently have little evidence as to whether a clinician should accept organs from such donors for transplantation. In these situations, guidance already in place in the EU and US have been used in conjunction with the UK guidance to create what is seen in the aide memoire. Expert clinical opinion was also sought, but it is clear that further research into the safety of different donor malignancies at different disease stages is required.

Conclusions

The research described in this thesis has explored the risks involved in using organs from donors dying with potentially transmissible diseases and with different risk profiles. It has demonstrated that organ donors who die from meningitis and encephalitis represent a relatively small but important cohort of donor organs. In donors where the causative agent of meningitis is known to be bacterial, the risk of disease transmission is very low, although it is important to ensure that recipients of organs from such donors receive appropriate prophylactic anti-microbial therapy. For organs where the causative agent is not known, the risk of disease transmission is greater, and more caution should be exercised in the use of such organs, as highlighted in various clinical guidelines. The risk of potentially fatal disease transmission should be balanced against the clinical benefit of an organ transplant and the present analysis provides national data that may help guide this decision.

It has also been demonstrated, that although the exact mechanism of Transplant Mediated Alloimmune Thrombocytopaenia (TMAT) is not fully understood, there is no evidence from UK experience of using kidneys, pancreata and hearts from donors with ITP to suggest it is unsafe. There is a small risk of TMAT following liver transplantation and this thesis has demonstrated inferior recipient survival following liver transplantation from donors with ITP. Transplant teams will have to consider the severity of liver disease and health of a potential recipient when balancing the risk of accepting the liver of a donor with ITP against the risk of further delay in transplantation. The risk might be lessened if the liver is biopsied before implantation and shown not to contain evidence of extramedullary haematopoiesis

Around 4% of UK deceased donors have an identifiable history of behaviour associated with an increased risk of blood borne transmissible viral infection, but are seronegative at time of donation. Three quarters of such donors provide organs for transplantation with good transplant outcomes, and apparently low risk of disease transmission. Recent advances in the treatment

of viral disease, particularly HCV, further reduce the risks associated with disease transmission. Donors with a history of IRB provide a valuable source of organs for transplantation with good transplant outcomes and there is scope for increasing the use of organs from donors with IRB, in particular for donors with a history of IVDU.

The use of DAA raises the possibility that organs from HCVpos donors can be used with safety in HCVneg recipients. It is important to emphasise that experience of this practice is still limited and while it appears safe and effective some recipients may suffer adverse effects from antiviral therapy and it cannot be assumed that anti-viral treatment will invariably be effective. Nevertheless, as the present analysis demonstrates, the use of organs from donors with HCV offers considerable scope for increasing the number of organ transplants performed. Should such an approach be adopted, it is of course essential that the recipients gave fully informed consent prior to transplantation.

The findings from this thesis also show that use of kidneys from both DBD and DCD donors who died following ligature asphyxiation results in excellent transplant outcomes. In view of this, increasing consideration should be given to the use of kidneys from potential donors who die following ligature asphyxiation and whose kidneys are currently declined for transplantation. To inform the increased use of such kidneys, the concept of total global tissue hypoxia from initiation of ligature asphyxiation to cold perfusion of the kidney with preservation solution may be helpful. Global hypoxia begins shortly after hanging is initiated and extends until discovery and initiation of resuscitation: its duration is highly variable and in many cases unknown. In most patients in the present cohort, this was followed by a period of “downtime” extending from discovery of a patient with no cardiac output until cardiac output is successfully re-established and the patient transferred to a critical care unit. Currently a minority of patients have recorded “downtimes” and there is a need for improved documentation. These two periods of global tissue hypoxia are, in the case of DCD donors, followed by a third period of tissue hypoxia from the time of withdrawal of life supporting treatment to cold perfusion of the kidneys, the duration of which is usually well documented. Although making

an assessment of the total duration of global tissue hypoxia is often problematic, incorporating this concept into decision making on the use of kidneys from donors who die following ligature asphyxiation may provide a basis for the safe utilisation of kidney from selected donors currently being declined for transplantation

Continuing to research the proportion of the donor population and the corresponding transplant recipient outcomes of organ donors with ‘risk’ attributes will help to inform the transplant community of the risks of using organs from such donors. This research will also aim to increase the number of organs used from such donors and hence substantially increase the number of transplants in the UK.

This thesis has also described the changes that have taken place in deceased donor kidney transplant practice in the UK over the last 10-years. It has shown that there is marked centre variation in risk appetite, with significant changes over time observed in some centres. Centres with higher risk appetites had shorter waiting times, were more likely to transplant their patients and there was no difference in death censored graft survival or patient survival compared to centres with lower risk appetites. This suggests that higher risk strategies may be of benefit to patients, and that centres with higher risk appetites may have attributes that enable their outcomes to be better than expected.

The aide memoire developed during my PhD will help aide decision making in organ transplantation, and potentially increase organ utilisation in the UK.

Overall, the work from my thesis has helped to inform policy on the use of organs from donors with risk attributes, in particular infections. The work on risk variation will allow UK transplant centres to audit their own practice and increase the use of organs from donors with risk attributes safely.

Future work

As mentioned in Chapter 1, the role of infectious diseases in transplantation is constantly changing. One area of particular importance to transplantation is the rise in multi-drug resistant organisms (MDRO). The increasing incidence of MDRO is a growing threat to public health (202-204). The frequency of antibiotic resistance to bacterial organisms results in over a hundred thousand deaths worldwide every year (202-204). Without effective antimicrobials for the effective treatment or prevention of infection, organ transplantation will become very high risk (202-204). The hope of mitigating this problem with the development of new antibiotics has been hindered by the low rate of antibiotic development and the likelihood that the pathogen will evolve to become resistant to this new antimicrobial (203,205). Hence, there is a pressing need to determine the scope of the problem and develop an effective response to antimicrobial resistance (AMR). Increasing numbers of cases of MDRO are being reported in solid organ transplant recipients, and one of the most common reported post-transplant infections is urinary tract infection (UTI) (205). An increasing number of studies are reporting a large incidence of UTI in renal transplant patients that are secondary to MDRO, in particular extended spectrum beta-lactamases (ESBL), and the other emerging MDRO are often gram negative organisms which are known to readily colonise the urinary tract (207-209). Transplant recipients receive multiple antimicrobials following transplantation but it is unknown what effect this antimicrobial prophylaxis has on the development of MDRO in organ transplant recipients and what impact this has on the transplant recipient's microbiome, which is known to interact in a dynamic way the host immune system and may help contribute to infective and immunological sequelae in the recipient (210). There is also increasing evidence that dysbiosis can contribute to diseases outside the GI tract, including cardiovascular disease and malignancy, two major causes of death of renal transplant recipients with a functioning graft (188,211). There is now also evidence that changes in the microbiome can also influence susceptibility to organ rejection (212). The transmission of a

MDRO from deceased organ donors to transplant recipients is thought to be a rare, but serious consequence of transplantation (59,60).

Currently, there has been no description of the incidence of MDRO isolates in UK deceased organ donors and what impact these isolates have to transplant recipients.

Another project investigating the role of donor disease transmission would be the effect of EBV transmission from organ donor to transplant recipient. EBV infection is associated with the development of PTLD (68-70). PTLD is associated with significant morbidity, graft dysfunction and mortality. The incidence, risk factors and natural history of PTLD in the UK population of solid organ allograft recipients is poorly understood. Routine matching of donor and recipient for EBV is not routinely done in the UK, or elsewhere (68-70). An improved understanding of the factors responsible for the development of PTLD and their association with EBV is essential for not only for identifying those transplant recipients who are at increased risk for the development of PTLD but will also allow the development of effective and cost-effective surveillance and interventions and will also ensure the transplant recipient gives adequately informed consent (68-70).

References

1. NHS Blood and Transplant. Introduction to Patient Selection and Organ Allocation Policies. 2015 Dec 16;1–22. Available from: http://odt.nhs.uk/pdf/introduction_to_selection_and_allocation_policies.pdf.

2. NHS Blood and Transplant. Organ Donation and Transplantation-Annual activity report 2013-2014. Available from: https://nhsbtmediaservices.blob.core.windows.net/organ-donation-assets/pdfs/activity_report_2013_14.pdf.

3. NHS Blood and Transplant. Organ Donation and Transplantation-Annual activity report 2017-18. Jan 6;1–174. Available from: https://nhsbtdbe.blob.core.windows.net/umbraco-assets/1848/transplant-activity-report-2017-2018.pdf

4. Tullius SG, Rabb H. Improving the Supply and Quality of Deceased-Donor Organs for Transplantation. Ingelfinger JR, editor. New England Journal of Medicine. 2018 May 17;378(20):1920–9.

5. Organ Procurement and Transplantation Network. OPTN/ SRTR 2015 Annual Data Report: Introduction. 2015 Jun 25;1–11.

6. Foley RN, Parfrey PS, Sarnak MJ. Clinical epidemiology of cardiovascular disease in chronic renal disease. American Journal of Kidney Diseases. 1998 Nov;32(3):S112–9.

7. Foley RN, Parfrey PS, Sarnak MJ. Epidemiology of cardiovascular disease in chronic renal disease. Journal of American Society of Nephrology. 1998 Dec;9(12):S16–23.

8. Sarnak MJ, Foley RN. Cardiovascular Mortality in the General Population Versus Dialysis: A Glass Half Full or Empty? American Journal of Kidney Diseases. 2011 Jul 1;58(1):4–6.

9. Methven S, Steenkamp R, Fraser S. UK Renal Registry 19th Annual Report: Chapter 5 Survival and Causes of Death in UK Adult Patients on Renal Replacement Therapy in 2015: National and Centre-specific Analyses. Nephron. 2017;137(1):117–50.

10. Neuberger J. Liver transplantation in the United Kingdom. Liver Transplantation. 2016; 22(8):1129–35.

11. Neuberger J. Developments in liver transplantation. Gut. 2004;53(5):759–68.

12. Neuberger J, Gimson A, Davies M, Akyol M, O'Grady J, Burroughs A, et al. Selection of patients for liver transplantation and allocation of donated livers in the UK. Gut. 2008;57(2):252–7.

13. Northup PG, Intagliata NM, Shah NL, Pelletier SJ, Berg CL, Argo CK. Excess mortality on the liver transplant waiting list: unintended policy consequences and Model for End-Stage Liver Disease (MELD) inflation. Hepatology.2015 Jan;61(1):285–91.

14. Johnson RJ, Bradbury LL, Martin K, Neuberger J, UK Transplant Registry. Organ donation and transplantation in the UK-the last decade: a report from the UK national transplant registry. Transplantation. 2014;97 Suppl 1:1–27.

15. Trotter PB, Summers DM, Robb M, Hulme W, Ushiro-Lumb I, Watson CJE, et al. Deceased Organ Donors With A History Of Increased Risk Behavior For The Transmission Of Blood-Borne Viral Infection: The UK Experience. Transplantation. 2017 Mar 13;

16. MacGowan GA, Crossland DS, Hasan A, Schueler S. Considerations for patients awaiting heart transplantation-Insights from the UK experience. Journal of Thoracic Diseases. 2015;7(3):527–31.

17. MacGowan GA, Parry G, Schueler S, Hasan A. The decline in heart transplantation in the UK. British Medical Journal. 2011;342:2483–3.

18. Titman A, Rogers CA, Bonser RS, Banner NR, Sharples LD. Disease-specific survival benefit of lung transplantation in adults: a national cohort study. American Journal of Transplantation. 2009 ;9(7):1640–9.

19. NHS Blood and Transplant. Lung Candidate Selection Criteria. NHS Blood and Transplant 2017 May 16;1–21.

20. Academy of Medical Royal Collages. A Code of Practice for the Diagnosis and Confirmation of Death. 2008;1–42.

21. Summers DM, Johnson RJ, Allen J, Fuggle SV, Collett D, Watson CJE, et al. Analysis of factors that affect outcome after transplantation of kidneys donated after cardiac death in the UK: a cohort study. The Lancet. 2010;376(9749):1303–11.

22. Callaghan CJ, Charman SC, Muiesan P, Powell JJ, Gimson AE, van der Meulen JHP, et al. Outcomes of transplantation of livers from donation after circulatory death donors in the UK: a cohort study. BMJ Open; 2013;3(9)

23. Thomas HL, Taylor R, Simon AR, Clark SC, Dunning J, Yonan N, et al. Donation after Circulatory Death Lung Activity in the UK –

100 Transplants and Counting. Journal of Heart and Lung Transplantation. 2013 ;32:S15.

24. NHS Blood and Transplant. Annual Report on Cardiothoracic Organ Transplantation. 2017;1–149.

25. Page A, Messer S, Large SR. Heart transplantation from donation after circulatory determined death. Annals of Cardiothoracic Surgery. 2018;7(1):75–81.

26. Messer S, Page A, Axell R, Berman M, Hernández-Sánchez J, Colah S, et al. Outcome after heart transplantation from donation after circulatory-determined death donors. Journal of Heart and Lung Transplantation. 2017;36(12):1311–8.

27. Dhital KK, Iyer A, Connellan M, Chew HC, Gao L, Doyle A, et al. Adult heart transplantation with distant procurement and ex-vivo preservation of donor hearts after circulatory death: a case series. Lancet. 2015;385(9987):2585–91.

28. Macdonald P, Verran D, O'Leary M, Cavazzoni E, Dhital K. Heart Transplantation From Donation After Circulatory Death Donors. Transplantation. 2015;99(6):1101–2.

29. Summers DM, Watson CJE, Pettigrew GJ, Johnson RJ, Collett D, Neuberger JM, et al. Kidney donation after circulatory death (DCD): state of the art. Kidney International. 2015;88(2):241–9.

30. Johnson RJ, Bradbury LL, Martin K, Neuberger J, UK Transplant Registry. Organ donation and transplantation in the UK-the last decade: a report from the UK national transplant registry. Transplantation. 2014;97 1:S1–S27.

31. O'Keeffe LM, Ramond A, Oliver-Williams C, Willeit P, Paige E, Trotter P, et al. Mid- and Long-Term Health Risks in Living Kidney Donors: A Systematic Review and Meta-analysis. Annals of Internal Medicine. 2018;168(4):276–84.

32. Narasimhan G, Safwan M, Kota V, Reddy MS, Bharathan A, Dabora A, et al. Donor Outcomes in Living Donor Liver Transplantation-Analysis of 275 Donors From a Single Centre in India. Transplantation. 2016;100(6):1251–6.

33. Narasimhan G, Kota V, Rela M. Liver transplantation in India. Liver Transplantation. 2016;22(7):1019–24.

34. British Transplant Society. United Kingdom Guidelines for Living Donor Liver Transplantation. 2015;1–155.

35. Porret PM, Olthoff KM. Current state of living donor liver transplantation. Clinical Liver Disease. 2013;2(4):160–4.

36. Freise CE, Gillespie BW, Koffron AJ, Lok ASF, Pruett TL, Emond JC, et al. Recipient morbidity after living and deceased donor liver transplantation: findings from the A2ALL Retrospective Cohort Study. Am J Transplant. 2008 ;8(12):2569–79.

37. NHS Blood and Transplant.Organ Donation and Transplantation Annual Activity report 2014-2015. 2015;1–167. http://www.odt.nhs.uk/pdf/activity-report/activity_report_2014_15.pdf

38. NHS Blood and Transplant: Organ Donation and Transplantation Activity Report 2015/ 2016. 2017 1-174. Available from: http://www.odt.nhs.uk/pdf/activity-report/activity_report_2015_16.pdf

39. NHS Blood and Transplant. Kidney allocation policy. 2017 1–11. Available from: http://www.odt.nhs.uk/pdf/kidney_allocation_policy.pdf

40. Callaghan CJ, Mumford L, Pankhurst L, Baker RJ, Bradley JA, Watson CJE. Early Outcomes of the New UK Deceased Donor Kidney Fast-Track Offering Scheme. Transplantation. 2017;101(12):2888–97.

41. Fuggle SV and Taylor CJ. Chapter 4-Histocompatibility and immunogenetics. Handbook of renal and pancreatic transplantation. 2012;55–75.

42. Salter RD, Benjamin RJ, Wesley PK, Buxton SE, Garrett TP, Clayberger C, et al. A binding site for the T-cell co-receptor CD8 on the alpha 3 domain of HLA-A2. Nature. 1990;345(6270):41–6.

43. Stern LJ, Brown JH, Jardetzky TS, Gorga JC, Urban RG, Strominger JL, et al. Crystal structure of the human class II MHC protein HLA-DR1 complexed with an influenza virus peptide. Nature.1994;368(6468):215–21.

44. Mizutani K, Shibata L, Ozawa M, Esquenazi V, Rosen A, Miller J, et al. Detection of HLA and MICA antibodies before kidney graft failure. Clinical Transplantation. 2006;255–64.

45. Kissmeyer-Nielsen F, Olsen S, Petersen VP, Fjeldborg O. Hyperacute Rejection of Kidney Allografts, Associated with Pre-existing Humoral Antibodies Against Donor Cells. The Lancet. 1966;288(7465):662–5.

46. Fuggle SV, Johnson RJ, Bradley JA, Rudge CJ, Kidney Advisory Group of NHS Blood and Transplant. Impact of the 1998 UK National Allocation Scheme for deceased heartbeating donor kidneys. Transplantation. 2010;89(4):372–8.

47. Morris PJ, Johnson RJ, Fuggle SV, Belger MA, Briggs JD. Analysis of factors that affect outcome of primary cadaveric renal transplantation in the UK. HLA Task Force of the Kidney Advisory Group of the United Kingdom Transplant Support Service Authority (UKTSSA). The Lancet. 1999;354(9185):1147–52.

48. NHS Blood and Transplant. Update from new kidney offering scheme meeting. 2017;1–18. Available from: https://nhsbtdbe.blob.core.windows.net/umbraco-assets-corp/11764/proposed-kidney-offering-scheme.pdf.

49. Johnson RJ, Fuggle SV, Mumford L, Bradley JA, Forsythe JLR, Rudge CJ, et al. A New UK 2006 National Kidney Allocation Scheme for deceased heart-beating donor kidneys. Transplantation. 2010;89(4):387–94.

50. NHS Blood and Transplant. Kidney Transplantation: Deceased Donor Organ Allocation. 2017;1–11.

51. Summers DM, Johnson RJ, Hudson AJ, Collett D, Murphy P, Watson CJE, et al. Standardized deceased donor kidney donation rates in the UK reveal marked regional variation and highlight the potential for increasing kidney donation: a prospective cohort study. British Journal of Anaesthesia. 2014;113(1):83–90.

52. NHS Blood and Transplant. Liver Selection Policy. 2018;1–24.

53. NHS Blood and Transplant. Deceased Donor Liver Distribution and Allocation. 2018;1–18.

54. Neuberger J. Liver allocation. Minerva Gastroenterol Dietol. 2018 ;64(2):170–9.

55. Fischer SA, Lu K, AST Infectious Diseases Community of Practice. Screening of donor and recipient in solid organ transplantation. American Journal of Transplantation. 2013;13 s4:9–21.

56. Grossi PA, Fishman JA, AST Infectious Disease Community of Practice. Donor-derived infections in solid organ transplant recipients. Am J Transplant. 2009; Suppl 10:S19–26.

57. Ison MG, Grossi P, the AST Infectious Diseases Community of Practice. Donor-Derived Infections in Solid Organ Transplantation. American Journal of Transplantation. 2013;13(s4):22–30.

58. Fishman JA. Infection in Organ Transplantation. Am J Transplant.2017;17(4):856–79.

59. Giani T, Conte V, Mandalà S, D'Andrea MM, Luzzaro F, Conaldi PG, et al. Cross-infection of solid organ transplant recipients by a multidrug-resistant Klebsiella pneumoniae isolate producing the

OXA-48 carbapenemase, likely derived from a multiorgan donor. Journal of Clinical Microbiology. 2014;52(7):2702–5.

60. Mularoni A, Bertani A, Vizzini G, Gona F, Campanella M, Spada M, et al. Outcome of Transplantation Using Organs From Donors Infected or Colonized With Carbapenem-Resistant Gram-Negative Bacteria. American Journal of Transplantation. 2015;15(10):2674–82.

61. Jacobson CA, LaCasce AS. Lymphoma: risk and response after solid organ transplant. Oncology. 2010;24(10):936–44.

62. The Advisory Committee on the Safety of Blood, Tissues and Organs. Guidance on the Microbiological Safety of Human Organs, Tissues and Cells used in Transplantation. 2011. Available from: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/.

63. The Advisory Committee on the Safety of Blood, Tissues and Organs. Guidance on the Microbiological Safety of Human Organs, Tissues and Cells used in Transplantation ser DH. Microbiological safety guidelines 2017. 2018;1–62.

64. The Advisory Committee on the Safety of Blood, Tissues and Organs. Guidance on the Microbiological Safety of Human Organs, Tissues and Cells used in Transplantation. Microbiological safety guidelines 2000.

65. Kucirka LM, Sarathy H, Govindan P, Wolf JH, Ellison TA, Hart LJ, et al. Risk of window period hepatitis-C infection in high infectious risk donors: systematic review and meta-analysis. American Journal of Transplantation. 2011;11(6):1188–200.

66. Kucirka LM, Sarathy H, Govindan P, Wolf JH, Ellison TA, Hart LJ, et al. Risk of Window Period HIV Infection in High Infectious Risk Donors: Systematic Review and Meta-Analysis. American Journal of Transplantation. 2011;11(6):1176–87.

67. Zou S, Dodd RY, Stramer SL, Strong DM, Tissue Safety Study Group. Probability of viremia with HBV, HCV, HIV, and HTLV among tissue donors in the United States. New England Journal Medicine. 2004;351(8):751–9.

68. Green M, Michaels MG. Epstein-Barr Virus Infection and Posttransplant Lymphoproliferative Disorder. American Journal of Transplantation. 2013;13(s3):41–54.

69. Morton M, Coupes B, Roberts SA, Johnson SL, Klapper PE, Vallely PJ, et al. Epstein-Barr Virus Infection in Adult Renal

Transplant Recipients. American Journal of Transplantation. 2014;14(7):1619–29.

70. Parker A, Bowles K, Bradley JA, Emery V, Featherstone C, Gupte G, et al. Diagnosis of post-transplant lymphoproliferative disorder in solid organ transplant recipients - BCSH and BTS Guidelines. British Journal of Haematology. 2010;149(5):675–92.

71. Newstead K. The Prevention and Management of CMV Disease after Solid Organ Transplantation. 2011;1–75.

72. Razonable RR, Humar A, the AST Infectious Diseases Community of Practice. Cytomegalovirus in Solid Organ Transplantation. American Journal of Transplantation. 2013;13(s4):93–106.

73. Lurain NS, Chou S. Antiviral Drug Resistance of Human Cytomegalovirus. Clinical Microbiology Reviews. 2010;23(4):689–712.

74. Cook LBM, Melamed A, Demontis MA, Laydon DJ, Fox JM, Tosswill JHC, et al. Rapid dissemination of human T-lymphotropic virus type 1 during primary infection in transplant recipients. Retrovirology. BioMed Central; 2016;13(1):3.

75. Kuroda Y, Takashima H, Yukitake M, Sakemi T. Development of HTLV-I-associated myelopathy after blood transfusion in a patient with aplastic anemia and a recipient of a renal transplant. Journal of Neuroogicall Sciences. 1992;109(2):196–9.

76. Ramanan P, Deziel PJ, Norby SM, Yao JD, Garza I, Razonable RR. Donor-transmitted HTLV-1-associated myelopathy in a kidney transplant recipient--case report and literature review. American Journal of Transplantation. 2014;14(10):2417–21.

77. World Health Organisation. World Health Organization Regional Office for Europe. Fact Sheet: Hepatitis C in the WHO European Region. 2015;1–2.

78. Public Health England. Hepatitis C in the UK 2016 report. 2016 . Available from: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/541317/Hepatitis_C_in_the_UK_2016_report.pdfeebeejaun K.

79. Manns MP, Buti M, Gane E, Pawlotsky J-M, Razavi H, Terrault N, et al. Hepatitis C virus infection. Nature Review Disease Primers. p; 2017;3:17006.

80. Centre for Disease Control. Viral Hepatitis Surveillance - United States, 2014. 2016:1–65. Available from: https://www.cdc.gov/hepatitis/statistics/2014surveillance/pdfs/2014hepsurveillancerpt.pdf.

81. Kumar D, Humar A, Kim SJ, Kiberd B. A Survey of Increased Infectious Risk Donor Utilization in Canadian Transplant Programs. Transplantation. 2016;100(2):461–4.

82. Reese PP, Feldman HI, Asch DA, Halpern SD, Blumberg EA, Thomasson A, et al. Transplantation of Kidneys from Donors at Increased Risk for Blood-Borne Viral Infection: Recipient Outcomes and Patterns of Organ Use. American Journal of Transplantation. 2009;9(10):2338–45.

83. Bose SK, Ray R. Hepatitis C virus infection and insulin resistance. World Journal of Diabetes.; 2014;5(1):52–8.

84. Mitchell O, Gurakar A. Management of Hepatitis C Post-liver Transplantation: a Comprehensive Review. Clin Transl Hepatol; 2015 Jun 28;3(2):140–8.

85. Kwo PY, Mantry PS, Coakley E, Te HS, Vargas HE, Brown R Jr., et al. An Interferon-free Antiviral Regimen for HCV after Liver Transplantation. N Engl J Med. 2014;371(25):2375–82.

86. Lawitz E, Gane E, Pearlman B, Tam E, Ghesquiere W, Alric L, et al. Efficacy and safety of 12 weeks versus 18 weeks of treatment with grazoprevir (MK-5172) and elbasvir (MK-8742) with or without ribavirin for hepatitis C virus genotype 1 infection in previously untreated patients with cirrhosis and patients with previous null response with or without cirrhosis (C-WORTHY): a randomised, open-label phase 2 trial. The Lancet. 2015. 21;385(9973):1075–86.

87. Reese PP, Abt PL, Blumberg EA, Goldberg DS. Transplanting Hepatitis C Positive Kidneys.New England Journal of Medicine. 2015;373:303-305.

88. Huprikar S, Danziger-Isakov L, Ahn J, Naugler S, Blumberg E, Avery RK, et al. Solid Organ Transplantation From Hepatitis B Virus-Positive Donors: Consensus Guidelines for Recipient Management. American Journal of Transplantation. 2015;15(5):1162–72.

89. Levitsky J, Doucette K, AST Infectious Diseases Community of Practice. Viral hepatitis in solid organ transplantation. Am J Transplant. 2013 ;13 Suppl 4(s4):147–68.

90. Johnston B, Conly J. Solid organ transplantation and HIV: A changing paradigm. Can J Infect Dis Med Microbiol. 2008 ;19(6):425–9.

91. Erice A, Rhame FS, Heussner RC, Dunn DL, Balfour HH. Human immunodeficiency virus infection in patients with solid-organ

transplants: report of five cases and review. Review Infectious Diseases. 1991;13(4):537–47.

92. Stock PG, Barin B, Murphy B, Hanto D, Diego JM, Light J, et al. Outcomes of kidney transplantation in HIV-infected recipients. N Engl J Med. Massachusetts Medical Society. 2010;363(21):2004–14.

93. Nolan E, Karydis N, Drage M, Hilton R. First UK case report of kidney transplantation from an HIV-infected deceased donor to two HIV-infected recipients. Clinical Kidney Journal. 2018;11(2):289–91.

94. Hoti E, Levesque E, Sebagh M, Heneghan HM, Khalfallah M, Castaing D, et al. Liver Transplantation With Grafts From Donors Who Die From Suicide by Hanging. Transplantation. 2014;98(11):1236–43.

95. Mohite PN, Patil NP, Sabashnikov A, Zych B, Sáez DG, Popov AF, et al. ``Hanging Donors“”: Are We Still Skeptical About the Lungs? 2015;47(2):261–6.

96. Ajdacic-Gross V. Methods of suicide: international suicide patters derived from the WHO mortality database. Bull World Health Organ. 2008;86(9):726–32.

97. Varnik A, Kolves K, van der Feltz-Cornelis CM, Marusic A, Oskarsson H, Palmer A, et al. Suicide methods in Europe: a gender-specific analysis of countries participating in the “European Alliance Against Depression.” Journal of Epidemiology & Community Health. 2008;62(6):545–51.

98. Taniguchi T, Saito S, Mizukoshi Y, Goto Y, Inaba H. Multiple organ failure after strangulation injury. Intensive Care Medicine. 2002;28(8):1193–3.

99. McNamee CJ, Modry DL, Lien D, Conlan AA. Drowned donor lung for bilateral lung transplantation. The Journal of Thoracic and Cardiovascular Surgery. 2003;126(3):910–2.

100. Taylor RM, Bockenstedt P, Su GL, Marrero JA, Pellitier SM, Fontana RJ. Immune thrombocytopenic purpura following liver transplantation: A case series and review of the literature. Liver Transplantation. 2006;12(5):781–91.

101. Sugumar D, Lionberger J, Fesler M, Bandlamundi R, Goyal SD. Donor Derived Systemic Lupus Erythematosus (SLE) after Allogeneic Transplantation. Biology of Blood and Marrow Transplantation. 2015;21(S):S127.

102. Zaja F, Barillari G, Russo D, Silvestri F, Fanin R, Baccarani M. Myasthenia gravis after allogeneic bone marrow transplantation: A

case report and a review of the literature.Acta Neurol Scand. 1997 ;96:256-259.

103. Farese S, Vogt B, Frey FJ, Huynh-Do U. Successful Kidney Transplantation from Donor with Marfan's Syndrome. American Journal of Transplantation. 2006;6(8):1972–4.

104. Watson CJE, Johnson RJ, Birch R, Collett D, Bradley JA. A Simplified Donor Risk Index for Predicting Outcome After Deceased Donor Kidney Transplantation. Transplantation. 2012;93(3):314–8.

105. Collett D, Friend PJ, Watson CJ. Factors associated with Short and Long Term Liver Graft Survival in the United Kingdom: Development of a UK Donor Liver Index. Transplantation. 2017;101(4):786-792.

106. Mittal S, Lee FJ, Bradbury L, Collett D, Reddy S, Sinha S, et al. Validation of the Pancreas Donor Risk Index for use in a UK population. Transplant International. 2015 Sep;28(9):1028–33.

107. Levey AS, Coresh J, Greene T, Stevens LA, Zhang YL, Hendriksen S, et al. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. Ann Intern Med. 2006;145(4):247–54.

108. Barber KM, Pioli SE, Blackwell JE, Collett D, Neuberger JM, Gimson AE. Development of a UK score for patients with end-stage liver disease. Hepatology. 2007;46(4):510A–510A.

109. Kamath P. A model to predict survival in patients with end-stage liver disease. Hepatology. 2001;33(2):464–70.

110. Jung GE, Encke J, Schmidt J, Rahmel A. Model for end-stage liver disease. Chirurg. 2008;79(2):157–63.

111. Kaplan EL, Meier P. Nonparametric Estimation from Incomplete Observations. Journal of the American Statistical Association.; 1958;53(282):457.

112. SAS Institute Inc. 2011. SAS 9.3 System Options: Reference, Second Edition.

113. Donor-Derived Disease Transmission Events in the United States: Data Reviewed by the OPTN/UNOS Disease Transmission Advisory Committee. 2015;1–7.

114. Lyon M, Kaul D, Ehsan A, Covington S, Taranto S, Taylor K, et al. Infectious Disease Transmission from Organ Donors with Meningitis or Encephalitis. American Journal of Transplantation. 2011;11:200–0

115. Cooper AJR, Dholakia S, Holland CV, Friend PJ. Helminths in organ transplantation. Lancet Infectious Diseases. 2017;17(6):e166–76.

116. Basavaraju SV, Kuehnert MJ, Zaki SR, Sejvar JJ. Encephalitis Caused by Pathogens Transmitted through Organ Transplants, United States, 2002–2013. Emerging Infectious Disease. 2014 ;20(9):1443–51.

117. Satlin MJ, Graham JK, Visvesvara GS, Mena H, Marks KM, Saal SD, et al. Fulminant and fatal encephalitis caused by Acanthamoebain a kidney transplant recipient: case report and literature review. Transplant Infectious Disease. 2013;15(6):619–26.

118. Gomez AJ, Waggoner JJ, Itoh M, Hollander SA, Gutierrez KM, Budvytiene I, et al. Fatal West Nile Virus Encephalitis in a Heart Transplant Recipient. Loeffelholz MJ, editor. Journal of Clinical Microbiology. 2015;53(8):2749–52.

119. Gupte AA, Hocevar SN, Lea AS, Kulkarni RD, Schain DC, Casey MJ, et al. Transmission of Balamuthia mandrillarisThrough Solid Organ Transplantation: Utility of Organ Recipient Serology to Guide Clinical Management. American Journal of Transplantation. 2014;14(6):1417–24.

120. MacNeil A, Ströher U, Farnon E, Campbell S, Cannon D, Paddock CD, et al. Solid Organ Transplant–associated Lymphocytic Choriomeningitis, United States, 2011. Emerging Infectious Disease. 2012;18(8):1256–62.

121. Ross RS, Wolters B, Hoffmann B, Geue L, Viazov S, Grüner N, et al. Instructive even after a decade: Complete results of initial virological diagnostics and re-evaluation of molecular data in the German rabies virus “outbreak” caused by transplantations. International Journal of Medical Microbiology.2015;305(7):636–43.

122. Vora NM, Orciari LA, Niezgoda M, Selvaggi G, Stosor V, Lyon GM III, et al. Clinical management and humoral immune responses to rabies post-exposure prophylaxis among three patients who received solid organs from a donor with rabies. Transplant Infectious Disease. 2015;17(3):389–95.

123. Advisory Committee on the Microbiological Safety of Blood and Tissues for Transplantation MSBT. Guidance on the Microbiological Safety of Human Organs, Tissues and Cells used in Transplantation. 2000.

124. Council of Europe. Guide to the quality and safety of tissues and cells for human application. 2015;1–31.

125. Rhee C, Eaton EF, Concepcion W, Blackburn BG. West Nile virus encephalitis acquired via liver transplantation and clinical response to intravenous immunoglobulin: case report and review of the literature. Transplant Infectious Disease. 2011;13(3):312–7.

126. Perri R, Assi M, Talwalkar J, Heimbach J, Hogan W, Moore SB, et al. Graft vs. host disease after liver transplantation: A new approach is needed. Liver Transplantation. 2007;13(8):1092–9.

127. Taylor AL, Gibbs P, Bradley JA. Acute Graft Versus Host Disease Following Liver Transplantation: The Enemy Within. American Journal of Transplantation. 2004;4(4):466–74.

128. Ainsworth CD, Crowther MA, Treleaven D, Evanovitch D, Webert KE, Blajchman MA. Severe Hemolytic Anemia Post–Renal Transplantation Produced by Donor Anti-D Passenger Lymphocytes: Case Report and Literature Review. Transfusion Medicine Reviews. 2009;23(2):155–9.

129. Pomper GJ, Joseph RA, Hartmann EL, Rohr MS, Adams PL, Stratta RJ. Massive Immune Hemolysis Caused by Anti-D After Dual Kidney Transplantation. American Journal of Transplantation. 2005;5(10):2586–9.

130. Pereboom ITA, de Boer MT, Haagsma EB, van der Heide F, Porcelijn L, Lisman T, et al. Transmission of idiopathic thrombocytopenic purpura during orthotopic liver transplantation. Transplant International. 2010;23(2):236–8.

131. Diaz GC, Prowda J, Lo IJ, Arepally GM, Evans N, Wheeless Y, et al. Transplantation-mediated alloimmune thrombocytopenia: Guidelines for utilization of thrombocytopenic donors. Liver Transpl. 2008;14(12):1803–9.

132. Kaestner F, Kutsogiannis DJ. Successful Kidney and Liver Transplantation From a Donor With Immune Thrombocytopenia. Transplant proceedings.2013;45(7):2838–40.

133. Rodeghiero F, Stasi R, Gernsheimer T, et al. Standardization of terminology, definitions and outcome criteria in immune thrombocytopenic purpura of adults and children: report from an international working group. *Blood.* 2009;113(11):2386-2393.

134. Provan D, Stasi R, Newland AC, et al. International consensus report on the investigation and management of primary immune thrombocytopenia. *Blood.* 2010;115(2):168-186.

135. Hill QA. Immune thrombocytopenia - in defence of the platelet count. British Journal of Haematology. 2018;182(1):128-130.

136. Schoonen WM, Kucera G, Coalson J, et al. Epidemiology of immune thrombocytopenic purpura in the General Practice

Research Database. British Journal of Haematology. 2009;145(2):235-244.

137. Bonser RS, Taylor R, Collett D, Thomas HL, Dark JH, Neuberger J. Effect of donor smoking on survival after lung transplantation: a cohort study of a prospective registry. The Lancet. 2012;380(9843):747–55.

138. Cserti-Gazdewich CM, Waddell TK, Singer LG, Chaparro C, Pendergrast JM, Hawes J, et al. Passenger Lymphocyte Syndrome With or Without Immune Hemolytic Anemia in all Rh-Positive Recipients of Lungs From Rhesus Alloimmunized Donors: Three New Cases and a Review of the Literature. Transfusion Medicine Reviews. 2009;23(2):134–45.

139. Mao W, Hu Y, Lou Y, Dou J, Zou L. Immature platelet fraction values predict recovery of platelet counts following liver transplantation. Clinics and Research in Hepatology and Gastroenterology. 2015;39(4):469–74.

140. Duan KI, Englesbe MJ, Volk ML. Centers for Disease Control "High-Risk" Donors and Kidney Utilization. American Journal of Transplantation. 2010;10(2):416–20.

141. Ison MG, Grossi P, the AST Infectious Diseases Community of Practice. Donor-Derived Infections in Solid Organ Transplantation. American Journal of Transplantation. 2013;13(s4):22–30.

142. Humar A, Morris M, Blumberg E, Freeman R, Preiksaitis J, Kiberd B, et al. Nucleic Acid Testing (NAT) of Organ Donors: Is the "Best" Test the Right Test? A Consensus Conference Report. American Journal of Transplantation. 2010;10(4):889–99.

143. European Centre for Disease Control and Prevention.Hepatitis B surveillance in Europe. 2015;1–8.

144. Pruett TL, Clark MA, Taranto SE. Deceased Organ Donors and PHS Risk Identification: Impact on Organ Usage and Outcomes. Transplantation. 2017 ;101(7):1670–8.

145. Trotter PB, Robb M, Hulme W, Summers DM, Watson CJE, Bradley JA, et al. Transplantation of organs from deceased donors with meningitis and encephalitis: a UK registry analysis. Transplant Infectious Disease. 2016;18(6):862–71.

146. Marshall DA, Kleinman SH, Wong JB, AuBuchon JP, Grima DT, Kulin NA, et al. Cost-effectiveness of nucleic acid test screening of volunteer blood donations for hepatitis B, hepatitis C and human immunodeficiency virus in the United States. Vox Sanguinis. 2004;86(1):28–40.

147. Assal A, Barlet V, Deschaseaux M, Dupont I, Gallian P, Guitton C, et al. Sensitivity of two hepatitis B virus, hepatitis C virus (HCV), and human immunodeficiency virus (HIV) nucleic acid test systems relative to hepatitis B surface antigen, anti-HCV, anti-HIV, and p24/anti-HIV combination assays in seroconversion panels. Transfusion. 2009;49(2):301–10.

148. Busch MP, Glynn SA, Stramer SL, Strong DM, Caglioti S, Wright DJ, et al. A new strategy for estimating risks of transfusion-transmitted viral infections based on rates of detection of recently infected donors. Transfusion. 2005;45(2):254–64.

149. Summers DM, Johnson RJ, Hudson A, Collet D, Watson CJE, Bradley JA. Analysis of factors that affect outcome after transplantation of kidneys donated after cardiac death in the UK: a cohort study. The Lancet. 2010;376(9749):1303–11.

150. Purcell DW, W Purcell D, Johnson CH, Lansky A, Prejean J, Stein R, et al. Estimating the Population Size of Men Who Have Sex with Men in the United States to Obtain HIV and Syphilis Rates. Open Aids Journal. 2012;6(1):98–107.

151. Aspinall PJ. Estimating the size and composition of the lesbian, gay, and bisexual population in Britain. 2009:1–135.

152. Ros RL, Kucirka LM, Govindan P, Sarathy H, Montgomery RA, Segev DL. Patient attitudes toward CDC high infectious risk donor kidney transplantation: inferences from focus groups. Clinical Transplantation. 2011;26(2):247–53.

153. Schold JD. Which Renal Transplant Candidates Should Accept Marginal Kidneys in Exchange for a Shorter Waiting Time on Dialysis? Clinical Journal of the American Society of Nephrology. 2006;1(3):532–8.

154. Merion RM, Ashby VB, Wolfe RA, Distant DA, Hulbert-Shearon TE, Metzger RA, et al. Deceased-Donor Characteristics and the Survival Benefit of Kidney Transplantation. Journal of the American Medical Association; 2005;294(21):2726–33.

155. Public Health England. Hepatitis C in the UK 2016 report. 2016:1–30.

156. Sawinski D, Kaur N, Ajeti A, Trofe-Clark J, Lim M, Bleicher M, et al. Successful Treatment of Hepatitis C in Renal Transplant Recipients With Direct-Acting Antiviral Agents. American Journal of Transplantation. 2016;16(5):1588–95.

157. Lubetzky M, Chun S, Joelson A, Coco M, Kamal L, Ajaimy M, et al. Safety and Efficacy of Treatment of Hepatitis C in Kidney

Transplant Recipients With Directly Acting Antiviral Agents. Transplantation. Transplantation. 2017 ;101(7):1704–10.

158. Martin MT, Koppe S. Elbasvir/Grazoprevir Use in Postliver Transplantation Patients on Hemodialysis. Transplantation. Transplantation. 2017;101(9):2088–91.

159. Levitsky J, Formica RN, Bloom RD, Charlton M, Curry M, Friedewald J, et al. The American Society of Transplantation Consensus Conference on the Use of Hepatitis C Viremic Donors in Solid Organ Transplantation. American Journal of Transplantation. 2017;65(Suppl 1):524.

160. Del Bello D, Ross MJ, Huprikar SS. Hepatitis C virus infection and kidney transplantation: newer options and a brighter future ahead. Kidney International. 2015;88(2):223–5.

161. Lin MV, Sise ME, Pavlakis M, Amundsen BM, Chute D, Rutherford AE, et al. Efficacy and Safety of Direct Acting Antivirals in Kidney Transplant Recipients with Chronic Hepatitis C Virus Infection. PLoS ONE.2016;11(7):e0158431–14.

162. Eisenberger U, Guberina H, Willuweit K, Bienholz A, Kribben A, Gerken G, et al. Successful Treatment of Chronic Hepatitis C Virus Infection With Sofosbuvir and Ledipasvir in Renal Transplant Recipients. Transplantation. 2017;101(5):980–6.

163. Hori T, Onishi Y, Kamei H, Kurata N, Ishigami M, Ishizu Y, et al. Fibrosing cholestatic hepatitis C in post-transplant adult recipients of liver transplantation. Annals of Gastroenterology. 2016;29(4):454–9.

164. Forns X, Charlton M, Denning J, McHutchison JG, Symonds WT, Brainard D, et al. Sofosbuvir compassionate use program for patients with severe recurrent hepatitis C after liver transplantation. Hepatology. 2015;61(5):1485–94.

165. Charlton M, Everson GT, Flamm SL, Kumar P, Landis C, Brown RS, et al. Ledipasvir and Sofosbuvir Plus Ribavirin for Treatment of HCV Infection in Patients With Advanced Liver Disease. Gastroenterology. 2015;149(3):649–59.

166. NHS Blood and Transplant. Potential Donor Audit: Summary report for the 12 month period. 2016:1–11.

167. Department of Health. Costs and Savings to the NHS from Solid Organ Transplantation. 2015. 1-19. Available from: http://www.odt.nhs.uk/pdf/Solid_Organ_Transplantation_Final.pdf sts and Savings to NHS from Solid Organ Transplantation. 2015 Oct 5;:1–19.

168. National Institue for Health and Care Excellence.Ledipasvir–sofosbuvir for treating chronic hepatitis C. Technology apprasial guidance. 2015;1–85.

169. National Institute for Health and Care Excellence.Sofosbuvir–velpatasvir for treating chronic hepatitis C. 2018;1–31.

170. National Institute for Health and Care Excellence.Ombitasvir–paritaprevir–ritonavir with or without dasabuvir for treating chronic hepatitis C. 2018;1–58.

171. Sawinski D, Lee DH, Doyle AM, Blumberg EA. Successful Posttransplant Treatment of Hepatitis C With Ledipasvir-Sofosbuvir in HIV+ Kidney Transplant Recipients. Transplantation. 2017;101(5):974–9.

172. Sawinski D, Patel N, Appolo B, Bloom RD. Use of HCV+ donors does not affect HCV clearance with directly acting antiviral therapy but shortens the wait time to kidney transplantation. Transplantation. 2016;101(5):968-973

173. Elfeki MA, Abou Mrad R, Modaresi Esfeh J, Zein NN, Eghtesad B, Zervos X, et al. Sofosbuvir/Ledipasvir Without Ribavirin Achieved High Sustained Virologic Response for Hepatitis C Recurrence After Liver Transplantation: Two-Center Experience. Transplantation. 2017;101(5):996–1000.

174. Muir AJ. The Rapid Evolution of Treatment Strategies for Hepatitis C. The American Journal of Gastroenterology. 2014;109(5):628–35.

175. Goldberg DS, Abt PL, Blumberg EA, Van Deerlin VM, Levine M, Reddy KR, et al. Trial of Transplantation of HCV-Infected Kidneys into Uninfected Recipients. New England Journal Medicine. 2017; 376:2394-2395.

176. Suraweera D, Sundaram V, Saab S. Treatment of Hepatitis C Virus Infection in Liver Transplant Recipients. Gastroenterology Hepatology. 2016;12(1):23–30.

177. Centres for Disease Contro.Donor Screening and Testing-Transplant Safety. 2018;1–1.

178. Suryaprasad A, Basavaraju SV, Hocevar SN, Theodoropoulos N, Zuckerman RA, Hayden T, et al. Transmission of Hepatitis C Virus From Organ Donors Despite Nucleic Acid Test Screening. American Journal of Transplantation. 2015;15(7):1827–35.

179. Reese PP, Abt PL, Blumberg EA, Goldberg DS. Transplanting Hepatitis C-Positive Kidneys. New England Journal of Medicine. 2015;373(4):303–5.

180. Raghavan R. New Opportunities for Funding Dialysis-Dependent Undocumented Individuals. Journal of American Society of Nephrology; 2017;12(2):370–5.

181. The American Association for the Study of Liver Diseases and the Infectious Diseases Society for America. HCV Guidance: Recommendations for Testing, Managing, and Treating Hepatitis C. 2018;1–263.

182. Ajdacic-Gross V, Weiss MG, Ring M, Hepp U,Bopp M, Gutzwiller F, et al. Methods of Suicide: International Suicide Patterns Derived from the WHO Mortality Database.World Health Organisation. 2008;86:657-736.

183. Office for National Statistics. Suicides in the UK: 2015 registrations. 2016;1–23.

184. Yaprak M, Turan MN, Sezer T, Tatar E, Sözbilen EM, Töz H, et al. Use of Suicidal Deaths as Kidney Donors: A Single-Center Experience.Transplant Proceedings; 2013;45(3):872–4.

185. Suicides in the UK: 2015 registrations. 2016 Dec 1;:1–23.

186. Watson CJE, Johnson RJ, Birch R, Collett D, Bradley JA. A Simplified Donor Risk Index for Predicting Outcome After Deceased Donor Kidney Transplantation. Transplantation. 2012;93(3):314–8.

187. Summers DM, Johnson RJ, Hudson A, Collett D, Watson CJ, Bradley JA. Effect of donor age and cold storage time on outcome in recipients of kidneys donated after circulatory death in the UK: a cohort study. Lancet. 2013;381(9868):727–34.

188. Bradbury L. Annual Report on Kidney Transplantation. 2016:1–99.

189. Ravanan R, Udayaraj U, Ansell D, Collett D, Johnson R, O'Neill J, et al. Variation between centres in access to renal transplantation in UK: longitudinal cohort study. British Medical Journal. 2010;341:3451–1.

190. Garonzik-Wang JM, James NT, Weatherspoon KC, Deshpande NA, Berger JA, Hall EC, et al. The aggressive phenotype: center-level patterns in the utilization of suboptimal kidneys. American Journal of Transplantation. 2012;12(2):400–8.

191. Garonzik-Wang JM, James NT, Van Arendonk KJ, Gupta N, Orandi BJ, Hall EC, et al. The aggressive phenotype revisited: utilization of higher-risk liver allografts. American Journal of Transplantation. 2013;13(4):936–42.

192. Rao PS, Schaubel DE, Guidinger MK, Andreoni KA, Wolfe RA, Merion RM, et al. A Comprehensive Risk Quantification Score for

Deceased Donor Kidneys: The Kidney Donor Risk Index. Transplantation. 2009;88(2):231–6.

193. Collett D, Mumford L, Banner NR, Neuberger J, Watson C. Comparison of the Incidence of Malignancy in Recipients of Different Types of Organ: A UK Registry Audit. American Journal of Transplantation. 2010;10(8):1889–96.

194. Watson CJE, Roberts R, Wright KA, Greenberg DC, Rous BA, Brown CH, et al. How Safe Is It to Transplant Organs from Deceased Donors with Primary Intracranial Malignancy? An Analysis of UK Registry Data. American Journal of Transplantation. 2010;10(6):1437–44.

195. Trotter PB, Robb M, Summers D, Watson CJE, Clatworthy M, Bradley JA, et al. Donors With Immune Thrombocytopenia: Do They Pose a Risk to Transplant Recipients? American Journal of Transplantation. 2017;17:796- 802.

196. Johnson RJ, Fuggle SV, Mumford L, Bradley JA, Forsythe JLR, Rudge CJ, et al. A New UK 2006 National Kidney Allocation Scheme for deceased heart-beating donor kidneys. Transplantation. 2010;89(4):387–94.

197. Boffa C, van de Leemkolk F, Curnow E, Homan van der Heide J, Gilbert J, Sharples E, Ploeg RJ. American Journal of Transplantation. 2017;17(2):411-419.

198. Watson CJE, Johnson RJ, Birch R, Collett D, Bradley JA. A Simplified Donor Risk Index for Predicting Outcome After Deceased Donor Kidney Transplantation. Transplantation. 2012;93(3):314–8.

199. Wong G, Howard K, Chapman JR, Chadban S, Cross N, Tong A, et al. Comparative survival and economic benefits of deceased donor kidney transplantation and dialysis in people with varying ages and co-morbidities. PLoS ONE. 2012;7(1):e29591.

200. Wyld M, Morton RL, Hayen A, Howard K, Webster AC. A systematic review and meta-analysis of utility-based quality of life in chronic kidney disease treatments. PLoS Medicine. 2012;9(9):e1001307.

201. NHS Blood and Transplant. Cost-effectiveness of transplantation. NHS Blood and Transplant Factsheet. 2009;1–2.

202. Baym M, Stone LK, Kishony R. Multidrug evolutionary strategies to reverse antibiotic resistance. Science. 2016;351(6268):aad3292–2.

203. Palmer AC, Kishony R. Understanding, predicting and manipulating the genotypic evolution of antibiotic resistance. Nature Reviews Genetics. 2013 ;14(4):243–8.

204. World Health Organisation. Implementation of the Global Action Plan on Antimicrobial Resistance. 2017;1–4.

205. Gerardin Y, Springer M, Kishony R. A competitive trade-off limits the selective advantage of increased antibiotic production. Nature Microbiology. 2016;1(12):16175.

206. Espinar MJ, Miranda IM, Costa-de-Oliveira S, Rocha R, Rodrigues AG, Pina-Vaz C. Urinary Tract Infections in Kidney Transplant Patients Due to Escherichia coli and Klebsiella pneumoniae-Producing Extended-Spectrum β-Lactamases: Risk Factors and Molecular Epidemiology. PLoS ONE. 2015 ;10(8):e0134737.

207. Pilmis B, Scemla A, Join-Lambert O, Mamzer M-F, Lortholary O, Legendre C, et al. ESBL-producing enterobacteriaceae-related urinary tract infections in kidney transplant recipients: incidence and risk factors for recurrence. Infectious Diseases. 2015;47(10):714–8.

208. Ramadas P, Rajendran PP, Krishnan P, Alex A, Siskind E, Kadiyala A, et al. Extended-spectrum-beta-lactamase producing bacteria related urinary tract infection in renal transplant recipients and effect on allograft function. PLoS ONE. 2014;9(3):e91289.

209. Centres for Disease Control. Antibiotic Resistance Threats: in the United States. 2013;1–114.

210. Rooks MG, Garrett WS. Gut microbiota, metabolites and host immunity. Nature Reviews Immunology. 2016;16(6):341–52.

211. Liu R, Hong J, Xu X, Feng Q, Zhang D, Gu Y, et al. Gut microbiome and serum metabolome alterations in obesity and after weight-loss intervention. Nature Medicine. 2017;1–14.

212. Lei YM, Chen L, Wang Y, Stefka AT, Molinero LL, Theriault B, et al. The composition of the microbiota modulates allograft rejection. Journal of Clinical Investigation.;2016;126(7):2736–44.

Appendices

1.46 Appendix 1: Free text search code

```
*NEW CATEGORIES -

Cause of death - Poisoning/overdose, drowning, hanging.

history - depression, alcohol abuse, cocaine abuse, other oral drug abuse, other intrvenous drug abuse, HRSB, imprisonment.

infection - active, recent, treated in past, encephalitis.

travel - outside europe.;


%let store = F:\Stats & Audit\Shared\Donation\Projects\High-risk donors;

libname store "&store.";


/*Choose a time period*/

%let date1='01-jan-2003';

%let date2='01-jan-2017';


%include 'F:\Stats & Audit\Shared\All\Software\SAS\Formats\SAS formats\allformats.SAS';




data donors00;

set standard.donors;

if dcountry = 'UNITED KINGDOM';

if "&date1."d <= ddate < "&date2."d ;

if dgrp not in (23,24,25);

run;



data all_cddf;

set donors00;

*if ddate>='01jul2012'd;

run;


data donor_comment1;

set database.donor_comment;

if record_type ne 2;

if note_type in (40,30,35,374,386);

note_text=compbl(" "||note_text);

note_text=TRANWRD(note_text,'.',' '); *replace full stops with spaces so that use of prxmatch function is easier;

note_text=TRANWRD(note_text,',',' '); *replace comma with dashes so that use of prxmatch function is easier;

note_text=TRANWRD(note_text,'/',' '); *replace slashes with dashes so that use of prxmatch function is easier;

note_text=TRANWRD(note_text,'\',' '); *replace slashes with dashes so that use of prxmatch function is easier;

note_text=TRANWRD(note_text,'(',' '); *replace bracket with dashes so that use of prxmatch function is easier;

note_text=TRANWRD(note_text,')',' '); *replace bracket with dashes so that use of prxmatch function is easier;

run;

data donor_comment2;

set database.donor_comment;

if record_type=2;

if note_type in (40,30,35,374,386);

note_text=compbl(" "||note_text);

note_text=TRANWRD(note_text,'.',' '); *replace full stops with spaces so that use of prxmatch function is easier;

note_text=TRANWRD(note_text,',',' '); *replace comma with dashes so that use of prxmatch function is easier;

note_text=TRANWRD(note_text,'/',' '); *replace slashes with dashes so that use of prxmatch function is easier;

note_text=TRANWRD(note_text,'\',' '); *replace slashes with dashes so that use of prxmatch function is easier;

note_text=TRANWRD(note_text,'(',' '); *replace bracket with dashes so that use of prxmatch function is easier;

note_text=TRANWRD(note_text,')',' '); *replace bracket with dashes so that use of prxmatch function is easier;

run;


proc sort data=donor_comment1 out=donor_comment_nodup1;

by donor_id descending note_type descending note_date;

run;

proc sort data=donor_comment_nodup1 nodupkey;

by donor_id descending note_type;

run;

proc sort data=donor_comment2 out=donor_comment_nodup2;

by donor_id descending note_type descending note_date;

run;

proc sort data=donor_comment_nodup2 nodupkey;

by donor_id descending note_type;

run;


proc transpose data=donor_comment_nodup1 out=trans_note_cdd1(drop=_name_ _label_) prefix=note1_;

by donor_id;

var note_text;

id note_type;

run;

proc transpose data=donor_comment_nodup2 out=trans_note_cdd2(drop=_name_ _label_) prefix=note2_;

by donor_id;

var note_text;

id note_type;

run;


data donors0;

merge donors00(in=a) trans_note_cdd1 trans_note_cdd2;

by donor_id;

if a;

run;


data donors;

set donors0;

if note1_40=note2_40 then note1_40=' ';
```

```
if note1_30=note2_30 then note1_30=' ';
if note1_35=note2_35 then note1_35=' ';
if note1_374=note2_374 then note1_374=' ';
if note1_386=note2_386 then note1_386=' ';
run;



%macro search(nums, group, terms);

        %local i num field;

                %let i=1;
                %let num=%scan(&nums,&i,%str( ));
                %do %while (&num ne);

                        %if &num=40 %then %let
field=cod;
                        %if &num=30 %then %let
field=pmh;
                        %if &num=386 %then %let
field=contra;
                        %if &num=35 %then %let
field=gen;
                        %if &num=374 %then %let
field=coroner;

                        ind_1_&group._&field. =
min(1, prxmatch( "m /&terms./ oi" , note1_&num.));
                        ind_2_&group._&field. =
min(1, prxmatch( "m /&terms./ oi" , note2_&num.));

                        %let i=%eval(&i+1);
                        %let
num=%scan(&nums,&i,%str( ));
                %end;

        risk1_&group.=0;
        if sum(of ind_1_&group._:)>0 then risk1_&group.=1;
        risk2_&group.=0;
        if sum(of ind_2_&group._:)>0 then risk2_&group.=1;

        risk_&group.= max(risk1_&group., risk2_&group.);
/*      risk_&group.= risk2_&group.;*/

%mend search;



%macro wrap ();

%search (40 374   386   ,  overdose,
        (OVERDOSE|OVER-DOSE| COCAIN| COCCAIN|
HEROIN| ECSTACY| EXTACY| KETAMINE| AMPHETAMINE| OPIOID|
BARBITURATE|
BENZODIAZEPINE|PARACETAMOL|PARACETEMOL|PARECETAMO
L|PARECETEMOL|ACETAMINOPHEN|OL-POISON|OL
POISON|CARBON-MONOXIDE|CARBON MONOXIDE|CO-
POISON|CO POISON)                       );

                                                        );

%search (40 374 30 386 35,              depression,
        (DEPRESSION|ANTIDEPRESS|ANTI-
DEPRESS|SUICIDE|SUICIDAL| JUMPED|SELF-POISON|SELF
POISON|SELF-HARM|SELF HARM)

                                                        );

%search (40 374 30 386 35,              alcohol,
        (ALCOHOLIC|ALCOHOL LIVER DISEASE|ALCOHOL
DISEASE|ALCOHOL ABUSE|ALCOHOL EXCESS|HEAVY
DRINK|DRINKS HEAVILY|DRUNK HEAVILY|DRANK HEAVILY|HIGH
ALCOHOL|ALCOHOL EXCESS|ALCOHOL DEPEND|ALCOHOL
MISUSE|ELEVATED ALCOHOL|ETOH |EXCESSIVE ALCOHOL)

                                                        );

%search (40 374 30 386 35,              drugs,
        (DRUG ABUSE|HEROIN| ECSTACY| EXTACY|
KETAMINE| AMPHETAMINE| OPIOID| BARBITURATE|
BENZODIAZEPINE)

        );

%search (40 374         30 386 35,      cocaine,
        (COCAIN| COCCAIN)

                                                                );

%search (40 374         30 386 35,      other,
        (ECSTACY| EXTACY| KETAMINE| AMPHETAMINE|
OPIOID| BARBITURATE| BENZODIAZEPINE)

        );

%search (40 374         30 386 35,      cannabis,
        (MARIJUANA|CANNAB|CANABIS)
                                        );

%search (40 374 30 386 35,              IV,
                (HEROIN|IV-DRUG| IV DRUG|
INTRAVENOUS DRUG| INTRA-VENOUS DRUG| INTRAVENOUS-
DRUG| INTRA-VENOUS-DRUG|IVDU|IVDA|IV DA|IV DU|INJECTED)
                                        );

%search (40 374 30 386 35,              HRSB,
        (SEX-WORKER|SEXWORKER|SEX
WORKER|PROSTITUTE|HIGH-RISK SEX|HIGH RISK SEX|HIGH-
RISK-SEX| MSM| GAY| HOMOSEXUAL| HOMO-SEXUAL)
                                                        );

%search (40 374 30 386 35,              prison,
        (PRISON| CUSTODY| JAIL| GAOL| INMATE| CONVICT)

                                        );


%search (40 374 30 386 35,              infection,              (
FLU | FLU-|INFLUENZA|H1N1| SWINE|BACTERIAL
MENINGITIS|BACTERIAL MENENGITIS|BACTERIAL
MENINGITUS|BACTERIAL MENENGITUS|BACTERIAL-
MENINGITIS|BACTERIAL-MENENGITIS|BACTERIAL-
MENINGITUS|BACTERIAL-MENENGITUS|PNEUMOCOCCAL| TB |
TB-| MTB | MTB-| TUBERCULOSIS|PNEUMONIA|SEPSIS
                                        );

%search (40 374 30 386 35,              encephalitis,
        (ENCEPHALITIS|ENCEPHALITUS|ENCEPHULITIS)


%search (40 374 30 386 35,  travel,
        (MALARIA| ASIA|AFRICA|SOUTH AMERICA|S
AMERICA|INDIA)
                                );

if dcod in (30,85) then risk_depression=1;

if dcod = 54 then risk_overdose=1;

if dcod = 80 then risk_alcohol=1;

if dcod = 81 then risk_overdose=1;

if dcod = 82 then risk_overdose=1;


%mend wrap;


%macro wrapdetail ();


%search (40 374 30 386 35,              inftub,
        ( TB | MTB | TUBERCULOSIS)                      );
```

```
%search (40 374 30 386 35,                infflu,
                ( FLU |INFLUENZA|H1N1| SWINE)                    );

%search (40 374 30 386 35,  travel,                                    (
MALARIA | AFRICA | ALGERIA | ANGOLA | BENIN | BOTSWANA |
BURKINA FASO | BURUNDI | CAMEROON | CAPE VERDE |
CENTRAL AFRICAN REPUBLIC | CHAD | DEMOCRATIC REPUBLIC
OF CONGO | DRC | REPUBLIC OF CONGO | IVOIRE | IVORY |
DJIBOUTI | EGYPT | EQUATORIAL GUINEA | ERITREA | ETHIOPIA |
GABON | GAMBIA | GHANA | GUINEA | GUINEA BISSAU | KENYA |
LESOTHO | LIBERIA | LIBYA | MADAGASCAR | MALAWI | MALI |
MAURITANIA | MAURITIUS | MOROCCO | MOZAMBIQUE | NAMIBIA
| NIGER | NIGERIA | REUNION | RWANDA | SAO TOME AND
PRINCIPE | SENEGAL | SEYCHELLES | SIERRA LEONE | SOMALIA
| SOUTH AFRICA | SOUTH SUDAN | SUDAN | SWAZILAND |
TANZANIA | TOGO | TUNISIA | UGANDA | ZAMBIA | ZIMBABWE |
SOUTH AMERICA | ARGENTINA | BOLIVIA | BRAZIL |  CHILE |
COLOMBIA | ECUADOR | FRENCH GUIANA | GUYANA | PARAGUAY
| PERU | SURINAME | URUGUAY | VENEZUELA | CENTRAL
AMERICA | BELIZE | COSTA RICA | EL SALVADOR | GUATEMALA |
HONDURAS | NICARAGUA | PANAMA | MEXICO | CARIBEAN |
CARRIBEAN | CARIBBEAN | JAMAICA | CUBA | HAITI | BARBADOS |
BAHAMAS | DOMINICAN | ARUBA | SAINT LUCIA | PUERTO RICO |
TRINIDAD | TOBAGO | GUADELOUPE | MARTINIQUE | GRENADA |
DOMINICA | ANTIGUA | BARBUDA | ASIA | AFGHANISTAN |
BAHRAIN | BANGLADESH | BHUTAN | BRUNEI | CAMBODIA |
CHINA | EAST TIMOR | HONG KONG | INDIA | INDONESIA | IRAN |
IRAQ | ISRAEL | JAPAN | JORDAN | KAZAKHSTAN | KOREA |
KUWAIT | KYRGYZSTAN | LAOS | LEBANON | MALAYSIA |
MALDIVES | MONGOLIA | MYANMAR | BURMA | NEPAL | OMAN |
PAKISTAN | PHILIPPINES | PHILLIPINES | QATAR | RUSSIA | SAUDI
ARABIA | SINGAPORE | SRI LANKA | SYRIA | TAIWAN | TAJIKISTAN
| THAILAND | TURKEY | TURKMENISTAN | UNITED ARAB
EMIRATES | UAE | UZBEKISTAN | VIETNAM | YEMEN | AUSTRALIA |
NEW ZEALAND));

%search (40 374 30 386 35,  malaria,       ( MALARIA | MALARONE |
MALARAI )                                                    );

%search (40 374 30 386 35,  travelinfe,      ( TRAVEL
|ZIKA|CHIKUNGUNYA|CHICKENGUNYA|CHIKUN|EBOLA|ARBOVIRU
S|WNV|WEST NILE VIRUS|DENGUE|H1N1|SWINE
FLU|HTLV|YELLOW FEVER|LASSA FEVER|VIRAL HAEMORRHAGIC
FEVER|CHAGAS|TRYPANASOMA CRUZI)
                                );

%search (40 374 30 386 35,  countriesB,     ( BAHAMAS|
BAHRAIN|BAKER ISLAND|BANGLADESH|COMILLA
CITY|BARBADOS|BELARUS|BELGIUM|BELIZE|BENIN|BERMUDA|B
HUTAN|CHUKHA|DAGANA|SAMTSE|SANDRUP|JON|ZHEMGANG|B
OLIVIA|BENIN|PANDO|SANTA
CRUZ|BORNEO|BOSNIA|HERZEGOVNIA|BOTSWANA|BOUVET
ISLAND|BRAZIL|AMAZONIA|ACRE|AMAPA|AMAZONAS|MARANHAO
|MATO GROSSO|PARA|RONDONIA|RORAMIA AND
TOCANTINS|PORTO VELHO|BOA VISTA|CRUZEIRO DO SOL|RIO
BRANCO|MACAPA|MANAUS|SAMTAREM|MARABA|BRITISH
VIRIGIN ISLAND|BRUNEI|DARUSSALAM|BULGARIA|BURKINA
FASO))

if risk_codparv=1 then risk_codpar=1;

if dcod = 30 then risk_histsuic=1;

if dcod = 85 then risk_histself=1;

if dcod = 85 then risk_histsuic=1;

if dcod = 54 then risk_codco=1;

if dcod = 80 then risk_codalc=1;

if dcod = 81 then risk_codpar=1;

if dcod = 81 then risk_codOD=1;

if dcod = 82 then risk_codother=1;

if dcod = 51 then risk_infpneu=1;

if dcod = 71 then risk_infsep=1;

if dcod = 70 then risk_infmen=1;

risk_infother=(dcod=72);

if past_alcohol_abuse=2 then risk_histalc=1;

if past_drug_abuse=2 then risk_histothdrug=1;

%mend wrapdetail;

data all_donors;

set donors;

/*%wrap();*/

%wrapdetail();

*if sum(of ind_:)>0 or dcod in (30,54,70,80,81,82,85);

/*if risk_TB OR risk_sex or risk_prison or risk_IV or risk_flu or
risk_meningitis then viral_risk=1;*/

/*if risk_drugs or risk_alcohol or risk_paracetamol or risk_CO or
risk_MSM or risk_hanging or risk_drowning or risk_suicide or
risk_overdose or risk_encephalitis or dcod in (30,54,80,81,82,85) then
organ_risk=1;*/

risky=(sum(of risk_:)>0);

run;

proc freq data=all_donors; table risk_:; where sod=1; run;
```

1.47 Appendix 2: SAS Code meningitis

```
data donors;
set standard.donors;
if mdy(01,01,2003)<=ddate<mdy(01,01,2015);
if dtype in (1,2);
if dCountry='UNITED KINGDOM';
if sod=1;
run;
proc freq data=donors;table dcod;
run;
data donorsinfo;
set standard.donors;
if dcountry='UNITED KINGDOM';
if donor_id in
(list of donor ids);if sod=1;
run;
ods graphics on;
run;
data note;set database.donor_comment; if donor_id=89087;run;
data kidney;
set standard.kidney_tx;
if mdy(01,01,2003)<=tx_date<mdy(01,01,2015);
if dtype in (1,2);
if txCountry='UNITED KINGDOM';
run;
proc sort data=kidney;
by donor_id;
run;
proc freq data=kidney;
table rec_unit;
run;
data kidneyUKM;
set kidney;
if donor_id in
(as above)''not actual code –abreviated for this thesis''
) then UKM='1';
else UKM='0';
run;=
data
data donors;
set standard.donors;
run;
proc sort data=donorsUKM;
by donor_id;
proc sort data=kidneyUKM;
by donor_id;
run;
data  kidneyUKM2;
merge kidneyUKM donors;
by donor_id;
if recip_id=. then delete;
run;
proc freq data=kidneyUKM2;
table UKM;
run;
proc freq data=kidneyUKM;
table Pcens;
run;
data Missing;
set kidneyUKM2;
if psurv=.;
run;
proc sort data=missing;
by recip_id;
run;
data all;
set standard.kidney_tx;
run;
proc sort data=all;
by recip_id;
run;
data Allmissing;
merge missing all;
by recip_id;
if UKM=. then delete;
run;
data Missing2;
set allmissing;
if psurv=. then delete;
rename tx_date=first_tx_date psurv=Patientdays
pcens=patientsurvival;
keep recip_id tx_date psurv pcens;
run;
proc sort data=missing2;
by recip_id;
run;
data missing3;
merge missing missing2;
by recip_id;
run;
data missing4;
set missing3;
if tx_date>first_tx_date then duration=tx_date-first_tx_date;
run;
data missing5;
set missing4;
if patientdays=>duration then psurvfinal=patientdays-duration;
run;
proc sort data=missing5;
by recip_id;
```

```
run;
proc sort data=kidneyUKM2;
by recip_id;
run;
data Kidneyall;
merge kidneyUKM2 missing5;
by recip_id;
run;
proc freq data=kidneyall;
table UKM;
run;
data Analysis;
set kidneyall;
if psurv=. then psurv=psurvfinal;
if pcens=. then pcens=patientsurvival;
run;
proc freq data=analysis;
table pcens;
run;
data analysis2;
set analysis;
if psurv=>3650 then psurvival=3650;
else psurvival=psurv;
if gsurv=>3650 then gsurvfinal=3650;
else gsurvfinal=gsurv;
if psurv=>3650 and pcens=1 then pcensor=0;
else pcensor=pcens;
if gsurv=>3650 and gcens=1 then gcensor=0;
else gcensor=gcens;
if rage>40 then rage_grp=2;
else recip_age_grp=1;
if dage>40 then dage_grp=2;
else donor_age_grp=1;
run;
proc freq data=analysis2;
table UKM;
run;



data analysis3;
set analysis2;
ptsurv= psurvival/365.25;
grsurv=gsurvfinal/365.25;
if dethnic=1 then ethnic=1;
else ethnic=2;
if rethnic=1 then recip_ethnic=1;
else recip_ethnic=2;
if graft_no=1 then Tx=1;
if graft_no=2 then Tx=2;
if graft_no>2 then Tx=3;
if crf_tx>85 then sensitised=1;
else sensitised=0;
if txcountry='UNITED KINGDOM';
if pcensor=. then delete;
if gcensor=. then delete;
if past_diabetes=1 then diabetes=1;
if past_diabetes=2 then diabetes=2;
if past_diabetes in (7,8) then diabetes=3;
if past_hypertension=1 then hypertension=1;
if past_hypertension=2 then hypertension=2;
if past_hypertension in (7,8) then hypertension=3;
if past_cardio_disease=1 then cardio=1;
if past_cardio_disease=2 then cardio=2;
if past_cardio_disease in (7,8) then cardio=3;
if past_alcohol_abuse=1 then alcohol=1;
if past_alcohol_abuse=2 then alcohol=2;
if past_alcohol_abuse in (7,8) then alcohol=3;
if past_liver_disease=1 then liver=1;
if past_liver_disease=2 then liver=2;
if past_liver_disease in (7,8) then liver=3;
if past_drug_abuse=1 then drug=1;
if past_drug_abuse=2 then drug=2;
if past_drug_absue in (7,8) then drug=3;
run;


proc freq data=analysis3;
table UKM;
run;
data analysisX;
set analysis3;
if UKM='0' and dage<40 and dtype=1 then Adjust=1;
if UKM='1' then adjust=2;
run;
proc freq data=analysisx;
table adjust;
run;
data analysisy;
set analysisx;
if donor_id in(as above ‘‘not actual code-abreviated for this thesis’’)
);
run;
proc print data=analysisy;
title 'Recipient ID from UKME donors';
var recip_id Ukm donor_id;
run;

/*survival analysis*/

proc lifetest data=analysisx notable plots=(S,LLS);
time ptsurv*pcensor(0);
strata adjust;
run;
proc lifetest data=analysis3 notable plots=(S,LLS);
time grsurv*gcensor(0);
strata UKM;
run;

/*proportionality of hazards*/
```

```
proc phreg data=analysis3;
class UKM;
model psurvival*pcensor(0)=UKM UKMt;
UKMt=UKM*log(psurvival);
test_proportionality: test UKMt;
run;

proc phreg data=analysis2;
class UKM;
model psurvival*pcensor(0)= UKM;
output out=schoen ressch=schUKM;
run;
data schoen;
set schoen;
logpsurvival=log(psurvival);
run;
proc loess data=schoen;
model schUKM=psurvival/smooth=(0.2 0.4 0.6 0.8);
run;
proc loess data=schoen plots=scoreplot;
model schUKM=logpsurvival/smooth=(0.2 0.4 0.6 0.8);
run;
/*Cox Hazards Model*/
proc phreg data=analysis3;
class UKM rsex rage_grp dage_grp HLA_GRP;
model psurvival*pcensor(0)=UKM rsex rage_grp dage_grp cld_isch
HLA_grp prd dtype dBMI dret_creat;
run;

/*Known Meningitis*/
data KM;
set analysis3;
if dcod=70 or donor_id in (83514,110501,80046,98482,
59763,71714,72577,74862,76751,90377

95722,102386,111621,64539,65259,67812,72570,85936,95968,10080
3,101518,104962,105756,75145,60045,60383,67812,69389,99593)
then KM='1';
else KM='0';
run;
data KM2;
set KM;
if donor_id in

(58028,58323,58656,59041,60981,61707,62369,63990,67774,68354,6
9512,71260,71288,71732,72867,72894

73885,76570,78835,79263,79508,80360,81256,81889,82668,8353383
144,83630,83911,84772,88300,88848

88880,88893,89094,93512,94350,94382,95461,99969,100000,102085
,105442,105726,109174,109546,110099,111727,71714,71887,80256,
82610,85062,87086,91968,105829,105902,107572,106743,104962,96
784,93440,80508,77453,75994,71746,71555,70730,69678,69389,685
85,67724,67289,64169,60383,60045,78432,95127,85746,88980,8920
2,106494,77900, 96615) then KM='0';
if txcountry= 'UNITED KINGDOM';
run;
proc freq data=KM2;
table KM;
run;
data km3;
set km2;
if km='1' then meningitis='2';
if ukm='1' then meningitis='1';
run;
proc freq data=km3;
table meningitis;
run;
data kidneywhoelse;set standard.kidney_tx;if donor_id in 125687

140709

data kmearly;set km3;if psurv<=30 and pcens=1 then early=1;run;
data kmearlyX;set kmearly; if donor_id=108133;run;
proc freq data=kmearly;table meningitis;run;
data kmearly2;set kmearly; if meningitis=2;run;
data notes;set database.recipient_note;if recip_id=111812;run;
data notes2;set database.grafted_organ_note;if tx_id=240198;run;
data notes3;set database.recip_ext_agency_death;if
recip_id=111812;run;
data kmnew;set km3;if psurv<=30 and pcens=1 then early=1;else
early=0;if meningitis=. then meningitis=3;run;
data kmnew2;set kmnew; if meningitis in (1,2)then menin=1;if
meningitis=3 then menin=2;run;
proc freq data=kmnew2;table menin*early/fisher;run;
proc freq data=kmnew; table meningitis*early/fisher;run;
data kmnew2;set kmnew; if meningitis in (1,2);if early=1;run;
proc freq data=kmnew2; table meningitis*rcod;run;
data kmnewstr;set kmnew;if rcod=522 then stroke=1;run;
data kmnewstroke;set kmnewstr;if pcens=1;if stroke=. then
stroke=0;run;
proc freq data=kmnewstroke; table meningitis*stroke/chisq;run;
I25.9;
data icds;set database.icd_code;if icd_code='E14.9';run;
data km4;
set km3;
if meningitis=. then meningitis='3';
if KM='0' and dage<40 and dtype=1 then adjusted='1';
if KM='1' then adjusted='2';
run;
proc freq data=km4;
table meningitis;
run;
data km5;
set km4;
if km='1' and dage<=40 then kmage=1;
if km='1' and dage>40 then kmage=2;
if km='0' and dage<=40 then kmage=3;
if km='0' and dage>40 then kmage=4;
run;
proc freq data=km5;
table HLA_GRP;
run;
data km6;
set km5;
if past_diabetes=. then diabetes=3;run;
/*Survival Analysis Known Meningitis*/
proc lifetest data=Km2 notable plots=(S,LLS);
time grsurv*gcensor(0);
```

```
strata KM;
run;
proc phreg data=km6;
class meningitis(ref='3') dtype(ref='1')HLA_GRP (ref='1')
diabetes(ref='1');
model psurvival*pcensor(0)=dage rage meningitis dtype HLA_GRP
diabetes;run;
data temp1;
a=1-CDF('CHISQUARE',43946.360 - 43941.697,2);
put a;
run;
proc phreg data=km5;
class kmage rsex meningitis HLA_GRP ethnic dtype diabetes cardio
hypertension past_smoker recip_ethnic ;
model psurvival*pcensor(0)=kmage rsex rage dage cld_isch HLA_grp
ethnic dtype diabetes cardio prd hypertension past_smoker
recip_ethnic prd;
run;
proc lifetest data=km4 plots=(S,LLS);
time ptsurv*pcensor(0);
strata meningitis;
run;
proc lifetest data=km4 notable plots=(S,LLS);
time grsurv*gcensor(0);
strata meningitis;
run;
proc freq data=km5; table rec_unit*meningitis/chisq;run;
data kmnew;set km5;if meningitis in (1,2) then test=1;else test=0;
run;

proc logistic data=kmnew;
class rec_unit;
model test=rec_unit;
run;



data km5;
set km4;
if UKM=1 then menin=1;if km=1 THEN MENIN=2;
IF ukm=0 AND km=0 THEN MENIN=0;
run;
PROC FREQ DATA=KM5;
TABLE REC_UNIT*menin;
RUN;
data kmX;
set km5;
if menin=>1 then alternate=1;
else alternate=0;
run;
data km7;
set kmx;
if alternate in (0,1) then transplant=1;
run;

proc freq data=kmx;
table alternate*rec_unit/chisq;
run;

proc npar1way data=kmx;
class alternate;
var rec_unit;
run;

data km6;
set km5;
if menin=>1;
run;
/*data updated tables*/
proc anova data=km4;
class meningitis;
model rage=meningitis;
means meningitis;
run;
proc freq data=km4;
table meningitis*rsex/chisq;
run;
proc freq data=km4;
table meningitis*recip_ethnic/chisq;
run;
proc freq data=km4;
table meningitis*sensitised/chisq;
run;
proc anova data=km4;
class meningitis;
model wait_time=meningitis;
means meningitis;
run;
proc npar1way data=km4;
class meningitis;
var wait_time;
run;
proc freq data=km4;
table meningitis*Tx/chisq;
run;
proc freq data=km4;
table meningitis*HLA_grp/chisq;
run;
proc freq data=km4;
table meningitis*prd;
run;
proc univariate data=km4;
class meningitis;
var prd;
run;
proc freq data=km4;
table rsex*meningitis/chisq;
run;

 proc npar1way data=km4;
 class meningitis;
```

```
 var prd;
 run;
/*Data for Tables-UKM-Donors*/
data analysisX;
set analysis3;
if UKM=1;
run;

proc freq data=analysis3;
table UKM;
run;
proc univariate data=analysis3;
class UKM;
var rage dage cld_isch crf_tx wait_time;
histogram;
run;
proc ttest data=Analysis3;
class UKM;
var rage;
run;
proc ttest data=analysis3;
class UKM;
var dage;
run;

proc freq data=analysis3;
table UKM*rsex/chisq;
where rsex in (1,2);
run;
proc freq data=analysis3;
table UKM*Dsex/chisq;
run;
proc freq data=analysis3;
table UKM*recip_ethnic/chisq;
run;
proc npar1way data=analysis3;
class UKM;
var cld_isch;
run;
proc npar1way data=analysis3;
class UKM;
var wait_time;
run;
proc freq data=analysis3;
table UKM*Tx/chisq;
run;
proc freq data=analysis3;
table UKM*sensitised/chisq;
run;
proc freq data=analysis3;
table UkM*gcensor;
where gcensor=1 and gsurvfinal<365.25;
run;
proc freq data=analysis3;
table UkM*gcensor;
run;
proc freq data=analysis3;
table UKM*pcensor;
run;
proc univariate data=analysis3;
class UKM;
var DBMI;
histogram;
run;
proc npar1way data=analysis3;
class UKM;
var dbmi;
run;
proc freq data=analysis3;
table UKM*COF;
run;
proc npar1way data=analysis3;
class UKM;
var cof;
run;
proc freq data=analysis3;
table UKM*PRD;
run;
proc npar1way data=analysis3;
class UKM;
var prd;
run;

proc univariate data=analysis3;
class UKM;
var prd;
run;
proc freq data=analysis3;
table UKM*RCOD;
run;
proc npar1way data=analysis3;
class UKM;
var rcod;
run;
proc freq data=analysis3;
table UKM*dtype/chisq;
run;
proc univariaTE DATa=analysis;
class UKM;
var rbmi;
run;
proc npar1way data=analysis3;
class UKm;
var rbmi;
run;
proc univariate data=analysis3;
class UKM;
var dret_creat;
```

```
histogram;
run;
proc npar1way data=analysis3;
class UKM;
var dret_creat;
run;
proc freq data=analysis3;
table UKM*hypertension/chisq;
run;
proc freq data=analysis3;
table UKM*diabetes/chisq;
run;
proc freq data=analysis3;
table UKM*liver/chisq;
run;
proc freq data=analysis3;
table UKM*drug/chisq;
run;
proc freq data=analysis3;
table UKM*alcohol/chisq;
run;
proc freq data=analysis3;
table UKM*cardio/chisq;
run;
data wcc;
set database.dcsd_organ_donor;
run;
proc sort data=wcc;
by donor_id;
run;
proc sort data=analysis3;
by donor_id;
run;
data wccUKm;
merge wcc analysis3;
by donor_id;
if UKM=. then delete;
run;
proc sort data=wccukm nodupkey;
by recip_id;
run;
proc univariate data=wccukm;
class UKM;
var white_cells;
run;
proc npar1way data=wccukm;
class UKM;
var white_cells;
run;
data wccukm2;
set wccukm;
if donor_id=105726;
run;
data cardiff;
set analysis3;
if uKM=1;
run;
data cardiff2;
set cardiff;
if rcod=534 then cardiff=1;
else cardiff=0;
run;
proc univariate data=cardiff2;
class cardiff;
var dage;
run;

/*Data for tables-KM-Donors*/
proc freq data=KM2;
table KM;
run;
proc univariate data=KM2;
class KM;
var rage dage cld_isch crf_tx wait_time;
histogram;
run;
proc ttest data=Km2;
class KM;
var rage;
run;
proc ttest data=KM2;
class KM;
var dage;
run;
proc freq data=Km2;
table KM*rsex/chisq;
run;
proc freq data=KM2;
table KM*Dsex/chisq;
where dsex in (1,2);
run;
proc freq data=KM2;
table KM*ethnic/chisq;
run;
proc freq data=KM2;
table KM*recip_ethnic/chisq;
run;
proc npar1way data=Km2;
class KM;
var cld_isch;
run;
proc npar1way data=Km2;
class KM;
var wait_time;
run;
proc freq data=Km2;
table KM*Tx/chisq;
```

```
run;
proc freq data=Km2;
table KM*sensitised/chisq;
run;
proc freq data=Km2;
table KM*COF;
run;
proc npar1way data=km2;
class KM;
var cof;
run;
proc freq data=KM2;
table KM*RCOD;
run;
proc npar1way data=km2;
class KM;
var rcod;
run;
proc freq data=km2;
table KM*prd;
run;
proc npar1way data=km2;
class KM;
var prd;
run;
proc univariate data=km2;
class KM;
var dbmi;
run;
proc npar1way data=Km2;
class KM;
var dbmi;
run;
proc univariate data=km2;
class km;
var dret_creat;
run;
proc npar1way data=km2;
class km;
var dret_creat;
run;
proc freq data=Km2;
table KM*dtype/chisq;
run;
data analyses4;
set analysis3;
if pcens=1 and psurv<365.25;
run;
proc sort data=analyses4;
by donor_id;
run;
data wcc;
set database.dcsd_organ_donor;
run;
proc sort data=wcc;
by donor_id;
run;
proc sort data=km2;
by donor_id;
run;
data km2allinfo;
merge km2 wcc;
by donor_id;
if km=. then delete;
run;
proc sort data=km2allinfo nodupkey;
by recip_id;
run;
proc freq data=km2allinfo;
table KM;
run;

proc univariate data=km2allinfo;
class KM;
var WHITE_CELLS;
run;
proc npar1way data=km2allinfo;
class KM;
var white_cells;
run;

/*Kidney survival since listing*/
data wait;
set standard.kidwait;
if mdy(01,01,2000)<=adate_on<mdy(01,01,2015);
run;
proc sort data=wait;
by recip_id;
run;
proc sort data=analysis3;
by recip_id;
run;
data kidneywait;
merge analysis3 wait;
by recip_id;
run;
data UKMkidneywait;
set kidneywait;
if endstat in('D','DA','DS') or pcensor=1 then pcenslisting=1;
else pcenslisting=0;
run;
data UKMkidneywait2;
set Ukmkidneywait;
if psurvival=>0 and wtime=>0 then survivaltime=psurvival + wtime;
if wtime=>0 and psurvival=. then survivaltime=wtime;
if psurvival=>0 and wtime=. then survivaltime=psurvival;
run;
data UKMkidneywait3;
```

```
set Ukmkidneywait2;
if pcenslisting=1 and survivaltime>3652.5 then pcens10=0 and
survivaltime=3652.5;
if pcenslisting=0 and survivaltime>3652.5 then pcens10=0;
if survivaltime>3652.5 then survivaltime=3652.5;
else pcens10=pcenslisting;
run;
data UKMkidneywait4;
set Ukmkidneywait3;
survival10=survivaltime/365.25;
if UKM=1 then unknown=3;
if UKM=0 then unknown=2;
if ukm=. then unknown=1;
run;
data ukmkidneywaitX;
set ukmkidneywait4;
if UKM=1;
run;
proc freq data=ukmkidneywait4;
table unknown;
run;
data ukmkidneywait5;
set ukmkidneywait4;
if UKM=1 and gcensor=. then delete;
run;
data ukmXX;
set ukmkidneywait5;
if UKM=1;
run;

proc lifetest data=Ukmkidneywait5  notable plots=(S,LLS);
time survival10*pcens10(0);
strata unknown;
run;

/*Survival from listing Known meningitis Kidney*/
proc sort data=km4;
by recip_id;
run;
data knownwait;
merge km4 wait;
by recip_id;
run;
data Kmwaitkidney;
set knownwait;
if endstat in('D','DA','DS') or pcensor=1 then pcenslisting=1;
else pcenslisting=0;
run;
data knownwaitkidney2;
set Kmwaitkidney;
if psurvival=>0 and wtime=>0 then survivaltime=psurvival + wtime;
if wtime=>0 and psurvival=. then survivaltime=wtime;
if psurvival=>0 and wtime=. then survivaltime=psurvival;
run;
data knownwaitkidney3;
set knownwaitkidney2;
if pcenslisting=1 and survivaltime>3652.5 then pcens10=0;
if survivaltime>3652.5 then survivaltime=3652.5;
if pcenslisting=0 and survivaltime>3652.5 then pcens10=0;
else pcens10=pcenslisting;
run;
data knownwaitkidney4;
set knownwaitkidney3;
survival10=survivaltime/365.25;
if KM=1 then known=3;
if Km=0 then known=2;
if km=. then known=1;
run;
proc freq data=knownwaitkidney4;
table known;
run;
data knownwaitkidney5;
set knownwaitkidney4;
if survival10=. then delete;
run;
proc lifetest data=knownwaitkidney5 notable plots=(S,LLS);
time survival10*pcens10(0);
strata known;
where known in (1,3);
run;

/*Liver analysis-UKM*/
data liver;
set standard.liver_tx;
if mdy(01,01,2003)<=tx_date<mdy(01,01,2015);
if dtype in (1,2);
run;
proc sort data=liver;
by donor_id;
run;
data liverethnic;
set standard.donors;
run;
proc sort data=liverethnic;
by donor_id;
run;
data liver1;
merge liver liverethnic;
by donor_id;
if recip_id=. then delete;
run;

proc sort data=liver;
by donor_id;
run;
data liverUKM;
set liver1;
if donor_id in
(as above-''not actual code-abreviated for this thesis'
```

```
) then UKM='1';
else UKM='0';
run;

/*Missing data*/
data LiverMissing;
set liverUKM;
if psurv=.;
run;
proc sort data=livermissing;
by recip_id;
run;
data allliver;
set standard.liver_tx;
run;
proc sort data=allliver;
by recip_id;
run;
data alllivermissing;
merge livermissing allliver;
by recip_id;
if UKM=. then delete;
run;
data livermissing2;
set alllivermissing;
if psurv=. then delete;
rename tx_date=first_tx_date psurv=patientdays pcens=patientsurvival;
keep recip_id donor_id tx_date psurv pcens;
run;
proc sort data=livermissing2;
by recip_id;
run;
proc sort data=liverukm;
by recip_id;
run;
data liverUKM2;
merge liverukm livermissing2;
by recip_id;
if tx_date >first_tx_date then duration=tx_date-first_tx_date;
run;
data liverUKM3;
set liverUKM2;
if patientdays=>duration then psurvfinal=patientdays-duration;
run;
data LiverUKM4;
set liverUKM3;
if psurv=. then psurv=psurvfinal;
if pcens=. then pcens=patientsurvival;
run;
data liverUKM5;
set liverukm4;
if psurv>1826.5 then psurvival=1826.5;
else psurvival=psurv;
if gsurv>1826.5 then gsurvival=1826.5;
else gsurvival=gsurv;
if pcens=1 and psurv>1826.5 then pcensor=0;
else pcensor=pcens;
if gcens=1 and gsurv>1826.5 then gcensor=0;
else gcensor=gcens;
if psurv=. then delete;
run;
data LUKMSA;
set liverukm5;
ptsurv=psurvival/365.25;
grsurv=gsurvival/365.25;
if dethnic=1 then ethnic=1;
else ethnic=2;
if rethnic=1 then recip_ethnic=1;
else recip_ethnic=2;
if graft_no=1 then Tx=1;
if graft_no=2 then Tx=2;
if graft_no>2 then Tx=3;
if crf_tx>85 then sensitised=1;
else sensitised=0;
if txcountry='UNITED KINGDOM';
if pcensor=. then delete;
if gcensor=. then delete;
if past_diabetes=1 then diabetes=1;
if past_diabetes=2 then diabetes=2;
if past_diabetes in (7,8) then diabetes=3;
if past_hypertension=1 then hypertension=1;
if past_hypertension=2 then hypertension=2;
if past_hypertension in (7,8) then hypertension=3;
if past_cardio_disease=1 then cardio=1;
if past_cardio_disease=2 then cardio=2;
if past_cardio_disease in (7,8) then cardio=3;
if past_alcohol_abuse=1 then alcohol=1;
if past_alcohol_abuse=2 then alcohol=2;
if past_alcohol_abuse in (7,8) then alcohol=3;
if past_liver_disease=1 then liver=1;
if past_liver_disease=2 then liver=2;
if past_liver_disease in (7,8) then liver=3;
if past_drug_abuse=1 then drug=1;
if past_drug_abuse=2 then drug=2;
if past_drug_abusee in (7,8) then drug=3;
if rhcv=1 then rhepc=1;
if rhcv=2 then rhepc=2;
if rhcv in (3,4,5,6,7,8) then rhepc=3;
if hcv=1 then hepC=1;
if hcv=2 then hepC=2;
if hcv in (3,4,5,6,7,8) then hepc=3;
run;
data lukmsa2;
set lukmsa;
if Ukm=1;
run;
proc print data=lukmsa2;
title 'liver recip_id ukme donors';
```

```
var recip_id ukm donor_id;
run;

/*SA for Liver UKM*/
proc lifetest data=LUKMSA notable plots=(S,LLS);
time ptsurv*pcensor(0);
strata UKM;
run;
proc lifetest data=lukmsa  plots=(S,LLS);
time grsurv*gcensor(0);
strata UKM;
run;
/*Proportionality of Hazards*/

proc phreg data=analysis2;
class UKM;
model psurvival*pcensor(0)=UKM UKMt;
UKMt=UKM*log(psurvival);
test_proportionality: test UKMt;
run;

/*Liver Tx Known Cause Meningitis*/
data liverKM;
set lUKMSA;
if dcod=70 or donor_id in (as above-not actuial code abbreviated for
this thesis'')
) then KM='1';
else KM='0';
run;
data LiverKm2;
set liverkm;
if donor_id in
(as above, not actual code abbreviated for this thesis'')
);run;

proc freq data=liverkm6;table recip_id*rcod;run;
/*updated tables*/
proc anova data=liverkm4;
class meningitis;
model rage=meningitis;
means meningitis;
run;
proc freq data=liverkm4;
table meningitis*urgent/chisq;
run;
proc anova data=liverkm4;
class meningitis;
model ukeld=meningitis;
means meningitis;
run;
proc anova data=liverkm4;
class meningitis;
model =meningitis;
means meningitis;
run;

proc freq data=liverkm4;
table meningitis*rsex/chisq;
where rsex in (1,2);
run;
proc freq data=liverkm4;
table meningitis*recip_ethnic/chisq;
run;
proc freq data=liverkm4;
table meningitis*rhepc/chisq;
run;
proc freq data=liverkm4;
table meningitis*graft_no/chisq;
run;
proc freq data=liverkm4;
table meningitis*pld;
run;
proc univariate data=liverkm4;
class meningitis;
var pld;
run;

proc univariate data=liverkm4;
class meningitis;
var pld;
run;
proc npar1way data=liverkm4;
class meningitis;
var pld;
run;
/*data for Tables-Liver UKM*/
proc freq data=LUKMSA;
table UKM;
run;
proc freq data=LUKMSA;
table UKM*past_diabetes/chisq;
where past_drug_abuse in (1,2);
run;

proc freq data=liverKM2;
table KM;
run;
proc univariate data=LUKMSA;
class UKM;
var rage dage cit;
run;
proc ttest data=lukmsa;
class UKM;
var rage;
run;
proc freq data=lukmsa;
table UKM*rsex/chisq;
where rsex in (1,2);
run;
proc freq data=lukmsa;
```

```
table UKM*urgent/chisq;
run;

proc freq data=LUKMSA;
table UKM*dsex/chisq;
where dsex in (1,2);
run;
proc freq data=LUKMSA;
table UKM*dtype/chisq;
run;
proc npar1way data=lukmsa;
class UKM;
var cit;
run;
data lukmsas;
set lukmsa;
if rethnic=1 then recip_ethnic=1;
else recip_ethnic=2;
if dethnic=1 then donor_ethnic=1;
else donor_ethnic=2;
if RHCV=1 then HCV=1;
if RHCV=2 then HCV=2;
if RHCV in (6,7,8,9) then HCV=3;
run;
proc freq data=lukmsas;
table UKM*recip_ethnic/chisq;
run;
proc freq data=lukmsas;
table UKM*donor_ethnic/chisq;
run;
proc univariate data=lukmsa;
class UKM;
var UKELD;
histogram;
run;
proc npar1way data=lukmsa;
class UKM;
var UKELD;
run;
proc freq data=lukmsa;
table UKM*COF;
run;
proc freq data=lukmsa;
table UKM*RCOD;
where RCOD>1;
run;
proc freq data=lukmsas;
table UKM*HCV/chisq;
run;
data lukmsas2;
set lukmsa;
if ukm=1 and pcens=1 and psurv<365.25;
run;

/* Known Meningitis Data*/
proc freq data=liverkm2;
table KM;
run;
proc freq data=liverKM2;
table KM;
run;
proc univariate data=liverkm2;
class KM;
var rage dage cit;
run;
proc ttest data=liverkm2;
class KM;
var dage;
run;
proc ttest data=liverkm2;
class KM;
var rage;
run;
proc freq data=liverkm2;
table KM*dsex/chisq;
where dsex in (1,2);
run;
proc freq data=liverkm2;
table KM*rsex/chisq;
where rsex in (1,2);
run;
proc freq data=liverkm2;
table KM*urgent/chisq;
run;

proc freq data=liverkm2;
table KM*dtype/chisq;
run;
proc npar1way data=liverkm2;
class KM;
var cit;
run;
proc univariate data=liverkm2;
class KM;
var cit;
run;
proc freq data=liverkm2;
table KM*pcens;
where pcens=1 and psurv<365.25;
run;
proc freq data=liverkm2;
table KM*gcens;
where gcens=1 and gsurv<365.25;
run;
data liverkm2s;
set liverkm2;
if rethnic=1 then recip_ethnic=1;
else recip_ethnic=2;
```

```
if dethnic=1 then donor_ethnic=1;
else donor_ethnic=2;
if RHCV=1 then HCV=1;
if RHCV=2 then HCV=2;
if RHCV in (6,7,8,9) then HCV=3;
run;
proc freq data=liverkm2s;
table KM*recip_ethnic/chisq;
run;
proc freq data=liverkm2s;
table km*donor_ethnic/chisq;
run;

proc univariate data=liverkm2;
class KM;
var UKELD;
histogram;
run;
proc npar1way data=liverkm2;
class KM;
var UKELD;
run;
proc freq data=liverkm2;
table KM*COF;
run;
proc freq data=liverkm2;
table KM*RCOD;
where RCOD>1;
run;
proc freq data=liverkm2s;
table KM*HCV/chisq;
run;

/*Survival Analysis From Listing*/
data waitlist;
set standard.livwait;
run;
data waitlist2;
set waitlist;
if endstat in ('D','DA','DS');
run;
proc sort data=waitlist;
by recip_id;
run;
proc sort data=lukmsa;
by recip_id;
run;
data UKMwaitlist;
merge lukmsa waitlist;
by recip_id;
if mdy(01,01,2000)<=adate_on<mdy(01,01,2015);
run;
data UKMwaitlist2;
set ukmwaitlist;
if endstat in('D','DA','DS') or pcensor=1 then pcenslisting=1;
else pcenslisting=0;
run;
data UKMwaitlist3;
set ukmwaitlist2;
if psurvival=>0 and rwtime=>0 then survivaltime=psurvival + rwtime;
if psurvival=>0 and suwtime=>0 and rwtime=. then
survivaltime=psurvival+suwtime;
if rwtime=>0 and psurvival=. then survivaltime=rwtime;
if suwtime=>0 and psurvival=. then survivaltime=suwtime;
run;
data UKMwaitlist4;
set ukmwaitlist3;
if pcenslisting=1 and survivaltime>1826.25 then pcens10=0 and
survivaltime=1826.25;
else pcens10=pcenslisting;
if survivaltime>1826.25 then survivaltime=1826.25;
run;
data UKMwaitlist5;
set ukmwaitlist4;
survival10=survivaltime/365.25;
if UKM=1 then Unknown=3;
if UKM=0 then unknown=2;
if UKM=. then unknown=1;
run;
proc freq data=ukmwaitlist5;
table Unknown*pcens10;
run;
proc lifetest data=ukmwaitlist5 notable plots=(S,LLS);
time survival10*pcens10(0);
strata unknown;
run;

/*known meningitis listing*/
proc sort data=liverkm2;
by recip_id;
run;
data KMwaitlist;
merge liverkm2 waitlist;
by recip_id;
if mdy(01,01,2000)<=adate_on<mdy(01,01,2015);
run;
data KMwaitlist2;
set kmwaitlist;
if endstat in('D','DA','DS') or pcensor=1 then pcenslisting=1;
else pcenslisting=0;
run;
data KMwaitlist3;
set kmwaitlist2;
if psurvival=>0 and rwtime=>0 then survivaltime=psurvival + rwtime;
if psurvival=>0 and suwtime=>0 and rwtime=. then
survivaltime=psurvival+suwtime;
if rwtime=>0 and psurvival=. then survivaltime=rwtime;
if suwtime=>0 and psurvival=. then survivaltime=suwtime;
run;
```

```
data KMwaitlist4;
set kmwaitlist3;
if pcenslisting=1 and survivaltime>1826.25 then pcens10=0 and
survivaltime=1826.25;
else pcens10=pcenslisting;
if survivaltime>1826.25 then survivaltime=1826.25;
run;
data KMwaitlist5;
set kmwaitlist4;
survival10=survivaltime/365.25;
if KM=1 then known=3;
if KM=0 then known=2;
if Km=. then known=1;
run;
proc freq data=ukmwaitlist5;
table known*pcens10;
run;
proc lifetest data=kmwaitlist5 notable plots=(S,LLS);
time survival10*pcens10(0);
strata known;
run;
*
;

proc lifetest data=analysis3 outsurv=dosurv2 notable plots=(S,LLS);
time ptsurv*pcensor(0);
strata UKM;
run;

data dom1;
set analysis2;
gsurvfin=gsurvfinal/365.25;
run;

proc lifetest data=dom1 outsurv=dosurv2 notable plots=(S,LLS);
time gsurvfin*gcensor(0);
strata UKM;
run;


/*Kidney Known Meningitis-Patient and Graft Survival*/
data dom2;
set km2;
gsurvfin=gsurvfinal/365.25;
psurvfin=psurvival/365.25;
run;

proc lifetest data=dom2 outsurv=dosurv2 notable  plots=(S,LLS);
time psurvfin*pcensor(0);
strata KM;
run;

proc lifetest data=dom2 outsurv=dosurv2 notable plots=(S,LLS);
time gsurvfin*gcensor(0);
strata KM;
run;

/*Liver Unknown Meningitis-Patient and Graft Survival*/
proc lifetest data=LUKMSA outsurv= dosurv2 notable plots=(S,LLS);
time ptsurv*pcensor(0);
strata UKM;
run;
proc lifetest data=lukmsa outsurv= dosurv2 notable plots=(S,LLS);
time grsurv*gcensor(0);
strata UKM;
run;
/*liver Known Meningitis-Patient and Graft Survival*/
proc lifetest data=liverKm2 outsurv=dosurv2 notable plots=(S,LLS);
time ptsurv*pcensor(0);
strata KM;
run;
proc lifetest data=liverKm4 outsurv=dosurv2 notable plots=(S,LLS);
time grsurv*gcensor(0);
strata meningitis;
run;
/*Thanks*/
/*Heart Meningitis and Unknown Meningitis*/
data Heart;
set standard.cardio_tx;
if mdy(01,01,2003)<=tx_date<mdy(01,01,2015);
if dtype in (1,2);
run;
proc sort data=heart;
by recip_id;
run;
data HeartKM;
set heart;
if dcod=70 or donor_id in (as above
) then KM='1';
else KM='0';
run;
data heartUKM;
set heartKM;
if donor_id in
(as above
) then KM='0';
run;
data heartUK;
set heartUKM;
if donor_id in
(as above)
) then UKM=1;
else UKM=0;
run;
proc freq data=heartUK;
table UKM*organ;
run;
data heartall;
set standard.cardio_tx;
```

```
run;
data heartukm2;
set heartuk;
if psurv=.;
run;
proc sort data=heartall;
by recip_id;
run;
proc sort data=heartUKM2;
by recip_id;
run;
data heartallmissing;
merge heartukm2 heartall;
by recip_id;
if KM=. then delete;
run;
data heartmissing;
set heartallmissing;
if psurv=. then delete;
rename tx_date=first_tx_date psurv=patientdays pcens=patientsurvival;
keep recip_id donor_id tx_date psurv pcens;
run;
proc sort data=heartmissing;
by recip_id;
run;
proc sort data=heartukm;
by recip_id;
run;
data heartall;
merge heartuk heartmissing;
by recip_id;
if tx_date >first_tx_date then duration=tx_date-first_tx_date;
run;
data heartall2;
set heartall;
if patientdays=>duration then psurvfinal=patientdays-duration;
run;
data heartall3;
set heartall2;
if psurv=. then psurv=psurvfinal;
if pcens=. then pcens=patientsurvival;
run;
data heartall4;
set heartall3;
if psurv>1826.25 then psurvival=1826.25;
else psurvival=psurv;
if gsurv>1826.25 then gsurvival=1826.25;
else gsurvival=gsurv;
if pcens=1 and psurv>1826.25 then pcensor=0;
else pcensor=pcens;
if gcens=1 and gsurv>1826.25 then gcensor=0;
else gcensor=gcens;
run;
data heartall5;
set heartall4;
ptsurv=psurvival/365.25;
grsurv=gsurvival/365.25;
if dnation='OVERSEAS' then delete;
if Txnation='OVERSEAS' then delete;
if pcensor=. then delete;
if km='1' then meningitis='2';
if ukm='1' then meningitis='1';
if dethnic=1 then ethnic=1;
else ethnic=2;
if rethnic=1 then recip_ethnic=1;
else recip_ethnic=2;
if graft_no=1 then Tx=1;
if graft_no=2 then Tx=2;
if graft_no>2 then Tx=3;
if crf_tx>85 then sensitised=1;
else sensitised=0;
if txcountry='UNITED KINGDOM';
if pcensor=. then delete;
if gcensor=. then delete;
if past_diabetes=1 then diabetes=1;
if past_diabetes=2 then diabetes=2;
if past_diabetes in (7,8) then diabetes=3;
if past_hypertension=1 then hypertension=1;
if past_hypertension=2 then hypertension=2;
if past_hypertension in (7,8) then hypertension=3;
if past_cardio_disease=1 then cardio=1;
if past_cardio_disease=2 then cardio=2;
if past_cardio_disease in (7,8) then cardio=3;
if past_alcohol_abuse=1 then alcohol=1;
if past_alcohol_abuse=2 then alcohol=2;
if past_alcohol_abuse in (7,8) then alcohol=3;
if past_liver_disease=1 then liver=1;
if past_liver_disease=2 then liver=2;
if past_liver_disease in (7,8) then liver=3;
if past_drug_abuse=1 then drug=1;
if past_drug_abuse=2 then drug=2;
if past_drug_abusee in (7,8) then drug=3;
if rhcv=1 then rhepc=1;
if rhcv=2 then rhepc=2;
if rhcv in (3,4,5,6,7,8) then rhepc=3;
if hcv=1 then hepC=1;
if hcv=2 then hepC=2;
if hcv in (3,4,5,6,7,8) then hepc=3;
run;
proc freq data=km3;
table meningitis;
run;
data heartall6;
set heartall5;
if meningitis=. then meningitis='3';
run;
data heartall7;
set heartall6;
```

```
if ukm=1 then meningitis=1;
if km=1 then meningitis=2;
run;
proc freq data=heartall7;table meningitis;run;
proc print data=heartall7;
title 'heart recip-id ukme donors';
var recip_id ukm donor_id;
run;
proc freq data=heartall5;
table KM*tx_type;
run;
/*updated heart table*/
proc freq data=heartall7;
table meningitis;
run;
proc anova data=heartall6;
class meningitis;
model rage=meningitis;
means meningitis;
run;
proc freq data=heartall6;
table meningitis*rsex/chisq;
run;
proc freq data=heartall6;
table meningitis*recip_ethnic/chisq;
run;
proc freq data=heartall6;
table meningitis*graft_no/chisq;
run;
proc freq data=heartall6;
table meningitis*urgent/chisq;
run;
proc freq data=heartall6;
table meningitis*pcd/chisq;
run;
proc univariate data=heartall6;
class meningitis;
var pcd;
run;
data donornotes;set database.donor_comment;if donor_id in (70730,
84772);run;
data heartall7;set heartall6;if psurv<=30 then early=1;else early=0;run;
proc freq data=heartall7; table meningitis;run;
data heartall8;set heartall7;if meningitis in (1,2);if early=1;keep recip_id
psurv pcens meningitis donor_id rcod;run;
data heartall8;set heartall7; if donor_id in  (70730,
84772);run;
data heartall9;set heartall8;if pcens=1;if stroke=. then stroke=0;run;
proc freq data=heartall9;table meningitis*stroke/fisher;run;
data heartall10;set heartall9;if stroke=1; if meningitis in (1,2);run;
data notes;set database.recipient_note;if recip_id in
(122117
182170);run;
data donorsnotes;set database.donor_comment;if
donor_id=108133;run;
/* donors*/
data donors;
set standard.donors;
if donor_id in
(70730,
84772);run;
/*SA known cause Meningitis Heart Tx*/
proc lifetest data=heartall5  plots=(S,LLS);
time ptsurv*pcensor(0);
strata KM;
where tx_type=30;
run;
proc lifetest data=heartall5 plots=(S,LLS);
time grsurv*gcensor(0);
strata KM;
where tx_type=30;
run;
proc lifetest data=heartall6  plots=(S,LLS);
time ptsurv*pcensor(0);
strata meningitis;
run;
proc lifetest data=heartall6 notable  plots=(S,LLS);
time grsurv*gcensor(0);
strata meningitis;
run;
/*Lung known meningitis*/
proc lifetest data=heartall5  plots=(S,LLS);
time ptsurv*pcensor(0);
strata KM;
where tx_type in (60,61,62,63,65,66);
run;
proc lifetest data=heartall5 plots=(S,LLS);
time grsurv*gcensor(0);
strata KM;
where tx_type=30;
run;
/*SA unknown cause Meningitis heart Tx*/
proc lifetest data=heartall5 notable plots=(s,LLS);
time ptsurv*pcensor(0);
strata UKM;
where tx_type=30;
run;
proc lifetest data=heartall5  plots=(s,LLS);
time grsurv*gcensor(0);
strata UKM;
where tx_type=30;
run;
proc lifetest data=heartall5 notable plots=(s,LLS);
time ptsurv*pcensor(0);
strata UKM;
where tx_type in (60,61,62,63,64,65,66);
run;
proc freq data=heartall5;
table UKM*rcod;
```

```
where pcens=1 and ptsurv<1;
run;
proc freq data=heartall5;
table UKM*cof;
where pcens=1 and ptsurv<1;
where tx_type=30;
run;
data heartcod;
set heartall5;
if pcens=1;
if UKM=1;
where tx_type=30;
run;
data codcomment;
set database.recipient_note;
if recip_id in (102596, 122117, 136814, 140065, 183762);
run;
data codcomment2;
set database.grafted_organ_note;
if donor_id in (59041, 71714, 88848, 78835, 109174, 105726);
run;
/*Heart Data Tables*/
proc freq data=heartall5;
table KM;
where tx_type=30;
run;
proc freq data=heartall5;
table KM*COf;
run;
proc univariate data=heartall5;
class KM;
var rage;
where tx_type=30;
run;
proc ttest data=heartall5;
class KM;
var dage;
where tx_type=30;
run;
data heartall6;
set heartall5;
if tx_type=30;
if rethnic=1 then ethnic=1;
else ethnic=2;
run;
proc freq data=heartall6;
table KM*dsex/chisq;
where dsex in (1,2);
run;
proc freq data=heartall6;
table UKM;
run;
proc freq data=heartall6;
table KM*dtype/chisq;
run;
proc univariate data=heartall6;
class KM;
var rage;
run;
proc ttest data=heartall6;
class KM;
var rage;
run;
proc freq data=heartall6;
table KM*rsex/chisq;
where rsex in (1,2);
run;
proc freq data=heartall6;
table KM*ethnic/chisq;
run;
proc freq data=heartall6;
table KM*urgent/chisq;
run;
proc freq data=heartall6;
table UKM*urgent/chisq;
run;
proc univariate data=heartall6;
class UKM;
var dage;
run;
proc ttest data=heartall6;
class UKM;
var dage;
run;
proc freq data=heartall6;
table UKM*dsex/chisq;
where dsex in (1,2);
run;
proc freq data=heartall6;
table UKM*dtype/chisq;
where dsex in (1,2);
run;
proc univariate data=heartall6;
class UKM;
var rage;
run;
proc ttest data=heartall6;
class UKM;
var rage;
run;
proc freq data=heartall6;
table UKM*ethnic/chisq;
run;
proc freq data=heartall6;
table UKM*rsex/chisq;
where rsex in (1,2);
run;
/*Pancreas UKM*/
```

```
data pancreas;
set standard.pancreas_tx;
if mdy(01,01,2003)<=tx_date<mdy(01,01,2015);
if dtype in (1,2);
run;
data pancreasUKM;
set pancreas;
if donor_id in
(as above
) then UKM='1';
else UKM='0';
run;
data PancreasKM;
set pancreasuKM;
if dcod=70 or donor_id in (as above
) then KM='1';
else KM='0';
run;
data KM;
set pancreasKM;
if donor_id in
(list of appropriate donor-ids)
) then KM='0';
run;
proc freq data=KM;
table KM*tx_type;
run;
data kmpanc;
set km;
if ukm=1 then meningitis=1;
if km=1 then meningitis=2;
run;
data kmpanc2;
set kmpanc;
if meningitis=. then meningitis=3;
run;
data kmpanc3;set kmpanc2; if psurv<=30 then early=1;else
early=0;run;
proc freq data=kmpanc3;table meningitis;run;
data kmpanc4;set kmpanc3;if early=1;if meningitis in (1,2)then
delete;keep recip_id psurv pcens rcod1;run;
data notes;
set database.recipient_note;if recip_id=72686;run;
data km3;set km2;if early=1;if km=1;run;
proc freq data=km3;table rcod;run;
/*Intestinal Tx UKM*/
data intestine;
set standard.intest_tx;
if mdy(01,01,2003)<=tx_date<mdy(01,01,2015);
if dtype in (1,2);
run;
data intestUKM;
set intestine;
if donor_id in
(list of corresponding donor ids
)then UKM='1';
else UKM='0';
run;
proc freq data=intestUKM;
table UKM*tx_type;
run;
data intestineKM;
set intestUKM;
if dcod=70 or donor_id in (list of corresponding donor ids)
) then KM='1';
else KM='0';
run;
data intestineKM2;
set intestineKM;
if donor_id in
(list of corresponding donor ids)
) then KM='0';
run;
proc freq data=intestineKM2;
table KM*tx_type;
run;
data intestinekm3;set intestinekm2;if ukm=1 or km=1 then
meningitis=1;run;
data intestinekm4;set intestinekm3;if meningitis=. then meningitis=0;if
psurv<=30 then early=1;else early=0;run;
proc freq data=intestinekm4;table meningitis*early/fishers;run;
data intestinekm5;set intestinekm4;if early=1;run;
DATA INTESTINEKM5;SET intestinekm4;IF MENINGITIS=1;IF
EARLY=1;RUN;


/*potential donor information*/
data pda;
set database.potential_donor;
if cod=99;
run;
proc sort data=pda;
by pda_id;
run;
data pdanote;
set database.potential_donor_note;
run;
proc sort data=pdanote;
by pda_id;
run;
data notepda;
merge pda pdanote;
by pda_id;
if cod=. then delete;
keep pda_id cod note_text;
run;
data pda2;
set database.potential_donor;
if contraindications=2;
run;
```

```
proc sort data=pda2;
by pda_id;
run;
data pda3;
merge pda2 pdanote;
by pda_id;
if contraindications=. then delete;
keep pda_id note_type note_text;
run;
data pdapilot;
set database.potential_donor_pilot;
if cod=70;
run;
proc sort data=pdapilot;
by pda_id;
run;
data pdapilotnote;
set database.potential_donor_pilot_note;
run;
proc sort data=pdapilotnote;
by pda_id;
run;
data pdapilot2;
merge pdapilot pdapilotnote;
by pda_id;
if cod=. then delete;
run;
data pdapilot3;
set database.potential_donor_pilot;
if contraindications=2;
run;
proc sort data=pdapilot3;
by pdA_ID;
RUN;
data pdapilot4;
merge pdapilot3 pdanote;
by pda_id;
if contraindications=. then delete;
run;
data donorunused;
set standard.donors;
if utilised=0 or organs_txd=0;
run;
data donorcomment;
set database.donor_comment;
run;
proc sort data=donorunused;
by donor_id;
run;
proc sort data=donorcomment;
by donor_id;
run;
data donorsunused;
merge donorunused donorcomment;
by donor_id;
if utilised=. then delete;
if note_type=. then delete;
if note_type=300;
keep donor_id note_type utilised note_text;
run;
data PDAall;
set standard.pda_new;
if cod=70;
if sorgan_donor=0;
run;
/*table of patient from cardiff*/
data wcc;
set database.dcsd_organ_donor;
if donor_id in
(list of corresponding donor ids)
)then UKM='1';
else UKM='0';
keep donor_id temperature white_cells secretions
causative_organisms UKM warm_isch_time;
run;
proc sort data=wcc nodupkey;
by donor_id;
run;
data DonorComment;
set database.donor_comment;
if donor_id in (list of corresponding donor ids)
) ;
keep note_text note_date note_type donor_id;
run;
proc sort data=donorcomment;
by donor_id;
run;

/*Donor Table*/
data donorsx;
set standard.donors;
if mdy(01,01,2003)<=ddate<mdy(01,01,2015);
run;
data donors;
set standard.donors;
if mdy(01,01,2003)<=ddate<mdy(01,01,2015);
if donor_id in
(list of corresponding donor ids)
)then UKM='1';
else UKM='0';
if dtype in (1,2);
where sod=1;
if dcountry='UNITED KINGDOM';
run;
data donorsUKMonly;
set donors;
if UKM=1;
run;
```

```
proc freq data=donors;
table dcod;
run;
proc freq data=donors;
table ukm;
run;
proc freq data=donors;
table dyr*ukm;
run;
proc plot data=donors;
plot dyr*ukm;
run;

proc sort data=donors;
by descending dyr;
run;
proc chart data=donors;
vbar dyr/ type=freq;
by ukm;
where UKM=1;
run;
proc sort data=donors nodupkey;
by donor_id;
run;
data donorwcc;
merge wcc donors;
by donor_id;
if ddate=. then delete;
run;
proc sort data=donorwcc nodupkey;
by donor_id;
run;
proc freq data=donorwcc;
table UKM*dsex/chisq;
run;
data donorwcc2;
set donorwcc;
if temperature=>38.0  then fever=2;
if temperature<38.0 then fever=1;
if temperature=. then fever=0;
if white_cells=>12.0 then WCC=2;
if white_cells<12.0 then wcc=1;
if white_cells=. then wcc=0;
if dethnic=1 then ethnic=1;
else ethnic=2;
if past_diabetes=1 then diabetes=1;
if past_diabetes=2 then diabetes=2;
if past_diabetes in (7,8) then diabetes=3;
if past_hypertension=1 then hypertension=1;
if past_hypertension=2 then hypertension=2;
if past_hypertension in (7,8) then hypertension=3;
if past_cardio_disease=1 then cardio=1;
if past_cardio_disease=2 then cardio=2;
if past_cardio_disease in (7,8) then cardio=3;
if past_alcohol_abuse=1 then alcohol=1;
if past_alcohol_abuse=2 then alcohol=2;
if past_alcohol_abuse in (7,8) then alcohol=3;
if past_liver_disease=1 then liver=1;
if past_liver_disease=2 then liver=2;
if past_liver_disease in (7,8) then liver=3;
if past_drug_abuse=1 then drug=1;
if past_drug_abuse=2 then drug=2;
if past_drug_abuse in (7,8) then drug=3;
if past_smoker=1 then smoker=1;
if past_smoker=2 then smoker=2;
if past_smoker in (7,8) then smoker=3;
run;
data donorwcc3;
set donorwcc2;
if dcod=70 or donor_id in (list of corresponding donor ids)
) then KM='1
else KM='0';
run;
data donorwcc4;
set donorwcc3;
if donor_id in
(list of corresponding donor ids
)then KM='0';
run;
data donormeningitis;
set donorwcc4;
if UKM='1' then meningitis='1';
if KM='1' then meningitis='1';
If UKM='0' and KM='0' then meningitis='0';
run;
proc univariate data=donormeningitis;class meningitis;var dage;run;
proc freq data=donormeningitis;
table meningitis;
run;
data donormenonly;
set donormeningitis;
if meningitis in ('1','2');
donation_year=year(ddate);
run;
data donmenon;
set donormenonly;
if donation_year=2003 then dyear='2003';
if donation_year=2004 then dyear='2004';
if donation_year=2005 then dyear='2005';
if donation_year=2006 then dyear='2006';
if donation_year=2007 then dyear='2007';
if donation_year=2008 then dyear='2008';
if donation_year=2009 then dyear='2009';
if donation_year=2010 then dyear='2010';
if donation_year=2011 then dyear='2011';
if donation_year=2012 then dyear='2012';
if donation_year=2013 then dyear='2013';
if donation_year=2014 then dyear='2014';
```

```
if donation_year=2015 then dyear='2015';
if meningitis=>1 then meningitisused=1;
run;
data theresttx2;
set therest4;
if meningoencephalitis=1 then meningitisused=0;
death_year=year(death_date);
run;
data therest5;set theresttx2;
if death_year=2003 then dyear='2003';
if death_year=2004 then dyear='2004';
if death_year=2005 then dyear='2005';
if death_year=2006 then dyear='2006';
if death_year=2007 then dyear='2007';
if death_year=2008 then dyear='2008';
if death_year=2009 then dyear='2009';
if death_year=2010 then dyear='2010';
if death_year=2011 then dyear='2011';
if death_year=2012 then dyear='2012';
if death_year=2013 then dyear='2013';
if death_year=2014 then dyear='2014';
if death_year=2015 then dyear='2015';
run;
proc sort data=therest5;by dyear;run;
data allinfo;
merge donmenon therest5;
by dyear;
if death_year=2003 then dyear='2003';
if death_year=2004 then dyear='2004';
if death_year=2005 then dyear='2005';
if death_year=2006 then dyear='2006';
if death_year=2007 then dyear='2007';
if death_year=2008 then dyear='2008';
if death_year=2009 then dyear='2009';
if death_year=2010 then dyear='2010';
if death_year=2011 then dyear='2011';
if death_year=2012 then dyear='2012';
if death_year=2013 then dyear='2013';
if death_year=2014 then dyear='2014';
if death_year=2015 then dyear='2015';
run;
proc freq data=donormeningitis;
table meningitis;
run;
data allinfo2;
set allinfo;
donor_age=age_years;
donor_sex=sex;
run;
data allinfo3;
set allinfo2;
if donor_id=. then donor_age=age_years;
if donor_id=. then donor_sex=sex;
run;
data allinfo4;set allinfo3;
donor_years=dage;
donorsex=dsex;run;
data allinfo5;set allinfo4;
if pda_id=. then donor_age=donor_years;
if encephalitis=1 then UKM=2;
run;
data allinfoX;set allinfo5;if pda_id=. then donor_sex=donorsex;run;
data allinfo6;set allinfox; if UKM in (1,2) then ME=1;run;
data allinfo7;set allinfo6;if ME=. then ME=0;run;
proc freq data=allinfo7;table meningitisused*ME/chisq;run;
proc ttest data=allinfo5;class meningitisused;var donor_age;run;
proc freq data=allinfo7;table meningitisused*donor_sex/chisq;run;
proc univariate data=donormeningitis;
class meningitis;var dage;run;
proc ttest data=donormeningitis;
class meningitis;
var dage;
run;
proc freq data=donormeningitis;
table meningitis*dsex/chisq;
where dsex in (1,2);
run;
proc freq data=donormeningitis;
table meningitis*dtype/chisq;
run;
proc npar1way data=donormeningitis;
class meningitis;
var organs_txd;
run;
proc univariate data=donormeningitis;
class meningitis;
var organs_txd;
run;
proc univariate data=donormeningitis;
class meningitis;
var dbmi;
run;
proc ttest data=donormeningitis;
class meningitis;
var dbmi;
run;
proc freq data=donormeningitis;
table meningitis*past_diabetes/chisq;
run;
proc freq data=donormeningitis;
table meningitis*past_hypertension/chisq;
run;
proc freq data=donormeningitis;
table meningitis*cardio/chisq;
run;
proc freq data=donormeningitis;
table meningitis*liver/chisq;
run;
```

```
proc freq data=donormeningitis;
table meningitis*alcohol/chisq;
run;
proc freq data=donormeningitis;
table meningitis*drug/chisq;
run;
proc freq data=donormeningitis;
table meningitis*smoker/chisq;
run;
proc univariate data=donormeningitis;
class meningitis;
var organs_dntd;
run;
proc npar1way data=donormeningitis;
class meningitis;
var organs_dntd;
run;
data donorUKM;
set donormeningitis;
if meningitis='1';
run;

data donorsEncph;
set standard.donors;
if mdy(01,01,2003)<=ddate<mdy(01,01,2015);
if dcod=70 or donor_id in (list of corresponding donor ids)
) then KM='1';
else KM='0';
if dtype in (1,2);
if dcountry='UNITED KINGDOM';
run;
data donorencph;
set donorsEncph;
if donor_id in
(list of corresponding donor ids)
)then UKM='1';
else UKM='0';
if sod=1;
run;
proc freq data=donorencph;
table uKM;
run;
data cardiff2;
set donorencph;
if UKM='1';
if donor_id=105726 then cardiff='1';
else cardiff='0';
run;
proc sort data=cardiff2;
by donor_id;
run;
data basics;
set database.donor_basics;
run;
proc sort data=basics;
by donor_id;
run;
data basicscardiff;
merge cardiff2 basics;
by donor_id;
if ukm=. then delete;
keep donor_id forename surname dcent ddate;
run;

proc sort data=basicscardiff nodupkey;
by donor_id;
run;
proc sort data=basicscardiff;
by dcent;
run;

proc univariate data=cardiff2;
class cardiff;
var dage;
run;
proc freq data=cardiff2;
table cardiff*dsex;
run;
proc freq data=cardiff2;
table cardiff*past_liver_disease;
run;
proc freq data=cardiff2;
table cardiff*past_alcohol_abuse;
run;
proc freq data=cardiff2;
table cardiff*past_diabetes;
run;
proc freq data=cardiff2;
table cardiff*dethnic;
run;
proc freq data=cardiff2;
table cardiff*past_hypertension;
run;
proc freq data=donorencph2;
table KM*dcod;
where KM='1';
RUN;
data donorcomment;
set database.donor_comment;
run;
proc sort data=donorencph2;
by donor_id;
run;
proc sort data=donorcomment;
by donor_id;
run;
data donorencephmen;
merge donorEncph2 DonorComment;
```

```
by donor_id;
keep donor_id dcod note_text note_type;
if km='1';
run;
data unused;
set database.unused_organ_note;
run;
proc sort data=donorencph2;
by donor_id;
run;
proc sort data=unused;
by donor_id;
run;
data unusednote;
merge donorencph2 unused;
by donor_id;
keep donor_id dcod note_text note_type;
if km='1';
run;
proc univariate data=donorwcc2;
class menin;
var white_cells;
run;
proc npar1way data=donorwcc;
class UKML;
var white_cells;
run;
proc freq data=donorwcc2;
table ukm*wcc/chisq;
run;
proc univariate data=donorwcc2;
class UKM;
var warm_isch_time;
run;
proc freq data=donorwcc2;
table UKM*dtype/chisq;
run;
proc univariate data=donorwcc2;
class UKM;
var dage;
run;
proc freq data=donorwcc2;
table UKM*diabetes/chisq;
run;
proc freq data=donorwcc2;
table UKM*hypertension/chisq;
run;
proc freq data=donorwcc2;
table UKM*cardio/chisq;
run;
proc freq data=donorwcc2;
table UKM*drug/chisq;
run;
proc freq data=donorwcc2;
table UKM*liver/chisq;
run;
proc freq data=donorwcc2;
table UKM*alcohol/chisq;
run;
proc univariate data=donorwcc2;
class UKM;
var organs_txd;
run;
proc npar1way data=donorwcc2;
class UKM;
var organs_txd;
run;

proc sort data=donorwcc nodupkey;
by donor_id;
run;
proc freq data=donors;
table UKM;
run;
proc univariate data=donors;
class UKM;
var dbmi;
run;
proc npar1way data=donors;
class UKM;
var dbmi;
run;

proc sort data=donors nodupkey;
by donor_id;
where sod=1;
run;
proc freq data=donors;
table UKM*past_diabetes;
run;
proc freq data=donors;
table UKM*past_hypertension;
run;
proc freq data=donors;
table UKM*past_alcohol_abuse;
run;
proc freq data=donors;
table UKM*past_liver_disease;
run;
proc freq data=donors;
table UKM*past_smoker;
run;
proc univariate data=donors;
var dage;
run;

DATA WORK.Meningitis_20for_20Prof_2_1_1;
  LENGTH
```

```
    D_id              8
    'Event History'n $ 267
    'LP done'n        $ 14
    CSF               $ 133
    temperature       8
    WCC               $ 4
    PMH               $ 202 ;
  FORMAT
    D_id            BEST12.
    'Event History'n $CHAR267.
    'LP done'n       $CHAR14.
    CSF             $CHAR133.
    temperature      BEST12.
    WCC              $CHAR4.
    PMH              $CHAR202. ;
  INFORMAT
    D_id            BEST12.
    'Event History'n $CHAR267.
    'LP done'n       $CHAR14.
    CSF             $CHAR133.
    temperature      BEST12.
    WCC              $CHAR4.
    PMH              $CHAR202. ;
  INFILE 'E:\SASWork\_TD10380_MSVSAS01_\#LN04585'
    LRECL=455
    ENCODING="WLATIN1"
    TERMSTR=CRLF
    DLM='7F'x
    MISSOVER
    DSD ;
  INPUT
    D_id            : BEST32.
    'Event History'n : $CHAR267.
    'LP done'n       : $CHAR14.
    CSF             : $CHAR133.
    temperature      : BEST32.
    WCC              : $CHAR4.
    PMH              : $CHAR202. ;
RUN;

proc sort data=Meningitis_20for_20Prof_2_1_1;
by d_id;
run;
data Meningitissummary;
set Meningitis_20for_20Prof_2_1_1;
rename d_id=donor_id;
run;
proc sort data=donors;
by donor_id;
run;
data cardiffdonor;
set donors;
if donor_id=105726 then cardiff=1;
else cardiff=0;
if UKM=1;
run;
proc sort data=cardiffdonor;
by donor_id;
run;
data cardiffmen;
merge Meningitissummary cardiffdonor;
by donor_id;
if sod=. then delete;
keep 'Event History'n 'LP done'n dsex CSF temperature WCC  PMH
past_liver_disease past_drug_abuse past_alcohol_abuse
past_diabetes past_hypertension ddate dage donor_id cardiff;
run;
proc univariate data=cardiffmen;
class cardiff;
var temperature;
run;
proc freq data=cardiffmen;
table cardiff*past_liver_disease;
run;
proc freq data=cardiffdonor;
table cardiff*past_alcohol_abuse;
run;
proc freq data=cardiffdonor;
table cardiff*past_smoker;
run;
proc freq data=cardiffdonor;
table cardiff*past_drug_abuse;
run;
proc freq data=cardiffdonor;
table cardiff*ORGANS_OFD;
run;
proc freq data=cardiffdonor;
table cardiff*ORGANS_TXD;
run;
proc univariate data=cardiffdonor;
class cardiff;
var organs_ofd organs_txd;
run;

/*PDA data*/
data pda;
set database.national_pda;
if cod=90;
if donor_id=.;
run;
proc freq data=pda;
table admission_date;
run;

data pdanote;
set database.national_PDA_note;
run;
proc freq data=pdanote;
table note_date;
```

```
run;
proc sort data=pda;
by pda_id;
run;
proc sort data=pdanote;
by pda_id;
run;
data pdanote2;
merge pda pdanote;
by pda_id;
if cod=. then delete;
keep pda_id note_text admission_date note_type;
run;

/*PDA DCOD=70*/
data pdamen;
set database.national_pda;
if cod=70;
if donor_id=.;
run;

proc sort data=pdamen;
by pda_id;
run;
proc sort data=pdanote;
by pda_id;
run;
data pdanote3;
merge pdamen  pdanote;
by pda_id;
if cod=. then delete;
keep pda_id note_text admission_date note_type;
run;
data pdanote4;
set pdanote3;
if note_text in ('OTHER') then delete;
run;
data pdanote5;
set pdanote4;
if note_type=. then delete;
run;

/*PDA DCOD=98*/

data pdaother;
set database.national_pda;
if cod=98;
if donor_id=.;
run;
data pdanote;
set database.national_PDA_note;
run;
proc freq data=pdanote;
table note_date;
run;
proc sort data=pdaother;
by pda_id;
run;
proc sort data=pdanote;
by pda_id;
run;
data pdanoteotherrr;
merge pdaother pdanote;
by pda_id;
if cod=. then delete;
keep pda_id note_text admission_date note_type;
run;

/*PDA DCOC=99*/

data pdaunknown;
set database.national_pda;
if cod=99;
if donor_id=.;
run;


data pdanote;
set database.national_PDA_note;
run;
proc freq data=pdanote;
table note_date;
run;
proc sort data=pdaunknown;
by pda_id;
run;
proc sort data=pdanote;
by pda_id;
run;
data pdanoteunknown2;
merge pdaunknown pdanote;
by pda_id;
if cod=. then delete;
keep pda_id note_text admission_date note_type;
run;

/*PDA DCOD=72*/

data pdainfection;
set database.national_pda;
if cod=72;
if donor_id=.;
run;

data pdanote;
set database.national_PDA_note;
run;
proc sort data=pdainfection;
```

```
by pda_id;
run;
proc sort data=pdanote;
by pda_id;
run;
data pdanoteinfection2;
merge pdainfection pdanote;
by pda_id;
if cod=. then delete;
keep pda_id note_text admission_date note_type;
run;
/*new PDA data*/

data pdanew;
set standard.pda_new;
if cod=90;
if donor_id=.;
run;
proc sort data=pdanew;
by pda_id;
run;
proc sort data=pdanote;
by pda_id;
run;
data pdanote3;
merge pdanew pdanote;
by pda_id;
if cod=. then delete;
keep pda_id note_text admission_date note_type;
run;

/*new PDA COD=99*/

data pdanew2;
set standard.pda_new;
if cod=99;
if donor_id=.;
run;
proc sort data=pdanew2;
by pda_id;
run;
proc sort data=pdanote;
by pda_id;
run;
data pdanote99;
merge pdanew2 pdanote;
by pda_id;
if cod=. then delete;
keep pda_id note_text admission_date note_type;
run;



/*PDAnew DCOD 98*/
data pdanew98;
set standard.pda_new;
if cod=98;
if donor_id=.;
run;
proc sort data=pdanew98;
by pda_id;
run;
proc sort data=pdanote;
by pda_id;
run;
data pdanote989;
merge pdanew98 pdanote;
by pda_id;
if cod=. then delete;
keep pda_id note_text admission_date note_type;
run;

/*new PDA DCOD=70*/
data pdaMennew;
set standard.pda_new;
if cod=70;
if donor_id=.;
run;
proc sort data=pdaMennew
by pda_id;
run;
proc sort data=pdanote;
by pda_id;
run;
data pdanoteMennew;
merge pdaMennew pdanote;
by pda_id;
if cod=. then delete;
keep pda_id note_text admission_date note_type;
run;



data donors1;
set standard.donors;
if dcod=70 or donor_id in (list of donor ids)od=0;
if dcountry='UNITED KINGDOM';
if mdy(01,01,2003)<=ddate<mdy(01,01,2015);
run;
proc sort data=donors1;
by donor_id;
run;
data donors3;
set donors1;
if donor_id in
(list of donor ids)
);
if sod=0;
```

```
run;
data notes;
set database.donor_comment;
run;
proc sort data=notes;
by donor_ID;
run;
proc sort data=donors3;
by donor_id;
run;
data basics;
set database.donor_basics;
run;
proc sort data=basics;
by donor_id;
run;

data notesunused;
merge donors1 notes;
by donor_id;
if sod=. then delete;
keep donor_id dcent dsex ddate dregion hospname note_type
note_text sod;
run;
proc sort data=notesunused;
by donor_id;
run;
data unusednames;
merge notesunused basics;
by donor_id;
if sod=. then delete;
keep donor_id forename surname ddate dregion hospname note_type
note_text;
run;
/* ---------------------------------------------------------------------
   Code generated by a SAS task

   Generated on Saturday, November 07, 2015 at 8:31:07 PM
   By task:     Import Data Wizard

   Source file: \\msfile1\home$\dsummers\My
   Documents\Meningitis%20for%20Prof-2(1).xlsx
   Server:      Local File System

   Output data: WORK.Meningitis_20for_20Prof_2_1_
   Server:      SASApp

   Note: In preparation for running the following code, the Import
   Data wizard has used internal routines to transfer the source data
   file from the local file system to SASApp. There is no SAS code
   available to represent this action.
   ------------------------------------------------------------------- */

/* ---------------------------------------------------------------------
   This DATA step reads the data values from a temporary text file
   created by the Import Data wizard. The values within the
   text file were extracted from the Excel source file.
   ----------------------------------------------------------------temporary------ */
data knewdata;
merge donors Meningitissummary;
by donor_id;
if UKM=0 then delete;
keep donor_id CSF temperature sod dbmi ddate dage WCC PMH
past_liver_disease past_hypertension past_diabetes past_smoker
past_drug_abuse  'LP done'n   'Event History'n;
if donor_id=105726 then cardiff='1';
else cardiff='0';
if donor_id=. then delete;
run;
data new;
set knewdata;
if donor_id=105726 then cardiff=1;
else cardiff=0;
run;

proc univariate data=new;
class cardiff;
var dage;
run;

proc freq data=new;
table cardiff*past_liver_disease;
run;

/*Bar chart tables of potential donors who were rejected with
meningitis*/
data pdanewandnational;
set database.national_pda;
run;
proc sort data=pdanewandnational;
by pda_id;
run;

data allpda;
set pdanewandnational;
if donor_id=.;
run;

/* PDA continued*/
data othercauses;
set pdd.potential_donor;
if donor_id=.;
run;
proc sort data=othercauses;
by potential_donor_id;
run;
data notes;
set pdd.potential_donor_note;
run;
proc sort data=notes;
```

```
by potential_donor_id;
run;
data combined;
merge othercauses notes;
if cod=. then delete;
iF potential_donor_id in
(list of donor ids)
)  THEN MENINGITIS=1;
run;
DATA COMBINED2;
SET COMBINED; IF MENINGITIS=1;keep potential_donor_id
note_text note_type;RUN;
PROC SORT DATA=COMBINED2 NODUPKEY;BY
POTENTIAL_DONOR_ID;RUN;
PROC FREQ DATA=COMBINED2;
TABLE PRIMARY_CONTRAINDICATION;RUN;

/*Meningitis*/
data allpdameningitis;
set allpda;
if cod=70 or pda_id in
(list of donor ids)
) then meningitis='1';
else meningitis='0';
run;
proc freq data=allpdameningitis;
table meningitis;
run;
proc sort data=allpdameningitis;
by pda_id;run;

data pdanote;
set database.national_PDA_note;
run;
proc freq data=pdanote;
table note_date;
run;
proc sort data=pdanote;
by pda_id;
run;
data combined2;
merge allpdameningitis pdanote;
by pDa_id;
if meningitis=1;
keep pda_id note_type cod note_text;
run;


data allpdamenin2;
set allpdameningitis;
if pda_id in
(list of donor ids) then encephalitis=1;
else encephalitis=0;
run;
proc sort data=allpdamenin2;
by death_date;
run;
proc freq data=allpdamenin2;
table encephalitis;
run;
data allpdameninX;
set allpdamenin2;
death_year=year(datepart(death_date));
if meningitis=1 or encephalitis=1 then meningoencephalitis=1;
else meningoencephalitis=0;
run;
proc freq data=allpdameninx;table meningoencephalitis;run;


data allpdameninX;
set allpdamenin2;
death_year=year(datepart(death_date));
if meningitis=1 then meningoencephalitis=1;
if encephalitis=1 then meningoencephalitis=2;
run;
proc freq data=allpdameninx;table meningoencephalitis;run;


data allpdameninx2;set allpdameninx; if meningoencephalitis in
(1,2);run;


data allpdamenin3;
set allpdameninX;
if death_year=2015 then delete;
run;


data meningitisonly;
set allpdamenin3;
if meningoencephalitis in (1,2);
if death_year=2003 then dyear='2003';
if death_year=2004 then dyear='2004';
if death_year=2005 then dyear='2005';
if death_year=2006 then dyear='2006';
if death_year=2007 then dyear='2007';
if death_year=2008 then dyear='2008';
if death_year=2009 then dyear='2009';
if death_year=2010 then dyear='2010';
if death_year=2011 then dyear='2011';
if death_year=2012 then dyear='2012';
if death_year=2013 then dyear='2013';
if death_year=2014 then dyear='2014';
if death_year=2015 then dyear='2015';
run;
data menon;
set meningitisonly;
if dyear='2015' then delete;
run;
proc freq data=meningitisonly;
table meningoencephalitis*dyear;
run;


proc freq data=meningitisonly;
```

```
table meningoencephalitis;
run;

proc freq data=allpdamenin3;
table meningoencephalitis*death_year;
run;
/* reason for refusal*/
data allpdamenin4;
set allpdamenin3;
if pda_id in
(list of pda ids
) then reason=1;
if pda_id in
(list of pda ids
) then reason=2;
If pda_id in
(188885
194555) then reason=3;
if pda_id in
(list of pda ids) then reason=4;
if pda_id in
(list of pda ids) then reason=5;
if pda_id in
(list of pda ids) then reason=6;
if pda_id in
(list of pda ids) then reason=7;
if pda_id in
(list of pda ids
) then reason=8;
if pda_id in
(list of pda ids) then reason=9;
if pda_id in
(list of pda ids) then reason=10;
if pda_id in
(list of pda ids
) then reason=13;
run;

proc freq data=allpdamenin4;
table reason;
run;



/*new reasons for TID publication*/
data allpdamenin5;
set allpdamenin4;
if pda_id in
(list of pda ids) then encephalitis=1;
run;
proc freq data=allpdamenin5;table encephalitis;run;
data allpdamenin6;
set allpdamenin5;
if pda_ID IN
(list of pda ids
) then reason=8;
if pda_id in
(list of pda ids
) then reason=11;
if pda_id in
(list of pda ids) then reason=13;
if pda_id in
(list of pda ids)then reason=12;
run;


data therest;
set allpdamenin6;
if encephalitis=1 then meningitis=3;
run;
data therest2;
set therest;
if meningitis in (1,3) then meningoencephalitis=1;else
meningoencephalitis=0;
run;
data therest3;set therest2;if meningoencephalitis=1;run;
data therest4;
set therest3;
if reason=8 then newreason='Not Stated';
if reason in (11,7) then newreason='Secondary to
meningitis/encephalitis';
if reason =13 then newreason='Family refusal';
if reason=2 then newreason='Treatment Not Withdrawn';
if reason in (1,4,5,6,9,10,12) then newreason='Other';
run;
proc freq data=therest4;
table newreason;
run;


data therest3;
set therest2;
if encephalitis=1;
run;
proc sort data=therest4;
by pda_id;
run;
proc sort data=pdanote;
by pda_id;
run;
data othereason;
merge therest3 pdanote;
by pda_id;
if encephalitis=1;
run;
data othereason2;
set othereason;
keep pda_id note_type note_text reason;
if reason in (1,4,5,6,9,10,12);
run;
proc freq data=othereason2;table reason;
run;
```

1.48 Appendix 3: ITP code

```
data names;
set database.donor_basics;
if donor_id in
(49500, 58575,59122,71187,79663, 90012, 92051, 92211, 92340,
104535, 105671, 108560, 62345, 71536, 104396, 105599, 107337,
72766, 83330, 96590, 55688, 108320, 95864, 109545);
keep donor_id forename surname donation_date hospital_id nhs_no
birth_date;
run;
proc sort data=names nodupkey;
by donor_id;
run;



data donors;
set standard.donors;
if mdy(01,01,2000)<=ddate<mdy(01,01,2015);
if dtype in (1,2);
run;

data donorspecific;
set donors;
if donor_id=71536;
run;
data basics;
set database.donor_basics;
if donor_id=71536;
run;
data note;
set database.donor_comment;
if donor_id=49483;
run;
data recip  itp;
set standard.final3;
if recip_id=111296;
run;
proc sort data=donors;
by donor_id;
run;
data donorcomment;
set database.donor_comment;
keep donor_id note_text;
if note_date=>mdy(01,01,2000);
run;
proc sort data=donorcomment;
by donor_id;
run;
data ITPidentify;
merge donors donorcomment;
by donor_id;
if dcod=. then delete;
keep donor_id dcod note_type note_text;
run;
data donors2;
set standard.donors;
if mdy(01,01,2000)<=ddate<mdy(01,01,2015);
if dtype in (1,2);
if dcod in (10,11,13,73,90,98,99) then delete;
run;
proc sort data=donors;
by donor_id;
run;
data donorcomment;
set database.donor_comment;
run;
proc sort data=donorcomment;
by donor_id;
run;
data ITPidentify;
merge donors2 donorcomment;
by donor_id;
if dcod=. then delete;
keep donor_id dcod note_type note_text;
run;

data ITP;
set standard.donors;
if donor_id not in
(49500, 58575,59122,71187,79663, 90012, 92051, 92211, 92340,
104535, 105671, 108560, 62345, 71536, 104396, 105599, 107337,
72766, 83330, 96590, 55688, 108320, 95864, 109545) then delete;
run;
data blood;
set database.donor_blood_result;
if donor_id  in (49500, 58575,59122,71187,79663, 90012, 92051,
92211, 92340, 104535, 105671, 108560, 62345, 71536, 104396,
105599, 107337, 72766, 83330, 96590, 55688, 108320, 95864,
109545)then ITP=1;else ITP=0;
run;

proc sort data=blood nodupkey;
by donor_id;run;
data blood2;set blood;keep donor_id haemoglobin platelets ITP;run;
proc univariate data=blood;class ITP;var platelets;run;
```

```
/*data tables for paper*/
data itptable;
set standard.donors;
if mdy(01,01,2000)<=ddate<mdy(01,01,2015);
if dtype in (1,2);
if dcountry='UNITED KINGDOM';
if donor_id in (49500, 58575,59122,71187,79663, 90012, 92051,
92211, 92340, 104535, 105671, 108560, 62345, 71536, 104396,
105599, 107337, 72766, 83330, 96590, 55688, 108320, 95864,
109545) then ITP=1;
else ITP=0;
if past_diabetes=1 then diabetes=1;
if past_diabetes=2 then diabetes=2;
if past_diabetes in (3,4,5,6,7,8,9,.) then diabetes=3;
if past_hypertension=1 then hypertension=1;
if past_hypertension=2 then hypertension=2;
if past_hypertension in (3,4,5,6,7,8,9,.) then hypertension=3;
if past_cardio_disease=1 then cardio=1;
if past_cardio_disease=2 then cardio=2;
if past_cardio_disease in (3,4,5,6,7,8,9,.) then cardio=3;
if past_alcohol_abuse=1 then alcohol=1;
if past_alcohol_abuse=2 then alcohol=2;
if past_alcohol_abuse in (3,4,5,6,7,8,.) then alcohol=3;
if past_liver_disease=1 then liver=1;
if past_liver_disease=2 then liver=2;
if past_liver_disease in (3,4,5,6,7,8,9,.) then liver=3;
if past_drug_abuse=1 then drug=1;
if past_drug_abuse=2 then drug=2;
if past_drug_abuse in (3,4,5,6,7,8,9,.) then drug=3;
IF PAST_SMOKER=1 THEN SMOKER=1;
IF PAST_SMOKER=2 THEN SMOKER=2;
IF PAST_SMOKER IN (3,4,5,6,7,8,9,.) THEN SMOKER=3;
if sod=1;
run;
proc sort data=itptable;by donor_id;run;
data blood;
set database.donor_blood_result;
if donor_id  in (49500, 58575,59122,71187,79663, 90012, 92051,
92211, 92340, 104535, 105671, 108560, 62345, 71536, 104396,
105599, 107337, 72766, 83330, 96590, 55688, 108320, 95864,
109545)then ITP=1;else ITP=0;
run;
proc sort data=blood; by donor_id;run;
data platelets;merge itptable blood; by donor_id;if dtype=. then
delete;run;
proc sort data=platelets nodupkey;by donor_id;run;
proc univariate data=platelets;class itp;var platelets;histogram;run;
proc npar1way data=platelets;class itp; var platelets;run;
data why;set itptable;if sod=1;if itp=1;run;
data unusednote;set database.unused_organ; if donor_id in(92211
92340
108560);run;

proc freq data=itptable;table itp;run;
proc ttest data=itptable;class itp;var dage;run;
proc univariate data=itptable;class itp;var dage;run;
proc freq data=itptable;table itp*dsex/fisher;run;
proc freq data=itptable;table itp*dcod;run;
data cod; set itptable; if dcod =10 then cause=1;if dcod=11 then
cause=2; if dcod=19 then cause=3; if dcod=20 then cause=4;run;
data cod2;set cod; if cause=. then cause=5;run;
proc freq data=cod2;table itp*cause/fisher;run;
proc univariate data=itptable;class itp;var dage;run;
PROC NPAR1WAY DATA=ITPTABLE;CLASS ITP;VAR DCOD;RUN;
PROC FREQ DATA=ITPTABLE;TABLE ITP*DTYPE/fisher;RUN;
PROC FREQ DATA=ITPTABLE;TABLE
ITP*HYPERTENSION/fisher;RUN;
PROC FREQ DATA=ITPTABLE;TABLE ITP*DIABETES/fisher;RUN;
PROC FREQ DATA=ITPTABLE;TABLE ITP*CARDIO/fisher;RUN;
PROC FREQ DATA=ITPTABLE;TABLE ITP*SMOKER/fisher;RUN;
PROC FREQ DATA=ITPTABLE;TABLE ITP*DRUG/fisher;RUN;
proc univariate data=itptable;
class itp;
var organs_dntd;
run;
PROC NPAR1WAY DATA=ITPTABLE;CLASS ITP;VAR
ORGANS_TXD;RUN;
PROC NPAR1WAY DATA=ITPTABLE;CLASS ITP;VAR
ORGANS_DNTD;RUN;
proc univariate data=itptable;
class itp;
var organs_DNTD;
run;

data fup;set database.rcs_liver_fup_annual;if donor_id in (49500,
58575,59122,71187,79663, 90012, 92051, 92211, 92340, 104535,
105671, 108560, 62345, 71536, 104396, 105599, 107337, 72766,
83330, 96590, 55688, 108320, 95864, 109545);
run;
proc sort data=fup;by donor_id;run;
proc sort data=itp;
by donor_id;
run;
```

```
data liverITP;
set standard.liver_tx;
if mdy(01,01,2000)<=tx_date<mdy(01,01,2015);
if dtype in (1,2);
run;
proc sort data=liveritp;
by donor_id;
run;
data liveritpx;
set liveritp;
if recip_id in (89677,177120,175466);
run;

data liveritp2;
SET liveritp;
if donor_id  in
(49500, 58575,59122,71187,79663, 90012, 92051, 92211, 92340,
104535, 105671, 108560, 62345, 71536, 104396, 105599, 107337,
72766, 83330, 96590, 55688, 108320, 95864, 109545) then
ITP=1;ELSE ITP=0;
if recip_id=. then delete;
run;
data liveritpX;set liveritp2;if itp=1;
run;
data liverdetails;set database.recipient;if recip_id=132368;run;
proc sort data=liveritpx;by rec_unit;run;
data organnote;
set database.recipient_status_history_note;
if recip_id =161349;
run;
data liverinfo;
set database.recip_ext_agency_death;
if recip_id=161349;
run;


/*Recipient note*/
data note;
set database.recipient  note;
if recip_id in (89677,177120,175466);
run;
proc sort data=note;
by recip_id;
run;
proc sort data=liveritp2;
by recip_id;
run;
data itpnote;
merge liveritp2 note;
by recip_id;
if dcod=. then delete;
keep donor_id recip_id dcod note_type note_text;
run;
/*missing data*/
data LiverMissing;
set liveritp2;
if psurv=.;
run;
proc sort data=livermissing;
by recip_id;
run;
data allliver;
set standard.liver_tx;
run;
proc sort data=allliver;
by recip_id;
run;
data alllivermissing;
merge livermissing allliver;
by recip_id;
if ITP=. then delete;
run;
data livermissing2;
set alllivermissing;
if psurv=. then delete;
rename tx_date=first_tx_date psurv=patientdays pcens=patientsurvival;
keep recip_id donor_id tx_date psurv pcens;
run;
proc sort data=livermissing2;
by recip_id;
run;
proc sort data=liveritp2;
by recip_id;
run;
data liverUKM2;
merge liveritp2 livermissing2;
by recip_id;
if tx_date >first_tx_date then duration=tx_date-first_tx_date;
run;
data liverUKM3;
set liverUKM2;
if patientdays=>duration then psurvfinal=patientdays-duration;
run;
data LiverUKM4;
set liverUKM3;
if psurv=. then psurv=psurvfinal;
if pcens=. then pcens=patientsurvival;
run;
data liverUKM5;
set liverukm4;
if psurv>1826.5 then psurvival=1826.5;
else psurvival=psurv;
if gsurv>1826.5 then gsurvival=1826.5;
else gsurvival=gsurv;
if pcens=1 and psurv>1826.5 then pcensor=0;
else pcensor=pcens;
if gcens=1 and gsurv>1826.5 then gcensor=0;
else gcensor=gcens;
if psurv=. then delete;
run;
data LITP;
set liverukm5;
ptsurv=psurvival/365.25;
grsurv=gsurvival/365.25;
if dethnic=1 then ethnic=1;
else ethnic=2;
if rethnic=1 then recip_ethnic=1;
else recip_ethnic=2;
if graft_no=1 then Tx=1;
if graft_no=2 then Tx=2;
if graft_no>2 then Tx=3;
if crf_tx>85 then sensitised=1;
else sensitised=0;
if txcountry='UNITED KINGDOM';
if pcensor=. then delete;
if gcensor=. then delete;
if past_diabetes=1 then diabetes=1;
if past_diabetes=2 then diabetes=2;
if past_diabetes in (7,8) then diabetes=3;
if past_hypertension=1 then hypertension=1;
if past_hypertension=2 then hypertension=2;
if past_hypertension in (7,8) then hypertension=3;
if past_cardio_disease=1 then cardio=1;
if past_cardio_disease=2 then cardio=2;
if past_cardio_disease in (7,8) then cardio=3;
if past_alcohol_abuse=1 then alcohol=1;
if past_alcohol_abuse=2 then alcohol=2;
if past_alcohol_abuse in (7,8) then alcohol=3;
if past_liver_disease=1 then liver=1;
if past  liver  disease=2 then liver=2;
if past_liver_disease in (7,8) then liver=3;
if past_drug_abuse=1 then drug=1;
if past_drug_abuse=2 then drug=2;
if past_drug_abusee in (7,8) then drug=3;
if rhcv=1 then rhepc=1;
if rhcv=2 then rhepc=2;
if rhcv in (3,4,5,6,7,8) then rhepc=3;
if hcv=1 then hepC=1;
if hcv=2 then hepC=2;
if hcv in (3,4,5,6,7,8) then hepc=3;
run;
proc freq data=litp;
table ITP;
run;
proc univariate data=litp;class itp;var rage;run;
PROC TTEST DATA=LITP;CLASS ITP;VAR RAGE;RUN;
PROC FREQ DATA=LITP;TABLE ITP*RSEX/CHISQ;RUN;
PROC FREQ DATA=liTP; TABLE ITP*pLd/CHISQ;RUN;
PROC NPAR1WAY DATA=LITP; CLASS ITP; VAR PLD;RUN;
PROC FREQ DATA=LITP; TABLE ITP*RECIP_ETHNIC/CHISQ;RUN;
PROC FREQ DATA=LITP;TABLE ITP*URGENT/CHISQ;RUN;
PROC NPAR1WAY DATA=LITP;CLASS ITP;VAR UKELD;RUN;
PROC UNIVARIATE DATA=LITP;CLASS ITP;VAR rplatelets;RUN;
PROC NPAR1WAY DATA=LITP;CLASS ITP;VAR rplatelets;RUN;
PROC FREQ DATA=LITP;TABLE gcens;where itp=1;RUN;
data litp2;set litp; if recip_id=177120 then delete;run;
data litp3;set litp; if rcod=526 then recip_death=1;
if rcod in (530,531,532,533) then recip_death=2;
if rcod=511 then recip_death=3;
if rcod=0 then recip_death=5;
run;

proc freq data=litp3;table rcod;run;
data litp4; set litp3; if recip_death=. then recip_death=4;run;
proc freq data=litp4; table itp*recip_death/fisher;run;
proc freq data=litp4; table itp*cof/fisher;run;

%survival(LITP2,psurvival,pcensor,Years,5,1,ITP,patient,0,ITP_p);
%survival(liTP2,gsurvival,gcensor,Years,5,1,ITP,graft,0,ITP_g);

data Platelets;
input
recip 1-2
day 4
plt 6-8
;
datalines;
1. 1 364
1. 3 51
2. 1 53.
2. 3 24.
3. 1 72.
3. 3 2
4. 1 23.
4. 3 56.
5. 1 73.
5. 3 36.
6. 1 304
6. 3 153
7. 1 131
7. 3 83.
8. 1 64.
```

```
8. 3 47.
9. 1 54.
9. 3 15.
10 1 197
10 3 74.
11 1 267
11 3 342
12 1 41.
12 3 24.
13 1 101
13 3 76.
14 1 103
14 3 44.
;
run;
proc  univariate data=Platelets;
class day;var plt;run;
data new;
input
day 1
plt 3-5;
datalines;
1 87
3 51
;run;
proc transpose data=platelets out=diff name=days prefix=out;by recip;
id day; run;
data difference;
set diff;
difference=out1-out3;
run;
proc univariate data=difference;var difference;run;
data recipplt;
input plt;
datalines;
51
24
2
56
153
36
83
47
15
74
342
24
76
44
;
run;
data recippltkidney;
input plt;
datalines;
58
85
85
91
91
100
108
124
135
138
139
140
149
163
172
186
187
189
190
191
196
198
210
215
219
239
259
262
267
280
;
run;



proc univariate data=recippltkidney;var plt;run;

data litp2;
set litp;
keep recip_id donor_id dtype dage rage rsex rethnic psurv pcens
rplatelets rcod cof;
if itp=1;
run;
proc freq data=litp;
table itp*cof;run;
run;
```

```
data notes;
set database.recipient_note;
if recip_id in (89677
97636
107240
129629
129922
130667
132368
157788
161349
163522
167678
172878
175466
177120);run;
data recipient_name;
set database.recipient;
if recip_id in (107240
129922
167678
175466);
run;

data leedsliver;
set litp;
if rec_unit='D0101';
run;

/*kidney ITP*/
data kidneyitp;
set standard.kidney_tx;
if mdy(01,01,2000)<=tx_date<mdy(01,01,2015);
if dtype in (1,2);
run;
proc sort data=itp;
by donor_id;
run;
proc sort data=kidneyitp;
by donor_id;
run;
data kidneyitp2;
set kidneyitp;
if donor_id  in
(49500, 58575,59122,71187,79663, 90012, 92051, 92211, 92340,
104535, 105671, 108560, 62345, 71536, 104396, 105599, 107337,
72766, 83330, 96590, 55688, 108320, 95864, 109545)then ITP=1;
else ITP=0;run;
data kidneyitp3;set kidneyitp2;if itp=1;run;
proc freq data=kidneyitp2;
table itp*recip_id;where ITP=1;
run;
data why;
/*kidney missing data*/
data Missing;
set kidneyitp2;
if psurv=.;
run;
proc sort data=missing;
by recip_id;
run;
data all;
set standard.kidney_tx;
run;
proc sort data=all;
by recip_id;
run;
data Allmissing;
merge missing all;
by recip_id;
if itp=. then delete;
run;
proc freq data=allmissing;
table itp;
run;
data Missing2;
set allmissing;
if psurv=. then delete;
rename tx_date=first_tx_date psurv=Patientdays
pcens=patientsurvival;
keep recip_id tx_date psurv pcens;
run;
proc sort data=missing2;
by recip_id;
run;
data missing3;
merge missing missing2;
by recip_id;
run;
proc freq data=missing3;
table itp;
run;



data missing4;
set missing3;
if tx_date>first_tx_date then duration=tx_date-first_tx_date;
run;
data missing5;
set missing4;
if patientdays=>duration then psurvfinal=patientdays-duration;
```

```
run;
proc sort data=missing5;
by recip_id;
run;
proc sort data=kidneyitp2;
by recip_id;
run;
data Kidneyall;
merge kidneyitp2 missing5;
by recip_id;
run;
proc freq data=kidneyall;
table itp;
run;

proc freq data=kidneyall;
table UKM;
run;
data Analysis;
set kidneyall;
if psurv=. then psurv=psurvfinal;
if pcens=. then pcens=patientsurvival;
run;
proc freq data=analysis;
table pcens;
run;
data analysis2;
set analysis;
if psurv=>3650 then psurvival=3650;
else psurvival=psurv;
if gsurv=>3650 then gsurvfinal=3650;
else gsurvfinal=gsurv;
if psurv=>3650 and pcens=1 then pcensor=0;
else pcensor=pcens;
if gsurv=>3650 and gcens=1 then gcensor=0;
else gcensor=gcens;
if rage>40 then rage_grp=2;
else recip_age_grp=1;
if dage>40 then dage_grp=2;
else donor_age_grp=1;
run;
proc freq data=analysis2;
table ITP;
run;
data analysis3;
set analysis2;
ptsurv= psurvival/365.25;
grsurv=gsurvfinal/365.25;
if dethnic=1 then ethnic=1;
else ethnic=2;
if rethnic=1 then recip_ethnic=1;
else recip_ethnic=2;
if graft_no=1 then Tx=1;
if graft_no=2 then Tx=2;
if graft_no>2 then Tx=3;
if crf_tx>85 then sensitised=1;
else sensitised=0;
if txcountry='UNITED KINGDOM';
if pcensor=. then delete;
if gcensor=. then delete;
if past_diabetes=1 then diabetes=1;
if past_diabetes=2 then diabetes=2;
if past_diabetes in (7,8) then diabetes=3;
if past_hypertension=1 then hypertension=1;
if past_hypertension=2 then hypertension=2;
if past_hypertension in (7,8) then hypertension=3;
if past_cardio_disease=1 then cardio=1;
if past_cardio_disease=2 then cardio=2;
if past_cardio_disease in (7,8) then cardio=3;
if past_alcohol_abuse=1 then alcohol=1;
if past_alcohol_abuse=2 then alcohol=2;
if past_alcohol_abuse in (7,8) then alcohol=3;
if past_liver_disease=1 then liver=1;
if past_liver_disease=2 then liver=2;
if past_liver_disease in (7,8) then liver=3;
if past_drug_abuse=1 then drug=1;
if past_drug_abuse=2 then drug=2;
if past_drug_abuse in (7,8) then drug=3;
if rECIP_ID IN (101160,108100)THEN ITP=2;
run;
DATA ANALYSIS4;SET ANALYSIS3; IF itp IN (1,2) THEN
IDIOPATHIC=1;ELSE IDIOPATHIC=0;
RUN;
PROC FREQ DATA=ANALYSIS4; TABLE IDIOPATHIC;RUN;
PROC SORT DATA=ANALYSIS4 NODUPKEY;
BY RECIP_ID;
RUN;

%macro
survival(data,surv,cens,period,end,end1,var,survival,yaxis,cgm);
ods listing;
/*READS IN YOUR DATASET AND CHANGES THE SURVIVAL
VARIABLES READY FOR USE*/
/*ALSO CHANGES THE DATA TO YEARS OR MONTHS OR DAYS*/
data surv;
set &data;
if &surv <0 then delete;
cens = &cens;
if lowcase("&period") = "months" then surv = &surv / 30.44;
if lowcase("&period") = "years" then surv = &surv / 365.25;
if lowcase("&period") = "days" then surv = &surv / 1;
if surv > &end then do; surv = &end; cens = 0; end;
fup = 0;
if surv = &end or cens ne 0 then fup = 1;
run;

/*GETS THE COUNT FOR EACH STRATA*/
proc freq data = surv noprint; table &var / out = num; run;

/*GETS THE COUNT FOR FOLLOW UP*/
proc freq data = surv noprint; table &var * fup / out = fup; run;

/*OPENS THE FILE TO SAVE THE PLOT*/
filename gsasfile "&file.\&cgm..emf";

/*RUNS THE LIFETEST PROCEDURE TO OUTPUT THE DATA
NEEDED FOR THE PLOT*/
ODS OUTPUT homtests=homtests;
proc lifetest data=surv plots=(s) outsurv=surv1;
time surv*cens(0); strata &var;
run;
quit;

/*SORTS OUT THE LAYOUT OF THE PLOT AND CHOOSES
COLOURS FOR THE LINES*/
goptions reset=all reset=symbol htext=1.8 cback=white colours=(black)
/*ftext=HWCGM005*/ ftext='Arial/bold'
noborder hsize=8.5 vsize=9.5 Gaccess=GSASFILE;run;
axis1 minor=none order=&yaxis to 100 by 10 label=(ANGLE=90 "%
&survival survival");
axis2 minor=none order=0 to &end by &end1 label=("&period post-
transplant");
symbol;
symbol1 c=CXFF6600 i=steplj w=4 l=1 v=none;
symbol2 c=CX99CCFF i=steplj w=4 l=2 v=none;
symbol3 c=CXFFCC00 i=steplj w=4 l=1 v=none;
symbol4 c=CX339966 i=steplj w=4 l=1 v=none;
symbol5 c=black    i=steplj w=4 l=1 v=none;
symbol6 c=CXFF6600 i=steplj w=4 l=2 v=none;
symbol7 c=CX99CCFF i=steplj w=4 l=2 v=none;
symbol8 c=CXFFCC00 i=steplj w=4 l=2 v=none;
symbol9 c=CX339966 i=steplj w=4 l=2 v=none;
symbol10 c=black   i=steplj w=4 l=2 v=none;

                LEGEND1 ACROSS=1
                POSITION=(BOTTOM INSIDE CENTER)
                MODE=SHARE
                OFFSET=(0,1.5)
                SHAPE=SYMBOL(5,1)
                                        CBORDER=Black
                LABEL=(POSITION=(TOP)
                JUSTIFY=CENTER H=1.2 "&var")
                                        VALUE=(H=1.2);

/*PRODUCES THE PLOT*/
data splot1; set surv1; retain lag_s; drop=lag_s; if survival=. then
survival=lag_s;
lag_s=survival; run;
data splot2; set splot1; survival=survival*100;
proc gplot data=splot2; plot survival * surv = &var /legend=legend1
noframe vaxis=axis1 haxis=axis2;
title ' '; run; quit;

/*USES THE DATA TO OBTAIN THE SURVIVAL ESTIMATES FOR
THE STRATA*/
data surv2; set surv1; if _censor_ = 0; run;
proc sort data = surv2; by &var survival; run;
proc sort data = surv2 nodupkey; by &var; run;

data surv3; set surv2; surv = (survival*100); lcl = (sdf_lcl*100); ucl =
(sdf_ucl*100);
format surv lcl ucl 10.1; run;

data surv4; merge surv3 num; by &var; run;

/*OBTAINS THE P-VALUE FOR THE STRATA*/
data _null_;
set homtests;
where test = 'Log-Rank';
call symput ("logrank",trim(left(put(ProbChiSq,PVALUE6.4))));
run;

/*PRINTS THE ESTIMATES, COUNT AND P-VALUE FOR THE
DATA*/
title1"&survival survival by &var p=&logrank";
proc print data = surv4; var &var count surv lcl ucl;  run;
%mend survival;

/*MACRO VARIABLES REQUIRED*/
/*%survival(data,surv,cens,time,end,end1,censor,var,survival,period,cg
m);*/
/*WHERE     data=dataset with survival variables
                        surv=name of survival variable - eg gsurv
                        cens=name of censoring variable - eg
gcens
                        period=years, months, days
                        end=put 10 if wanting 10 year survival, 12
for 12 month survival, 30 for 30 day survival
                        end1=how big you want your x-label gap eg
1 if you want 10 years by 1 year
                        var=variable you want to strata by - eg
centre
```

```
                        survival=either graft, patient or transplant
                        yaxis=point at which you want the yaxis to
start, 40 is standard
                        emf=name of emf file you want to save
*/

%survival(analysis4,gsurvival,gcensor,Years,10,1,IDIOPATHIC,graft,0
,ITP_g);
%survival(analysis4,psurvival,pcensor,Years,10,1,IDIOPATHIC,patient
,0,ITP_p);

/*DATA TABLES KIDNEY RECIPIENTS*/
proc univariate data=analysis4;class idiopathic;var rage;run;
PROC TTEST DATA=ANALYSIS4;CLASS IDIOPATHIC;VAR
RAGE;RUN;
PROC FREQ DATA=ANALYSIS4;TABLE
IDIOPATHIC*RSEX/CHISQ;RUN;
PROC FREQ DATA=ANALYSIS4; TABLE
IDIOPATHIC*HLA_GRP/CHISQ;RUN;
PROC FREQ DATA=ANALYSIS4; TABLE
IDIOPATHIC*prd/CHISQ;RUN;
PROC NPAR1WAY; CLASS IDIOPATHIC; VAR PRD;RUN;
PROC FREQ DATA=ANALYSIS4; TABLE
IDIOPATHIC*RECIP_ETHNIC/CHISQ;RUN;
PROC FREQ DATA=ANALYSIS4; TABLE
IDIOPATHIC*SENSITISED/CHISQ;RUN;


data tabelinfo;
set analysis3;
keep donor_id recip_id pcens rec_unit psurv gcens gsurv rcod cof dage
rage tx_date ddate dtype;
run;

proc freq data=analysis3;
table rec_unit*recip_id;
run;
proc freq data=analysis3;
table gcens;
run;
data leeds;
set analysis3;
keep recip_id rec_unit tx_date donor_id;
run;
data recip_names;
set database.recipient;
run;
proc sort data=leeds;
by recip_id;
run;
proc sort data=recip_names;
by recip_id;
run;
data missingkidneydata;
merge leeds recip_names;
by recip_id;
if tx_date=. then delete;
run;
data royalfree;
set missingkidneydata;
IF REC_UNIT='F1212';
RUN;
PROC FREQ DATA=ROYALFREE;
TABLE REC_UNIT;
RUN;

/*note information*/
data note;
set database.recipient_note;
run;
proc sort data=note;
by recip_id;
run;
proc sort data=analysis3;
by recip_id;
run;
data itpnote;
merge analysis3 note;
by recip_id;
if dcod=. then delete;
keep donor_id recip_id rcod note_type note_text;
run;
data grafted;
set database.grafted_organ_note;
run;
proc sort data=grafted;
by donor_id;
run;
proc sort data=analysis3;
by donor_id;
run;
data grafteditp;
merge grafted analysis3;
by donor_id;
if dcod=. then delete;
keep donor_id recip_id note_type note_text pcens gcens rcod;
run;

/*heart ITP*/
data heartitp;
set standard.cardio_tx;
if mdy(01,01,2000)<=tx_date<mdy(01,01,2015);
if dtype in (1,2);
run;
proc sort data=itp;
by donor_id;
run;
proc sort data=heartitp;
by donor_id;
run;
data heartitp2;
merge heartitp itp;
by donor_id;
if sod=. then delete;
if donor_id  in
(49500, 58575,59122,71187,79663, 90012, 92051, 92211, 92340,
104535, 105671, 108560, 62345, 71536, 104396, 105599, 107337,
72766, 83330, 96590, 55688, 108320, 95864, 109545) then ITP=1;
if recip_id=. then delete;
run;
proc univariate data=heartitp2;var rage;run;
pROC FREQ DATA=HEARTITP2;TABLE RSEX;RUN;
pROC FREQ DATA=U;TABLE RSEX;RUN;
pROC FREQ DATA=HEARTITP2;TABLE RECIP_ID*PCD;RUN;
pROC FREQ DATA=HEARTITP2;TABLE cof;RUN;
data newcastleh;
set heartitp2;
if rec_unit='A1313';
run;
proc sort data=heartitp2;
by recip_id;
run;
proc sort data=note;
by recip_id;
run;
data heartinfo;
merge heartitp2 note;
by recip_id;
if dcod=. then delete;
if recip_id =132754;
run;

proc freq data=heartinfo;
table rcod;
run;
proc freq data=heartitp2;
table recip_id*rec_unit;
run;

data plateletsheart;
input recip_id 1-6
plts 8-10;
datalines;
177831 143
175849 096
142526 053
132754 096
run;
proc univariate data=plateletsheart;var plts;run;
/* notes*/

data note;
set database.recipient_note;
run;
proc sort data=note;
by recip_id;
run;
proc sort data=heartitp2;
by recip_id;
run;
data itpnote;
merge heartitp2 note;
by recip_id;
if dcod=. then delete;
keep donor_id recip_id dcod note_type note_text;
run;

data plt;
set database.dcsd_organ_donor;
run;
proc sort data=itp;
by donor_id;
run;
proc sort data=plt;
by donor_id;
run;
data itpplt;
merge itp plt;
by donor_id;
if sod=. then delete;
run;
proc sort data= itpplt nodupkey;
by donor_id;
run;


/*MG donors*/
data MGdonors;
set standard.donors;
if mdy(01,01,2000)<=ddate<mdy(01,01,2016);
if dtype in (1,2);
if dcountry='UNITED KINGDOM';
```

```
if donor_id in (78281
91672
105989
56140
102119
60609
55985
64208
66829
67819
78281
78592
84814
85565
89718
89871
91672
95506
100682
100984
105278
113415
113723
114468
105794) then MG=1;
run;
data MGdonors2;
set mgdonors;
if mg=1;
run;

proc sort data=mgdonors;
by donor_id;
run;
data kindeymg;
set standard.kidney_tx;
run;
proc sort data=kindeymg;
by donor_id;
run;
data kindeymg2;
merge mgdonors2 kindeymg;
by donor_id;
if MG=1;
if recip_id=. then delete;
run;
proc sort data=kindeymg2;
by recip_id;
run;
data mgnotes;
merge kindeymg2 note;
by recip_id;
if mg=1;
run;
data mgnotes2;
set mgnotes;
if rec_unit='D0101';
run;

proc freq data=kindeymg2;
table cof;
run;
data livermg;
set standard.liver_tx;
run;
proc sort data=livermg;
by donor_id;
run;
proc sort data=mgdonors2;
by donor_id;
run;

data livermg2;
merge mgdonors2 livermg;
by donor_id;
if MG=1;
if recip_ID=. THEN DELETE;
run;
PROC FREQ DATA=LIVERMG2;
TABLE RCOD;
RUN;


data cambridgeplatelets;
input day0 1-2 day3 4-6;
datalines;
47    34
50    22
83    58
52    44
107   115
316   269
135   NA
56    29
62    47
86    33
85    110
34    13
38    28
91    58
175   83
216   38
56    27
74    41
47    67
90    80
77    54
64    103
69    65
59    44
37    17
39    53
84    76
122   169
53    40
74    72
52    36
218   390
61    86
101   110
69    51
98    125
82    152
81    56
28    16
47    31
70    53
78    55
255   216
83    50
60    35
36    43
19    19
32    30
61    50
72    60
150   274
86    51
38    35
44    30
46    39
26    130
36    44
45    52
648   430
39    41
63    32
27    35
121   63
133   71
95    51
53    50
80    47
73    28
36    71
86    41
47    45
47    45
62    30
90    31
53    27
229   118
199   138
75    18
57    26
52    65
241   299
93    70
26    32
69    46
41    29
74    111
158   169
85    29
83    34
59    51
60    20
69    58
101   69
79    48
68    37
121   80
67    63
64    74
44    35
31    51
NA    NA
47    50
57    79
113   61
88    52
39    64
30    27
69    80
72    98
57    20
66    34
98    69
86    86
61    46
39    13
65    Death post tx
```

```
60 30
115 62
72 69
105 55
197 162
60 46
34 51
47 80
88 72
52 61
144 235
66 64
402 56
71 40
43 73
46 33
35 40
66 55
59 36
68 36
79 27
37 37
48 61
55 29
71 50
109 94
60 58
71 87
48 33
91 53
38 39
74 73
46 47
24 28
73 59
134 60
24 30
80 103
36 54
52 51
84 44
20 24
17 42
251 145
33 44
62 35
71 57
NA 42
33 24
44 44
54 NA
51 46
35 52
66 38
92 69
27 32
128 124
70 37
35 61
NA 56
38 49
40 60
58 47
181 111
117 137
74 39
49 31
310 201
69 19
71 43
51 26
57 23
38 45
89 53
75 54
121 117
46 32
96 118
72 30
44 22
54 35
41 33
53 44
91 58
50 33
90 55
19 25
80 91
61 31
142 58
52 38
37 37
105 68
93 53
97 26
103 38
70 76
35 34
56 60
221 162
65 50
47 NA
37 NA
52 41
40 54
120 139
98 107
30 16
33 36
116 117
47 29
55 64
60 34
83* 56
43 23
53 68
42 57
168 66
42 26
91 55
39 32
51 51
119 99
198 102
30 15
60 48
31 78
77 47
32 52
40 40
41 52
60 35
47 43
55 49
37 61
100 55
51 35
33 28
22 55
34 19
40 53
63 40
68 72
run;
proc univariate data=cambridgeplatelets;
var day3;
run;
data new;set cambridgeplatelets;
new=day0-day3;run;
data new2;set new;
if new=>1 then new2=new;
if day0=>1 then itpseries=0;
run;
proc univariate data=new2;
var new2;
run;


data Platelets;
input
day0 1-3
day3 5-7

;
datalines;
364 51
53  24.
372 2
23  56.
73  36.
304 153
131 83.
64. 47.
54. 15.
197 74.
267 342
41. 24.
101 76.
103 44.
;
run;
data plat;set platelets;
if day0=>1 then ITPseries=1;
run;
data new2;set new2;run;
proc sort data=new2;by itpseries;
run;
data together;
merge plat new2;
by itpseries;
run;
proc npar1way data=together;
class ITPseries;
var day3;
run;
```

1.49 Appendix 4: Increased risk behaviour code

```
data risk;
set standard.donors;
if dtype in (1,2);
if dcountry='UNITED KINGDOM';
if mdy(01,01,2003)<=ddate<mdy(01,01,2016);
run;

data sexualbehaviour;
set risk;
if donor_id in
(115653, 114819, 114136, 113244,
112746,111880,111572,103242,109999,108539,107940,107896,
107849,107794,107722,106546,105751,100500,103558,102676,1005
66,114819,114509,113104,111880,
111522,107940,107129,106178,105751,104542,103242,101459,1151
76,114914,59285,60885,61131,64452,
67161,71186,77320,79519,80637,82199,83710,84762,85674,85793,8
6693,87348,89139,91848,93337,
93810,97175,97653,97756,99346,101459,103242,104542,105751,106
411,107129,107794,107940,
107995, 58039
) then HRSB=1;
if donor_id in
(117081,114581,114528,113303,113109,112934,112724,112152,1119
33,111411,110559,110334,108118,
107661,106679,106218,105697,105372,103592,103309,100703,1010
56,77195,80869,92742,99921,
59736,62488,63081,63167,63602,64498,65325,66680,66727,66875,6
8083,69664,70386,72500,
72799,73146,73381,74724,74914,76083,77196,77218,78059,81437,8
2709,83910,84948,85603,
85707,87151,87669,88203,90161,90392,90960,91959,92742,93127,9
3656,94862,95205,95478,95968,
96216,96492,97332,99921,100060,100375,100703,101056,101843,10
1994,103309,103592,104542,105372,
105634,105697,106218,106679,107661
) then HRSB=2;
if donor_id in
(117857,110250,100375,60864,65391,68140,68929,80495,92918,933
82,94416,95615,100064,100375,
100500,106178) then HrsB=3;
if donor_id in
(108989,106611,103899,87004,95478,100566,101759,
103899) then HrsB=4;
if donor_id in
(117391,112783,109881,109142,106279,104587,100319,72941,80501
,83817,98976,100319,104587,
106279,106839) then HrsB=5;
run;
proc univariate data=sexualbehaviour;
class hrsb;
var dage;
run;

data sexualbehaviour2;set sexualbehaviour;if hrsb=>1;run;
proc sort data=sexualbehaviour2; by ddate;run;
proc freq data=sexualbehaviour;table hrsb;run;
data IVDU;
set sexualbehaviour;
if donor_id in
(117907,117881,117857,117685,117646,117601,117526,117473,1174
22,116954,116950,116936,116717,
116476,116402,116017,115643,115616,115524,115523,115382,1151
67,115102,114912,114804,114676,
114648,114535,114480,114364,114322,114239,114156,113996,1136
15,113324,113303,113228,113192,
113114,112807,112699,112430,112276,112152,111830,111819,1118
01,111604,111230,110087,110713,
110608,110461,110345,110343,109999,109917,109887,109493,1093
20,108996,108972,108757,108667,
108572,108526,108441,108305,108043,108029,107995,107994,1078
49,107809,107794,107652,107279,
106939,106931,106841,106715,106456,106425,106265,106178,1060
98,105786,105109,105106,105059,
104842,104749,104467,104273,104253,104204,104080,104037,1038
00,103535,103259,103211,103066,
102995,102676,102590,102291,102225,102100,102056,101759,1015
17,101408,101270,100702,100597,
100521,60623,62721,65651,66117,66214,70439,72753,73451,73860,
76439,77166,77787,78912,79509,
81805,81990,83005,83150,85331,85631,85687,86122,86198,86715,8
7414,87676,88380,90424,90999,
91090,91458,91630,92145,92768,92771,94331,94944,95352,95459,9
6238,96250,97295,97316,97558,
100014,100105,100702,101270,101517,101548,57586,91569
94602
82390
77389)
then IVDU=1;
if donor_id in
(117428,117330,116530,116361,116210,115749,115556,115356,1153
05,114938,114890,114869,114833,
114578,114299,114176,114011,113912,113414,112390,111762,1117
26,111535,111388,111264,111034,
110768,110378,110346,109836,109321,109163,108618,108156,1071
07,106489,106340,106244,106213,
105698,105201,105187,104989,104964,104941,104659,104410,1040
97,102506,102305,102253,101769,
101599,101548,101197,100730,100500,100272,100161,58665,58916,
59101,59445,60540,60569,60580,
61844,63033,64020,64695,64909,66131,67989,68289,68717,69134,7
0590,70842,71094,71358,73154,
73286,73290,73473,75084,75086,76102,76447,78089,78844,79485,7
9906,80537,80863,80981,81688,
81785,82184,82291,82345,83698,84327,84744,85053,85081,85450,8
5545,86681,87648,88076,88730,
90766,91468,91678,92169,93679,93756,93919,94423,95126,95286,9
6390,97187,97216,98377,98928,
99003,99321,99401,100272,100377,100521,101006,101197,101577,1
01599, 69302
94075
114353
88713
90532
102640
65083
89928
62081
72094
78609
97155
)
then IVDU=2;
run;
proc freq data=IVDU;table IVDU;run;
data prison;
set IVDU;
if donor_id in
(117877,116676,115957,115675,115643,115638,115523,115287,1152
52,115167,115069,115061,114833,
114827,114739,114256,114194,114176,114011,113149,112807,1127
46,112683,112430,112408,112152,
111916,111893,111765,111604,111572,111189,110776,110662,1105
02,110378,109907,109407,109380,
109233,109189,109045,109039,108747,108247,108134,108029,1071
27,106931,106839,106698,106429,
106411,106316,106016,105914,105682,105221,104749,104499,1043
99,104275,103726,103592,103511,
103066,102753,102225,101994,101474,100457,100105,61620,61348,
60947, 63529, 63474, 60947
63989,64365,64403,65845,67094,67652,68140,68405,69684,72979,7
3565,73809,74789,76548,
76751,78028,79050,79519,79940,80085,80240,81533,82169,83082,8
4433,84589,86693,87032,
87112,87441,88333,88771,89139,89740,90429,90495,90635,90677,9
0918,91377,91524,91915,
92031,92166,92946,93808,94219,94265,94527,94627,95114,96246,9
6356,96671,96986,97154,
97246,97787,97885,98806,99069,100161,100462,101177,101204,101
408,101873,102056,102291,
102590,102696,103278,103726,103995,104068,104143,105059,1058
41,106546,106699,106931,107127,
107279,107652,107794,107809,107995
108009)
then prison=1;
if donor_id in
(117907,117896,117526,117422,116954,116867,115699,115654,1155
24,115102,114912,114018,113285,
113176,112810,112384,111864,111535,111393,111268,111230,1110
88,110947,110345,110296,109989,
109989,109261,108667,108009,107995,107940,107849,107809,1077
94,107652,107557,106546,106061,
105841,105059,104143,104068,103995,103278,102696,102590,1022
91,102069,102056,101873,101408,
101303,101263,101204,101177,100597,100462,100161,61639,63907,
63482,64118,66352,73563,
74914,75055,75381,75697,76254,78149,78407,79589,80869,82145,8
2199,82842,83959,85344,85793,
85857,86798,87368,88067,89464,90212,90520,92723,93182,93186,9
3379,93558,93571,93587,93884,
93964,94057,94086,94947,95015,95153,95342,95373,96072,96285,9
6692,96946,97313,97557,97751,
97887,98543,98636,99258,99272,99515,99866,100597,101263,10147
4,102225,102753,103066,103511,
104399,104499,104749,105221,105682,106016,106316,106429,1066
11,106698,106839
107557,83682
) then prison=2;
donation_year=year(ddate);
run;
data barchartforpaper1;set prison;if IVDU or prison or HRSB =>1 then
high_risk=1;
else high_risk=0;
if donation_year=2000 then dyear='2000';
if donation_year=2001 then dyear='2001';
if donation_year=2002 then dyear='2002';
if donation_year=2003 then dyear='2003';
if donation_year=2004 then dyear='2004';
```

```
if donation_year=2005 then dyear='2005';
if donation_year=2006 then dyear='2006';
if donation_year=2007 then dyear='2007';
if donation_year=2008 then dyear='2008';
if donation_year=2009 then dyear='2009';
if donation_year=2010 then dyear='2010';
if donation_year=2011 then dyear='2011';
if donation_year=2012 then dyear='2012';
if donation_year=2013 then dyear='2013';
if donation_year=2014 then dyear='2014';
if donation_year=2015 then dyear='2015';
if dethnic=1 then ethnic=1;
else ethnic=2;
if past_diabetes=1 then diabetes=1;if past_diabetes=2 then
diabetes=2;if past_diabetes in (3,4,5,6,7,8,9,.) then diabetes=3;
if past_hypertension=1 then hypertension=1;if past_hypertension=2
then hypertension=2;if past_hypertension in (3,4,5,6,7,8,9,.) then
hypertension=3;
if past_cardio_disease=1 then cardio=1;if past_cardio_disease=2 then
cardio=2;if past_cardio_disease in (3,4,5,6,7,8,9,.) then cardio=3;
if past_alcohol_abuse=1 then alcohol=1;if past_alcohol_abuse=2 then
alcohol=2;if past_alcohol_abuse in (3,4,5,6,7,8,9,.) then alcohol=3;
if past_liver_disease=1 then liver=1;if past_liver_disease=2 then
liver=2;if past_liver_disease in (3,4,5,6,7,8,9,.) then liver=3;
if past_drug_abuse=1 then drug=1;if past_drug_abuse=2 then
drug=2;if past_drug_abusee in (3,4,5,6,7,8,9,.) then drug=3;
if hcv=1 then hepC=1;if hcv=2 then hepC=2;if hcv in (3,4,5,6,7,8,.) then
hepc=3;
if past_smoker=1 then smoker=1;if past_smoker=2 then smoker=2;if
past_smoker in (3,4,5,6,7,8,9,.) then smoker=3;
run;
data infor;
set barchartforpaper1;
if dyear=>2009;
run;
proc freq data=infor;
table high_risk*sod;
run;


/*data PHE data collection*/
data phe;
set barchartforpaper1;
if high_risk=1 or HCV=2;
if mdy(01,01,2010)<=ddate;
x=1;
run;

data names;
set database.donor_basics;
run;
proc sort data=names;
by donor_id;
run;
proc sort data=phe;
by donor_id;
run;

data togetherphe;
merge phe names;
by donor_id;
if x=1;
run;

proc sort data=togetherphe nodupkey;
by donor_id;
run;
data togetherphe2;
set togetherphe;
keep donor_id surname forename sod dregion hospname IVDU prison
HRSB HCV HIB HBV ddate;
run;
proc sort data=togetherphe2;
by dregion;
run;


/*for Q-Pulse */
data Q;set barchartforpaper1;if high_risk=1;if
ddate=>mdy(01,01,2012);if sod=1; run;

/*unused reason*/
data unused;
set database.unused_organ;
run;
data unusednote;
set database.unused_organ_note;
run;
proc sort data=unused;by donor_id;run;
proc sort data=unusednote;by donor_id;run;
data unused2;merge unused unusednote;by donor_id;run;
data notdonated;set viralnone; if sod=0;if high_risk=1;run;
proc sort data=notdonated;by donor_id;run;
proc sort data=unused2; by donor_id;run;
data sod; merge notdonated unused2;by donor_id; if high_risk=1;keep
ddate donor_id primary_reason secondary_reason high_risk donor_id
organ_type HBCAB note_type note_text;run;
data sod2;set sod;if organ_type in
(10,11,12,13,30,40,41,42,50,60,61,62,63,81,83,85,101,102,105);run;

proc sort data=sod2 nodupkey; by donor_id;run;
proc freq data=sod2;table organ_type*primary_reason;run;

/*number high_risk*/
proc freq data=barchartforpaper1;table high_risk;run;
/*data tables-figure 1-how many proceed and dont proceed*/



/*return*/

data barchartforpaper2;set barchartforpaper1; if high_risk=1 or
hCV=2;run;
proc freq data=barchartforpaper2;
table hcv;
run;
/*for Ines*/
data ines;
set barchartforpaper2;
keep donor_id HCV ddate trust_name new_dtc_team ddob high_risk;
run;
proc sort data=ines;by ddate;
by donor_id;
run;

data basics;
set database.donor_basics;
run;
proc sort data=basics;
by donor_id;
run;

data inesbasics;
merge ines basics;
by donor_id;
if high_risk=. then delete;
keep donor_id HCV ddate trust_name new_dtc_team ddob forename
surname;
run;

proc sort data=inesbasics nodupkey;
by donor_id;
run;


data inesbasics2;
set inesbasics;
if ddate=>mdy(01,01,2012);
run;



/*table for Ines*/
data barchartforpaperX;set barchartforpaper2;keep donor_id ddate
IVDU prison HRSB sod trust_name HCV ethnic;run;

data barchartpaper3;set barchartforpaper2;if sod=1;run;
data barchartIVDU;set barchartforpaper1;if IVDU=>1;run;
data barchartPrison;set barchartforpaper1;if prison=>1;run;
proc freq data=prison; table prison*IVDU*HRSB;run;


/*data Tables-How many of each type of high risk donor-how many
multiple?*/
proc freq data=barchartforpaper2; table high_risk*sod;run;
proc freq data=barchartforpaper2; table IVDU*sod;run;
proc freq data=barchartforpaper2; table prison*sod;run;
proc freq data=barchartforpaper2; table HRSB*sod;run;
proc freq data=barchartforpaper2; table HRSB*IVDU;where
sod=1;run;
proc freq data=barchartforpaper2; table HRSB*prison;where
sod=1;run;
proc freq data=barchartforpaper2; table IVDU*prison;where
sod=1;run;
proc freq data=barchartforpaper2; table HRSB*IVDU;where
sod=0;run;
proc freq data=barchartforpaper2; table HRSB*prison;where
sod=0;run;
proc freq data=barchartforpaper2; table IVDU*prison;where
sod=0;run;


/*number of viral positive in each group*/
data virus;set barchartforpaper1;if HCV=2 or HIV=2 or HBSAG=2 or
HTLV=2;run;
data viralcombination; set virus;if hcv=2 and htlv=2;run;
proc freq data=virus;table sod*risk/chisq;run;

data alldata;set final2;if HCV=2 or HIV=2 or HBSAG=2 or HTLV=2 then
viral=1;else viral=0;IF SOD=1;run;
proc freq data=ALLDATA;table virAl*UTILISED/CHISQ;run;

/*Ines to request samples*/
data hospitals;set final2;if high_risk=1;keep donor_id hospname
dregion ddate risk HCV;run;
proc sort data=hospitals;by dregion;run;
proc freq data=hospitals;table DREGION;run;


proc sort data=hospitals nodupkey;by dregion;run;
```

```
proc freq data=alldata; table risk/chisq;where risk in (1,2,3);run;

/*compare*/
data compare;
input behaviour 1 type 3 percent 5-7;
datalines;
1 1 133
1 2 97.
2 1 311
2 2 188
3 1 215
3 2 169
run;
proc freq data=compare;
weight percent;
table behaviour*type/chisq;run;
data viralonly;set final2;if HCV=2 or HIV=2 or HBSAG=2 or
HTLV=2;run;
proc univariate data=viralonly;class high_risk;var organs_ofd;run;
data compare2;
input organ highrisk number;
datalines;
1 1 32
1 2 11
2 1 29
2 2 44
run;
proc freq data=compare2;
weight number;
table organ*highrisk/chisq;
run;

data viralonly1;
set viralonly;
if hTLV=2 then HTV=2;
if HTLV=1 then HTV=1;
if hTLV in (3,4,5,6,7,8,9,.) then HTLV=3;
run;

proc npar1way data=viralonly;
class high_risk;
var dage;
run;

proc freq data=viralonly1;table sod*risk/chisq;run;
DATA FINAL3;SET FINAL2;IF DDATE=>MDY(01,01,2013);RUN;
PROC FREQ DATA=FINAL3;TABLE HIGH_RISK;RUN;



data viralnone;set final2;if HCV=2 or HIV=2 or HBSAG=2 or HTLV=2
then delete;if donor_id=. then count=0;else count=1;
if IVDU=. then IVDU=0;run;
proc freq data=viralnone;table high_risk*sod;run;

/*new data table-all potential with no viral positivity*/
proc univariate data=viralnone;class high_risk;var
dage;histogram/normal;run;
proc npar1way data=viralnone;class high_risk;var dage;
run;
proc freq data=viralnone;table dsex*high_risk/chisq;run;
proc freq data=viralnone;table diabetes*high_risk/chisq;run;
proc freq data=viralnone;table smoker*high_risk/chisq;run;

proc freq data=viralnone2;
table high_risk;
run;

data viralnone2;
set viralnone;
if sod=1;
run;
proc univariate data=viralnone2;
class high_risk;
var dbmi;
run;
proc npar1way data=viralnone2;
class high_risk;
var dbmi;
run;
proc freq data=viralnone2;
table dtype*high_risk/chisq;
run;
proc freq data=viralnone2;
table ethnic*high_risk/chisq;
run;
proc freq data=viralnone2;
table alcohol*high_risk/chisq;
run;
proc freq data=viralnone2;
table smoker*high_risk/chisq;
run;
proc freq data=viralnone2;
table cardio*high_risk/chisq;
run;
proc freq data=viralnone2;
table diabetes*high_risk/chisq;
run;

/*New figure 2 barchart*/
data viralnonb;
set viralnone;
if high_risk=1;
run;
proc freq data=viralnone;
table dyear*high_risk*sod;
run;
data rate;
input rate;
datalines;
19.2
29.7
27.5
23.6
21.7
33.7
30.4
run;
proc univariate data=rate;
var rate;
run;

proc freq data=viralnone;
table sod*high_risk/chisq;
run;


/*bonferonni adjustment without viral disease present*/

ods output chisq(persist)=chisq(where=(statistic="Chi-squared")
                        rename=(Prob=Raw_P));
proc freq data=viralnone;
where risk in (0,1);
weight count;
table sod*risk/chisq cellchi2 nopercent;
run;
proc freq data=viralnone;
where risk in (0,2);
weight count;
table sod*risk/chisq cellchi2 nopercent;
run;
proc freq data=viralnone;
where risk in (0,3);
weight count;
table sod*risk/chisq cellchi2 nopercent;
run;
proc freq data=viralnone;
where risk in (0,4);
weight count;
table sod*risk/chisq cellchi2 nopercent;
run;
proc freq data=viralnone;
where IVDU in (1,0);
weight count;
table sod*IVDU/chisq cellchi2 nopercent;
proc freq data=viralnone;
where IVDU in (2,0);
weight count;
table sod*IVDU/chisq cellchi2 nopercent;
proc freq data=viralnone;
where IVDU in (2,1);
weight count;
table sod*IVDU/chisq cellchi2 nopercent;
ods output clear;

proc print data=chisq noobs;
var value raw_p;
run;
proc multtest pdata=chisq bon;
run;
proc freq data=viralnone;
table dsex*sod/chisq;
where high_risk=1;
run;

/*with extra IVDU variable*/
data viralIVDU;set viralnone;if IVDU=. then IVDU=0;run;
proc freq data=viralivdu;
table sod*IVDU/chisq;where IVDU in (2,0);run;
data viralnone2;
set viralnone;
if ivdu=1 then risk=4;
if ivdu=2 then risk=2;
run;
proc freq data=viralnone2;
table HRSB*sod;
where hrsb in (1,2,3,4,5);
run;


proc logistic data=viralnone2;
class risk(ref='0') hypertension(ref='1')/param=ref;
model sod=risk dage hypertension;
run;
proc freq data=viralnone;
table risk*prison;
run;


proc multtest data=viralnone boot bon sid permutation hoc stepbon;
class risk;
test mean(sod);
```

```
contrast 'Risk1 V Risk0' 1 -1 0;
contrast 'Risk2 V Risk0' ;
contrast 'Risk3 V Risk0';
contrast 'Risk4 V Risk0';
run;


/*Data tables-High-risk solid organ donors vs. All other deceased
donors*/
data donortests;set barchartforpaper1;run;
proc freq data=donortests;table high_risk;run;proc freq
data=donortests;table smoker*high_risk/chisq;run;
proc univariate data=donortests;class high_risk;var
dage;histogram;run;
proc ttest data=donortests;class high_risk;var dage;run;
proc freq data=donortests;table dsex*high_risk/chisq;run;
proc freq data=donortests;table ethnic*high_risk/chisq;run;
proc freq data=donortests;table HepC*high_risk/chisq;run;
proc freq data=donortests;table HIV*high_risk/chisq;where HIV in
(1,2,3);run;
proc freq data=donortests;table alcohol*high_risk/chisq;run;
proc freq data=donortests;table diabetes*high_risk/chisq;run;
proc freq data=donortests;table smoker*high_risk/chisq;run;
proc freq data=donortests;table cardio*high_risk/chisq;run;
proc npar1way data=donortests;class high_risk;var dbmi;run;
proc univariate data=donortests;class high_risk; var dbmi;
histogram;run;
proc freq data=donortests;table HBSAG*high_risk/chisq;where
HBSAG in (1,2,3);run;

/*Individual risk factors vs. all other deaceased donors*/
data donortestsone;set donortests;if IVDU=1 then HRSB=6;if IVDU=2
then HRSB=7; if prison=1 then HRSB=8; if prison=2 then HRSB=9;
run;
data final;set donortestsone; if HRSB in (1,2,3,4,5) then SB=1;else
SB=0;If IVDU in (1,2) then IV=1; else IV=0;
if prison in (1,2) then Jail=1;else jail=0;run;
proc freq data=final;table IV;run;
data finals;set final; if SB=1 then Risk=1;;if Jail=1 then risk=3;if IV=1
then risk=2;run;
data final2;set finals;if risk=. then risk=0;run;proc freq
data=final2;table risk;run;
data IV;set final2;if IV=1;run;
data donortesttwo;set donortestsone;if HRSB=>1;run;
proc anova data=donortestsone; class HRSB; model dage=HRSB;
means HRSB;run;
proc freq data=final2;table risk;run;

data barchartforpapervirus;set barchartforpaper1;if high_risk=1 and
HCV=2 or HIV=2 or HBV=2 then delete;run;
proc freq data=barchartforpapervirus;table sod*ivdu/chisq;run;

/*Donor Data Table-4 sub groups*/
proc univariate data=final2;class risk;var dbmi;run;
proc anova data=final2; class risk; model dage=risk; means risk;run;
proc anova data=final2; class risk; model dage=risk; means risk/
tukey;run;
proc freq data=final2;table dsex*risk/chisq;run;
proc freq data=final2;table dtype*risk/chisq;run;
proc freq data=final2; table ethnic*risk/chisq;run;
proc npar1way data=final2;class risk;var dbmi;run;
proc univariate data=final2;class risk;var dbmi;run;
proc freq data=final2; table HepC*risk/chisq; where HepC in (1,2);run;
proc freq data=final2; table HBSAG*risk/chisq; where HBSAG in
(1,2,3);run;
proc freq data=final2; table HIV*risk/chisq;where HIV in (1,2,3);run;
proc freq data=final2;table alcohol*risk/chisq;run;
proc freq data=final2;table liver*risk/chisq;run;
proc freq data=final2;table smoker*risk/chisq;run;
proc freq data=final2;table risk;run;

/*offers table/figure for the paper*/
data offers;set standard.current_offers;run;
proc sort data=offers;by donor_id;run;
proc sort data=barchartforpaper1;by donor_id;run;

data alloffers;merge offers barchartforpaper1;by donor_id;if high_risk=.
then delete;run;
data alloffers2;set alloffers;if result=5 then outcome=1;if result=2 then
outcome=2;
if off_cent in ('G1501' 'G0101' 'G0501' 'G1403') then off_cent='G1111';
if off_cent in ('E1301' 'T0701') then off_cent='T2222';
if off_cent in ('F0708' 'F0835') then off_cent='F2222';
if off_cent in ('H1305' 'H1202') then off_cent='H3333';
if off_cent in ('D0921' 'E0425') then delete;
run;
data alloffers3;set alloffers2;
if off_cent in
('02020','M1202','L1330','D0101','W7001','M1701','Y0003','ST101','SS2
26','L3101','SG516','B6313',
'C0301','N2117','E1420','T0101','G1501','E1301','T0701','F1006','H1305
','H1202','G1301','F0708',
'F1212','P1101','A1313','C0851','K4102','L3395','J2102','C1201','M0701'
,'F0890','J2103','X0101');
if org_type in
(10,11,12,13,29,30,31,32,33,34,40,41,42,45,46,47,50,51,52,53,60,61,6
2,63,
64,65,66,67,68 ,69 ,70,81,82,83,84,85,99,100,101,102,105,109,110);
if outcome=. then outcome=3;
run;

proc freq data=alloffers3;table high_risk*reason1/chisq;run;
proc univariate data=alloffers3;class high_risk;
proc sort data=alloffers3 nodupkey;by donor_id;run; /*number of
donors in this analysis-16,112*/
proc freq data=alloffers3;table high_risk;run;/*609 high risk
behaviour*/


data allofersnohighrisk;set alloffers3;if high_risk=0;run;
data highriskonly;set alloffers3;if high_risk=1;run;
proc freq data=highriskonly;table reason1;run;
proc freq data=allofersnohighrisk;table outcome;run;

proc freq data=alloffers3;table off_cent*outcome;run;

/*logistic regression HepC*/
data model;set final2;if hepc=1 then yes=1;else yes=0;run;
proc logistic data=model descending;
class risk(ref='0')  /param=ref;
model yes= dage;
run;
proc logistic data=model descending;
class risk(ref='0')  /param=ref;
model yes= dage risk;
run;
proc logistic data=model descending;
class risk(ref='0')  /param=ref;
model yes=  risk ;
run;

/* Renal Recipients High-risk Behaviour Donors*/
/*Code taken from Meningitis Paper*/
proc sort data=viralnone2;by donor_id;run;
data kidney;set standard.kidney_tx;if
mdy(01,01,2003)<=tx_date<mdy(01,01,2016);
if txcountry='UNITED KINGDOM';if dtype in (1,2);if Tx_type in
(10,11,12,13,14);run;
proc sort data=kidney;by donor_id;run;
data kidneyrisk;merge viralnone2 kidney;by donor_id;if recip_id=. then
delete;
run;

/*Find missing patient survival data*/
proc freq data=kidneyrisk;table pcens;run;
data donors;set standard.donors;run;
proc sort data=kidneyrisk;by donor_id;run;
proc sort data=donors;by donor_id;run;
data kidneyrisk2;set kidneyrisk; if psurv=.;run;
proc sort data=kidneyrisk2;by recip_id;run;
data all;set standard.kidney_tx;run;
proc sort data=all;by recip_id;run;
data Allmissing;merge kidneyrisk2 all;
by recip_id;if high_risk=. then delete;run;
data Missing2;set allmissing;if psurv=. then delete;
rename tx_date=first_tx_date psurv=Patientdays
pcens=patientsurvival;
keep recip_id tx_date psurv pcens;
run;
proc sort data=missing2;by recip_id;run;
data missing3;merge kidneyrisk2 missing2;by recip_id;run;
data missing4;set missing3;if tx_date>first_tx_date then
duration=tx_date-first_tx_date;
run;
data missing5;set missing4;if patientdays=>duration then
psurvfinal=patientdays-duration;
run;
proc sort data=missing5;by recip_id;run;
proc sort data=kidneyrisk;by recip_id;run;
data Kidneyall;merge kidneyrisk missing5;by recip_id;run;
proc freq data=kidneyall;table high_risk;run;
data Analysis;set kidneyall;if psurv=. then psurv=psurvfinal;if pcens=.
then pcens=patientsurvival;
run;
proc freq data=analysis;table pcens;run;/*190 bits of data missing
<10% total*/

/*Censor to 10 years graft and patient survival*/

data analysis2;set analysis;
if psurv=>3650 then psurvival=3650;else psurvival=psurv;
if gsurv=>3650 then gsurvfinal=3650;else gsurvfinal=gsurv;
if psurv=>3650 and pcens=1 then pcensor=0;else pcensor=pcens;
if gsurv=>3650 and gcens=1 then gcensor=0;else gcensor=gcens;
if rage>40 then rage_grp=2;else recip_age_grp=1;
if dage>40 then dage_grp=2;else donor_age_grp=1;
if pcensor=. then delete;
dialysis=datepart(dial_staRT_date);
run;
data analysis3;
set analysis2;date1=dialysis;
label date1="DATE with DATE9. format";
format dialysis date9.;run;
data analysis4;
set analysis3;
dialysis_time=tx_date-dialysis;
run;
proc univariate data=analysis4;
class high_risk;
```

```
var dialysis_time;
run;
proc npar1way data=analysis4;
class high_risk;
var dialysis_time;
run;
proc univariate data=analysis4;
class high_risk;
var wait_time;
run;
proc npar1way data=analysis4;
class high_risk;
var wait_time;
run;

proc freq data=analysis2;table HIV;run;
proc lifetest data=analysis2 notable plots=(S,LLS);
Time psurvival*pcensor(0);
strata risk;
run;

/*Format for data tables*/
data recipientinfo;
set database.recipient;
rename HCV=RHCV;
rename HIV=RHIV;
rename HBSAG=RHBV;
run;
proc sort data=recipientinfo;
by recip_id;
run;
proc sort data=analysis2;
by recip_id;
run;
data analysis3;
merge analysis2 recipientinfo;
by recip_id;
if donor_id=. then delete;
run;
data KidneyFinal;set analysis3;
if rethnic=1 then recip_ethnic=1;else recip_ethnic=2;
if graft_no=1 then Tx=1;if graft_no=2 then Tx=2;if graft_no>2 then
Tx=3;
if crf_tx>85 then sensitised=1;else sensitised=0;
if txcountry='UNITED KINGDOM';if pcensor=. then delete;if gcensor=.
then delete;
if rhcv=1 then rhepc=1;if rhcv=2 then rhepc=2;if rhcv in (3,4,5,6,7,8,9,.)
then rhepc=3;
if prd in (210,211,212,213,214,215,216,217,219) then renal=1;
if prd in (220,221,222,223,224,225,229) then renal=2;
if prd in (241,242) then renal=3;
if prd in (280,281) then renal=4;
run;

proc freq data=viralnone2;
table risk;
run;


%macro
survival(data,surv,cens,period,end,end1,var,survival,yaxis,cgm);
ods listing;
/*READS IN YOUR DATASET AND CHANGES THE SURVIVAL
VARIABLES READY FOR USE*/
/*ALSO CHANGES THE DATA TO YEARS OR MONTHS OR DAYS*/
data surv;
set &data;
if &surv <0 then delete;
cens = &cens;
/*survival analysis-Initially all High risk behaviour together*/
/*Survival macro used*/
if lowcase("&period") = "months" then surv = &surv / 30.44;
if lowcase("&period") = "years" then surv = &surv / 365.25;
if lowcase("&period") = "days" then surv = &surv / 1;
if surv > &end then do; surv = &end; cens = 0; end;
fup = 0;
if surv = &end or cens ne 0 then fup = 1;
run;

/*GETS THE COUNT FOR EACH STRATA*/
proc freq data = surv noprint; table &var / out = num; run;

/*GETS THE COUNT FOR FOLLOW UP*/
proc freq data = surv noprint; table &var * fup / out = fup; run;

/*OPENS THE FILE TO SAVE THE PLOT*/
filename gsasfile "&file.\&cgm..emf";

/*RUNS THE LIFETEST PROCEDURE TO OUTPUT THE DATA
NEEDED FOR THE PLOT*/
ODS OUTPUT homtests=homtests;
proc lifetest data=surv plots=(s) outsurv=surv1;
time surv*cens(0); strata &var;
run;
quit;

/*SORTS OUT THE LAYOUT OF THE PLOT AND CHOOSES
COLOURS FOR THE LINES*/
goptions reset=all reset=symbol htext=1.8 cback=white colours=(black)
/*ftext=HWCGM005*/ ftext='Arial/bold'
noborder hsize=8.5 vsize=9.5 Gaccess=GSASFILE;run;

axis1 minor=none order=&yaxis to 100 by 10 label=(ANGLE=90 "%
&survival survival");
axis2 minor=none order=0 to &end by &end1 label=("&period post-
transplant");
symbol;
symbol1 c=CXFF6600 i=steplj w=4 l=1 v=none;
symbol2 c=CX99CCFF i=steplj w=4 l=1 v=none;
symbol3 c=CXFFCC00 i=steplj w=4 l=1 v=none;
symbol4 c=CX339966 i=steplj w=4 l=1 v=none;
symbol5 c=black    i=steplj w=4 l=1 v=none;
symbol6 c=CXFF6600 i=steplj w=4 l=2 v=none;
symbol7 c=CX99CCFF i=steplj w=4 l=2 v=none;
symbol8 c=CXFFCC00 i=steplj w=4 l=2 v=none;
symbol9 c=CX339966 i=steplj w=4 l=2 v=none;
symbol10 c=black   i=steplj w=4 l=2 v=none;

                LEGEND1 ACROSS=1
                POSITION=(BOTTOM INSIDE CENTER)
                MODE=SHARE
                OFFSET=(0,1.5)
                SHAPE=SYMBOL(5,1)
                                CBORDER=Black
                LABEL=(POSITION=(TOP)
                JUSTIFY=CENTER H=1.2 "&var")
                                VALUE=(H=1.2);

/*PRODUCES THE PLOT*/
data splot1; set surv1; retain lag_s; drop=lag_s; if survival=. then
survival=lag_s;
lag_s=survival; run;
data splot2; set splot1; survival=survival*100;
proc gplot data=splot2; plot survival * surv = &var /legend=legend1
noframe vaxis=axis1 haxis=axis2;
title ' '; run; quit;

/*USES THE DATA TO OBTAIN THE SURVIVAL ESTIMATES FOR
THE STRATA*/
data surv2; set surv1; if _censor_ = 0; run;
proc sort data = surv2; by &var survival; run;
proc sort data = surv2 nodupkey; by &var; run;

data surv3; set surv2; surv = (survival*100); lcl = (sdf_lcl*100); ucl =
(sdf_ucl*100);
format surv lcl ucl 10.1; run;

data surv4; merge surv3 num; by &var; run;

/*OBTAINS THE P-VALUE FOR THE STRATA*/
data _null_;
set homtests;
where test = 'Log-Rank';
call symput ("logrank",trim(left(put(ProbChiSq,PVALUE6.4))));
run;

/*PRINTS THE ESTIMATES, COUNT AND P-VALUE FOR THE
DATA*/
title1"&survival survival by &var p=&logrank";
proc print data = surv4; var &var count surv lcl ucl;  run;
%mend survival;

/*MACRO VARIABLES REQUIRED*/
/*%survival(data,surv,cens,time,end,end1,censor,var,survival,period,cg
m);*/
/*WHERE     data=dataset with survival variables
                surv=name of survival variable - eg gsurv
                cens=name of censoring variable - eg
gcens
                period=years, months, days
                end=put 10 if wanting 10 year survival, 12
for 12 month survival, 30 for 30 day survival
                end1=how big you want your x-label gap eg
1 if you want 10 years by 1 year
                var=variable you want to strata by - eg
centre
                survival=either graft, patient or transplant
                yaxis=point at which you want the yaxis to
start, 40 is standard
                emf=name of emf file you want to save
*/

%survival(analysis2,gsurvfinal,gcensor,Years,10,1,risk,graft,0,HR_g);
%survival(analysis2,psurvival,pcensor,Years,10,1,risk,patient,0,HR_p)
;

data analysis3;set analysis2;
if risk in (0,4);
run;

proc lifetest data=analysis2 notable plots=(S,LLS); time
psurvival*pcensor(0);strata risk;where risk in (0,4);run;

/*Cox regression model*/
data model;set prd;
if hypertension in (3,.) then hypertension=3;if diabetes in (3,.)then
diabetes=3;
if smoker in (3,.)then smoker=3;if alcohol in (3,.) then alcohol=3; if
rhepc in (3,.)then rhepc=3;
if hepc in (3,.) then hepc=3;if ethnic in (2,.) then ethnic=2;
if risk in (0,.)then risk=0;
if cardio in (3,.)then cardio=3;
if prison=. then prison=0;
```

```
if hrsb=. then hrsb=0;
if hrsb=1 then higher=1;if hrsb=2 then higher=2;if hrsb=3 then
higher=3;if hrsb=4 then higher=4; if hrsb=5 then higher=5;
run;

data mod;set model;if hypertension in (3,.) then hypertension=3;if
higher=. then higher=0;run;
proc freq data=mod;table sexy*ivdu;run;
proc phreg data=mod;
class renal(ref='5')hypertension(ref='1') HLA_grp (ref='4') rsex(ref='2')
dtype (ref='1') higher(ref='0');
model psurv*pcens(0)=dage rage renal hypertension risk cld_isch
HLA_grp dtype rsex Higher;
hazardratio Higher/diff=ref;
run;

proc freq data=mod;table higher*rcod;run;

data mod2; set mod;if higher=1;
run;
data recipcomment;
set datABASE.RECIPIENT_note;
if recip_id in (36105
44470
46002
77804
92140
96488
97955
101497
101738
102847
104921
106035
106074
106074
109201
110263
115079
128197
130503
132149
132919
133079
133122
134907
135071
135825
135825
136109
138370
139630
139721
143716
144920
145894
146889
152936
153630
156151
159164
160296
162546
164674
165290
166623
167256
172598
172789
173323
175226
178688
188268
190433);run;
proc sort data=recipcomment;
by recip_id;
run;
proc sort data=mod2;by recip_id;run;
data reciphigher;
merge mod2 recipcomment;
by recip_id;
keep recip_id higher rcod note_type note_text;
run;

data kidneycheck;
set database.recipient;
if recip_id=138370;
run;

data temp1;
a=1-CDF('CHISQUARE',44418.454- 44411.457,4);
put a;
run;

/*Kidney HCV Ines Table*/
data kidneyhcv;set kidneyfinal;if HCV=2;keep ddate tx_date rec_unit
recip_id donor_id HCV RHCV HRSB IVDU Prison ethnic pld
RHCV_RNA;run;
proc sort data=kidneyHCV;by ddate;run;

/*Clinical Characteristics of Kidney Recipients from High Risk Donors*/

proc freq data=KidneyFinal;table high_risk;run;
proc univariate data=kidneyfinal;
class high_risk;
var rage;
run;
proc npar1way data=kidneyfinal;class high_risk;var rage;run;


proc anova data=kidneyfinal; class risk;model rage=risk;means
risk;run;
proc freq data=KidneyFinal;table rsex*high_risk/chisq;where rsex in
(1,2);run;
proc freq data=KidneyFinal;table recip_ethnic*high_risk/chisq;where
rsex in (1,2);run;
proc freq data=KidneyFinal;table sensitised*high_risk/chisq;run;

proc univariate data=kidneyfinal;class risk;var
wait_time;histogram;run;
proc freq data=kidneyfinal;table rhepc*risk/chisq;run;
proc freq data=KidneyFinal;table rhepc*risk/chisq;run;
proc freq data=KidneyFinal;table HLA_grp*high_risk/chisq;run;
proc anova data=kidneyfinal;class high_risk; model
rage=high_risk;means high_risk;run;
data barchartkidney; set kidneyfinal; txyear=year(tx_date);run;
data kidneychart; set barchartkidney; if txyear=2000 then year='2000';
if txyear=2001 then tyear='2001';
if txyear=2002 then tyear='2002';
if txyear=2003 then tyear='2003';
if txyear=2004 then tyear='2004';
if txyear=2005 then tyear='2005';
if txyear=2006 then tyear='2006';
if txyear=2007 then tyear='2007';
if txyear=2008 then tyear='2008';
if txyear=2009 then tyear='2009';
if txyear=2010 then tyear='2010';
if txyear=2011 then tyear='2011';
if txyear=2012 then tyear='2012';
if txyear=2013 then tyear='2013';
if txyear=2014 then tyear='2014';
if txyear=2015 then tyear='2015';
if high_risk=1;
run;

data prd;set kidneyfinal; if renal=. then renal=5;run;
proc freq data=prd; table renal*high_risk/chisq;run;
data kidneyealrier;set kidneyfinal;if hcv=2 or HIV=2 or HBSAG=2 or
HTLV=2;if high_risk=0;run;
proc freq data=kidneyealrier;table HTLV;run;

/* Liver Recipients*/
proc sort data=viralnone2;by donor_id;run;
data liver;set standard.liver_tx;if
mdy(01,01,2003)<=tx_date<mdy(01,01,2016);
if txcountry='UNITED KINGDOM';if dtype in (1,2);run;
proc sort data=liver;by donor_id;run;
data liverrisk;merge viralnone2 liver;by donor_id;if recip_id=. then
delete;
run;


/*Find missing patient survival data*/
proc freq data=liverrisk;table pcens;run;
data donors;set standard.donors;run;
proc sort data=liverrisk;by donor_id;run;
proc sort data=donors;by donor_id;run;
data liverrisk2;set liverrisk; if psurv=.;run;
proc sort data=liverrisk2;by recip_id;run;
data total;set standard.liver_tx;run;
proc sort data=total;by recip_id;run;
data totalmissing;merge liverrisk2 total;
by recip_id;if high_risk=. then delete;run;
data LiverMissing2;set totalmissing;if psurv=. then delete;
rename tx_date=first_tx_date psurv=Patientdays
pcens=patientsurvival;
keep recip_id tx_date psurv pcens;
run;
proc sort data=Livermissing2;by recip_id;run;
data Livermissing3;merge liverrisk2 livermissing2;by recip_id;run;
data Livermissing4;set livermissing3;if tx_date>first_tx_date then
duration=tx_date-first_tx_date;
run;
data Livermissing5;set livermissing4;if patientdays=>duration then
psurvfinal=patientdays-duration;
run;
proc sort data=livermissing5;by recip_id;run;
proc sort data=liverrisk;by recip_id;run;
data liverall;merge liverrisk livermissing5;by recip_id;run;
proc freq data=liverall;table high_risk;run;
data liverAnalysis;set liverall;if psurv=. then psurv=psurvfinal;if pcens=.
then pcens=patientsurvival;
run;
proc freq data=liveranalysis;table high_risk;run;

/*5 year censor for Liver analysis*//*104 patients deleted due to no
survival information=1%of data*/

data liveranalysis2;set liveranalysis;
if psurv=>3650 then psurvival=3650;else psurvival=psurv;
if gsurv=>3650 then gsurvfinal=3650;else gsurvfinal=gsurv;
if psurv=>3650 and pcens=1 then pcensor=0;else pcensor=pcens;
if gsurv=>3650 and gcens=1 then gcensor=0;else gcensor=gcens;
```

```
if rage>40 then rage_grp=2;else recip_age_grp=1;
if dage>40 then dage_grp=2;else donor_age_grp=1;
if pcensor=. then delete;
run;
proc lifetest data=liveranalysis2 notable plots=(S,LLS);
time psurvival*pcensor(0);
strata high_risk;run;

/*Data Tables Liver*/
data LiverFinal;set Liveranalysis2;
if rethnic=1 then recip_ethnic=1;else recip_ethnic=2;
if graft_no=1 then Tx=1;if graft_no=2 then Tx=2;if graft_no>2 then
Tx=3;
if crf_tx>85 then sensitised=1;else sensitised=0;
if txcountry='UNITED KINGDOM';if pcensor=. then delete;if gcensor=.
then delete;
if dcountry='UNITED KINGDOM';
if rhcv=1 then rhepc=1;if rhcv=2 then rhepc=2;if rhcv in (3,4,5,6,7,8,9,.)
then rhepc=3;
run;

/*data liver Ines HCV*/
data liverhcv;set liverfinal;if HCV=2;keep recip_id donor_id HCV RHCV
HRSB IVDU Prison ethnic pld RHCV_RNA;run;


data barchartliver; set liverfinal; txyear=year(tx_date);run;
data liverchart; set barchartliver; if txyear=2000 then year='2000';
if txyear=2001 then tyear='2001';
if txyear=2002 then tyear='2002';
if txyear=2003 then tyear='2003';
if txyear=2004 then tyear='2004';
if txyear=2005 then tyear='2005';
if txyear=2006 then tyear='2006';
if txyear=2007 then tyear='2007';
if txyear=2008 then tyear='2008';
if txyear=2009 then tyear='2009';
if txyear=2010 then tyear='2010';
if txyear=2011 then tyear='2011';
if txyear=2012 then tyear='2012';
if txyear=2013 then tyear='2013';
if txyear=2014 then tyear='2014';
if txyear=2015 then tyear='2015';
if high_risk=1;
run;
data liverchart2; set barchartliver; if txyear=2000 then year='2000';
if txyear=2001 then tyear='2001';
if txyear=2002 then tyear='2002';
if txyear=2003 then tyear='2003';
if txyear=2004 then tyear='2004';
if txyear=2005 then tyear='2005';
if txyear=2006 then tyear='2006';
if txyear=2007 then tyear='2007';
if txyear=2008 then tyear='2008';
if txyear=2009 then tyear='2009';
if txyear=2010 then tyear='2010';
if txyear=2011 then tyear='2011';
if txyear=2012 then tyear='2012';
if txyear=2013 then tyear='2013';
if txyear=2014 then tyear='2014';
if txyear=2015 then tyear='2015';
run;

data Q;
set liverfinal;if risk=.;run;

/* Clinical Characteristics of Liver Transplant Recipients*/
proc freq data=liverFinal;table high_risk;run;
proc univariate data=liverfinal; class high_risk;var rage;run;
proc npar1way data=liverfinal;class high_risk;var rage;
run;
proc freq data=liverfinal;table high_risk*rsex/chisq;run;

proc anova data=liverfinal; class risk; model rage=risk; means risk/
tukey;run;
proc ttest data=liverfinal;class high_risk;var rage;run;
proc freq data=liverFinal;table rsex*risk/chisq;where rsex in (1,2);run;
proc freq data=liverFinal;table rsex*HIGH_risk/chisq;where rsex in
(1,2);run;
proc freq data=LIVERFinal;table recip_ethnic*risk/chisq;run;
proc freq data=LIVERFinal;table recip_ethnic*HIGH_risk/chisq;run;
proc freq data=LIVERFinal;table URGENT*risk/chisq;run;
Proc freq data=LIVERFinal;table URGENT*HIGH_risk/chisq;run;
proc freq data=LIVERFinal;table recip_ethnic*HIGH_risk/chisq;run;
proc freq data=LIVERfinal;table rhepc*high_risk/chisq;run;
PROC npar1way DATA=liverfinal;class risk; var UKELD;run;
PROC univariate DATA=liverfinal;class risk; var UKELD;run;
PROC npar1way DATA=liverfinal;class high_risk; var UKELD;run;
PROC univariate DATA=liverfinal;class high_risk; var UKELD;run;
data pld;set liverfinal; if pld= 424 then liverd=1;if pld=419 then liverd=2;
if pld in
(428,430,431,432,435,436,437,438,439,471,472,473,474,475,476,477,
478,479,480,481,482)then liverd=3;
run;
data pld2;set pld;if liverd=. then liverd=4;
if hypertension in (3,.) then hypertension=3;if diabetes in (3,.)then
diabetes=3;
if smoker in (3,.)then smoker=3;if alcohol in (3,.) then alcohol=3; if
rhepc in (3,.)then rhepc=3;
if hepc in (3,.) then hepc=3;if ethnic in (2,.) then ethnic=2;
if risk in (0,.)then risk=0;
if cardio in (3,.)then cardio=3;
if prison=. then prison=0;
if hrsb=. then hrsb=0;
if hrsb=1 then higher=1;if hrsb=2 then higher=2;if hrsb=3 then
higher=3;if hrsb=4 then higher=4; if hrsb=5 then higher=5;
run;
data pld3;set pld2;if higher=. then higher=0;run;

data mod;set model;if hypertension in (3,.) then hypertension=3;if
higher=. then higher=0;run;
proc freq data=mod;table sexy*ivdu;run;run;
proc freq data=pld2;table liverd*high_risk/chisq;run;

/*liver positive virology*/
data liverviral;set liverfinal;if HCV=2 or HIV=2 or HTLV=2 or
HBSAG=2;if high_risk=0;run;
proc freq data=liverviral;table hbsag;run;

/*reviewer comment*/
data liversf;set liverfinal;if risk in (1,0);run;

/*Liver survival analysis*/
%survival(liverfinal,gsurvfinal,gcensor,Years,5,1,risk,graft,0,HR_g);
%survival(liversf,psurvival,pcensor,Years,5,1,risk,patient,0,HR_p);

/*Liver multivariate model*/

proc phreg data=pld3;
class liverd(ref='4') risk(ref='0') urgent (ref='0');
model psurvival*pcensor(0)=dage rage risk urgent cit liverd;
hazardratio risk/diff=ref;
run;

proc anova data=liverfinal;
class risk;
model dage=risk;
means risk;
run;
run;



/* Heart Recipients from High risk behaviour donors*/
proc sort data=final2;by donor_id;run;
data finalhcv;set final2;if hcv=2;run;
data heart;set standard.cardio_tx;if
mdy(01,01,2000)<=tx_date<mdy(01,01,2016);
if txcountry='UNITED KINGDOM';if dtype in (1,2);run;
proc sort data=heart;by donor_id;run;
data heartrisk;merge final2 heart;by donor_id;if recip_id=. then delete;
run;

/*Heart recipients from HCV positive donors*/
proc sort data=finalhcv;by donor_id;run;
data hearthcv; merge heart finalhcv;by donor_id;if HCV=2;run;

/*Find missing patient survival data*/
proc freq data=heartrisk;table pcens;run;
data donors;set standard.donors;run;
proc sort data=heartrisk;by donor_id;run;
proc sort data=donors;by donor_id;run;
data heartrisk2;set heartrisk; if psurv=.;run;
proc sort data=heartrisk2;by recip_id;run;
data complete;set standard.cardio_tx;run;
proc sort data=total;by recip_id;run;
data completemissing;merge heartrisk2 complete;
by recip_id;if high_risk=. then delete;run;
data heartMissing2;set completemissing;if psurv=. then delete;
rename tx_date=first_tx_date psurv=Patientdays
pcens=patientsurvival;
keep recip_id tx_date psurv pcens;
run;
proc sort data=heartmissing2;by recip_id;run;
data heartmissing3;merge heartrisk2 heartmissing2;by recip_id;run;
data heartmissing4;set heartmissing3;if tx_date>first_tx_date then
duration=tx_date-first_tx_date;
run;
data heartmissing5;set heartmissing4;if patientdays=>duration then
psurvfinal=patientdays-duration;
run;
proc sort data=heartmissing5;by recip_id;run;
proc sort data=heartrisk;by recip_id;run;
data heartall;merge heartrisk heartmissing5;by recip_id;run;
proc freq data=heartall;table high_risk;run;
data heartAnalysis;set heartall;if psurv=. then psurv=psurvfinal;if
pcens=. then pcens=patientsurvival;
run;
proc freq data=heartanalysis;table high_risk*tx_type;run;

/*censor data at 5 years*/

data heartanalysis2;set heartanalysis;
if psurv=>3650 then psurvival=3650;else psurvival=psurv;
if gsurv=>3650 then gsurvfinal=3650;else gsurvfinal=gsurv;
if psurv=>3650 and pcens=1 then pcensor=0;else pcensor=pcens;
if gsurv=>3650 and gcens=1 then gcensor=0;else gcensor=gcens;
if rage>40 then rage_grp=2;else recip_age_grp=1;
if dage>40 then dage_grp=2;else donor_age_grp=1;
if pcensor=. then delete;
run;
```

```
proc lifetest data=heartanalysis2 notable plots=(S,LLS);
time psurvival*pcensor(0);
strata high_risk;run;

/*Data Tables heart*/
data heartFinal;set heartanalysis2;
if rethnic=1 then recip_ethnic=1;else recip_ethnic=2;
if graft_no=1 then Tx=1;if graft_no=2 then Tx=2;if graft_no>2 then
Tx=3;
if crf_tx>85 then sensitised=1;else sensitised=0;
if txcountry='UNITED KINGDOM';if pcensor=. then delete;if gcensor=.
then delete;
if dcountry='UNITED KINGDOM';
if rhcv=1 then rhepc=1;if rhcv=2 then rhepc=2;if rhcv in (3,4,5,6,7,8)
then rhepc=3;
run;



/* Clinical Characteristics of Heart Tx recipients from high risk
behaviour donors*/
data hearttable;set heartfinal;if tx_type=30;run;
proc freq data=hearttable;table risk;run;
proc freq data=hearttable;table HIGH_risk;run;
proc anova; class risk; model rage=risk;means risk; run;
proc anova; class risk; model rage=risk;means risk /tukey; run;
proc ttest data=hearttable; class high_risk;var rage;run;
proc univariate data=hearttable; class high_risk;var rage;run;
proc freq data=hearttable;table rsex*risk/chisq;where rsex in (1,2);run;
proc freq data=hearttable;table rsex*high_risk/chisq;where rsex in
(1,2);run;
proc freq data=hearttable;table recip_ethnic*risk/chisq;run;
proc freq data=hearttable;table recip_ethnic*high_risk/chisq;;run;
proc freq data=hearttable;table urgent*risk/chisq;run;
proc freq data=hearttable;table urgent*high_risk/chisq;;run;


/*Heart transplant survival analysis*/

%survival(hearttable,gsurvfinal,gcensor,Years,5,1,high_risk,graft,0,HR
_g);
%survival(hearttable,psurvival,pcensor,Years,5,1,high_risk,patient,0,H
R_p);



/*Q-Pulse for disease transmission*/



/* All other organ transplants*/
proc sort data=final2;by donor_id;run;
data pancreas;set standard.pancreas_tx;if
mdy(01,01,2003)<=tx_date<mdy(01,01,2016);
if txcountry='UNITED KINGDOM';if dtype in (1,2);run;
proc sort data=pancreas;by donor_id;run;
data pancreasrisk;merge final2 pancreas;by donor_id;if recip_id=. then
delete;
run;
proc freq data=pancreasrisk; table high_risk*tx_type;run;

/*MVT recipients*/

proc sort data=final2;by donor_id;run;
data GI;set standard.intest_tx;if
mdy(01,01,2003)<=tx_date<mdy(01,01,2016);
if txcountry='UNITED KINGDOM';if dtype in (1,2);run;
proc sort data=GI;by donor_id;run;
data GIrisk;merge final2 GI;by donor_id;if recip_id=. then delete;
run;
proc freq data=GIrisk; table high_risk*tx_type;run;
```

1.50 Appendix 5: HCV code

```
data liver;
set standard.liver_tx;
if mdy(01,01,2003)<=tx_date<mdy(01,01,2015);
if dtype in (1,2);
run;
proc freq data=liver;
table RHCV;
run;

data liverHCV;
set standard.donors;
if mdy(01,01,2000)<=ddate<mdy(01,01,2015);
if dcountry='UNITED KINGDOM';
if sod=1;
run;
proc freq data=liverHCV;
table HCV;
run;
data liver1;
set liver;
run;
proc sort data=liver1;
by donor_id;
run;
proc sort data=liverHCV;
by donor_id;
run;
data liverHCV2;
merge liver1 liverHCV;
by donor_id;
if recip_id=. then delete;
run;
data liverHCV3;
set liverHCV2;
if HCV=2 then hepatitis=1;
else hepatitis=0;
if RHCV=2 and HCV=2 then Super=2;
if RHCV=1 and HCV=2 then Super=1;
if RHCV=1 and HCV=1 then Super=0;
run;
/*Missing data*/

data livermissingdata;
set liverHCV3;
if psurv=.;
run;
proc sort data=livermissingdata;
by recip_id;
run;
proc sort data=liver;
by recip_id;
run;
data livermissing;
merge livermissingdata liver;
by recip_id;
if hepatitis=. then delete;
run;
data livermiss;
set livermissing;
keep recip_id tx_id psurv pcens  tsurv tcens tx_date;
if psurv=. then delete;
rename psurv=survivaldays pcens=patient_survival;
run;
proc sort data=livermiss;
by recip_id;
run;

data liverall;
merge livermiss livermissingdata;
by recip_id;
run;
proc freq data=liverall;
table patient_survival;
run;
data livermissy;
set livermissing;
keep recip_id tx_id psurv pcens  tsurv tcens tx_date;
run;
data liverlongtime;
set standard.liver_tx;
run;

proc sort data=liverlongtime;
by recip_id;
run;
data livermissing2;
merge livermissingdata liverlongtime;
by recip_id;
if hepatitis=-. then delete;
run;
data livermissy2;
set livermissing2;
keep recip_id tx_id psurv pcens  tsurv tcens tx_date;
keep recip_id tx_id psurv pcens  tsurv tcens tx_date;
if psurv=. then delete;
rename psurv=survivaldays pcens=patient_survival;
rename tx_date=first_transplant_date;
run;
proc sort data=livermissy2;
by recip_id;
```

```
run;
data liverall2;
merge livermissingdata livermissy2;
by recip_id;
run;
data liverPcens;
set liverall2;
if tx_date>first_transplant_date then duration=tx_date-
first_transplant_date;
run;
data liverPcens2;
set liverpcens;
if duration<=survivaldays then Psurvfinal=survivaldays-duration;
run;
proc sort data=LiverPcens2;
by donor_id;
run;
proc freq data=liverpcens2;
table patient_survival;
run;
proc freq data=liverall2;
table patient_survival;
run;
proc sort data=liverall2;
by donor_id;
run;
proc sort data=liverHCV3;
by donor_id;
run;
data liveranalysisfull;
merge liverPcens2 liverHCV3;
by donor_id;
run;
proc freq data=liveranalysisfull;
table patient_survival;
run;
proc freq data=liveranalysisfull;
table pcens;
run;
data liveranalysisfull2;
set liveranalysisfull;
if pcens=. then pcens=patient_survival;
if psurv=. then psurv=Psurvfinal;
run;
proc freq data=liveranalysisfull2;
table pcens;
run;
data liveranalysisfull3;
set liveranalysisfull2;
if psurv=>1826.25 then psurvival=1826.25;
else psurvival=psurv;
if gsurv=>1826.25 then gsurvfinal=1826.25;
else gsurvfinal=gsurv;
if psurv=>1826.25 and pcens=1 then pcensor=0;
else pcensor=pcens;
if gsurv=>1826.25 and gcens=1 then gcensor=0;
else gcensor=gcens;
if rage>40 then recip_age_grp=2;
else recip_age_grp=1;
if dage>40 then donor_age_grp=2;
else donor_age_grp=1;
run;
data recipientinfo;
set database.recipient;
rename HCV=RecipHCV;
run;
proc sort data=recipientinfo;
by recip_id;
run;
proc sort data=liveranalysisfull3;
by recip_id;
run;
data liveranalysisfull4;
merge liveranalysisfull3 recipientinfo;
by recip_id;
if donor_id=. then delete;
run;
proc freq data=liveranalysisfull4;
table rHCV;
run;

data liveranalysis3;
set liveranalysisfull4;
ptsurv= psurvival/365.25;
grsurv=gsurvfinal/365.25;
if dethnic=1 then ethnic=1;
else ethnic=2;
if rethnic=1 then recip_ethnic=1;
else recip_ethnic=2;
if graft_no=1 then Tx=1;
if graft_no=2 then Tx=2;
if graft_no>2 then Tx=3;
if crf_tx>85 then sensitised=1;
else sensitised=0;
if txcountry='UNITED KINGDOM';
if pcensor=. then delete;
if gcensor=. then delete;
if past_diabetes=1 then diabetes=1;
if past_diabetes=2 then diabetes=2;
if past_diabetes in (7,8) then diabetes=3;
if past_hypertension=1 then hypertension=1;
if past_hypertension=2 then hypertension=2;
if past_hypertension in (7,8) then hypertension=3;
if past_cardio_disease=1 then cardio=1;
if past_cardio_disease=2 then cardio=2;
if past_cardio_disease in (7,8) then cardio=3;
if past_alcohol_abuse=1 then alcohol=1;
if past_alcohol_abuse=2 then alcohol=2;
if past_alcohol_abuse in (7,8) then alcohol=3;
```

```
if past_liver_disease=1 then liver=1;
if past_liver_disease=2 then liver=2;
if past_liver_disease in (7,8) then liver=3;
if past_drug_abuse=1 then drug=1;
if past_drug_abuse=2 then drug=2;
if past_drug_abuse in (7,8) then drug=3;
if RHCV=2 and hepatitis=1 then HCVmatch=1;
if RHCV=2 and hepatitis=0 then HCVMatch=2;
if RHCV=1 and hepatitis=1 then HCVMatch=3;
if RHCV=1 and hepatitis=0 then HCVmatch=4;
if RHCV in(.,3,4,5,6,7,8,9) and hepatitis=1 then HCVmatch=5;
if RHCV in (.,3,4,5,6,7,8,9) and hepatitis=0 then HCVmatch=6;
run;
data liverhcv;
set liveranalysis3;
if HCV in (2,3);
run;

proc freq data=liveranalysis3;
table rhcv;
run;
proc freq data=liveranalysis3;
table HCVmatch;
run;
proc lifetest data=liveranalysis3 plots=(S,LLS);
time ptsurv*pcensor(0);
strata hcvmatch;
where HCVmatch IN (1,2);
run;
proc lifetest data=liveranalysis3 plots=(S,LLS);
time grsurv*gcensor(0);
strata hcvmatch;
where hcvmatch in (1,2);
run;
data liverquestion;
set liveranalysis3;
if hcvmatch=3;
run;
proc freq data=liveranalysis3;
table HCVmatch*urgent/chisq;
where HCVmatch in (1,2);
run;

/*proportionality of Hazards*/
proc phreg data=liveranalysis3;
class HCVmatch;
model ptsurv*pcensor(0)=HCVmatch HCVmatcht;
HCVmatcht=HCVmatch*log(ptsurv);
test_proportionality: test HCVmatcht;
run;

/*waiting list data*/
data livingwaitinglist;
set standard.livwait;
run;
proc sort data=livingwaitinglist;
by recip_id;
run;
proc sort data=liveranalysis3;
by recip_id;
run;
data allanalysis;
merge liveranalysis3 livingwaitinglist;
by recip_id;
if donor_id=. then delete;
if hcvmatch=1;
run;
proc freq data=allanalysis;
table HCVmatch;
run;

/*Cox Hazards regression model*/

proc phreg data=allanalysis;
class rsex dtype renceph rab_surgery tx_type rascites hepatitis
hcvmatch RHCV(ref='1') abomatch/param=ref;
model ptsurv*pcensor(0)= pld hcvmatch cit tx_type dtype hepatitis
abomatch rhcv rsodium rpotassium rsex rab_surgery renceph rascites
ralbumin rinr diabetes dbmi dage rage dcod rbilirubin rwtime;
run;

proc phreg data=allanalysis;
class rsex dtype renceph rab_surgery tx_type rascites hcvmatch
RHCV(ref='9') abomatch/param=ref;
model grsurv*gcensor(0)= pld hcvmatch cit tx_type dtype abomatch
rhcv rsodium rpotassium rsex rab_surgery renceph rascites ralbumin
rinr diabetes dbmi dage rage dcod rbilirubin rwtime;
run;
/* datA FOR TABLES*/
proc univariate data=allanalysis;
class HCVMatch;
var rage;
where HCVmatch in (1,2);
histogram;
run;
proc ttest data=allanalysis;
class HCVmatch;
var rage;
where hcvmatch in (1,2);
run;

proc npar1way data=allanalysis;
class hcvmatch;
var rwtime;
where hcvmatch in (1,2);
run;
proc univariate data=liveranalysis3;
class hepatitis;
var dage;
run;
proc ttest data=liveranalysis3;
```

```
class hcvmatch;
var dage;
where hcvmatch in (1,2);
run;

/*HCV data from lisiting*/
data waitlist;
set standard.livwait;
run;
data waitlist2;
set waitlist;
if endstat in ('D','DA','DS');
run;
proc sort data=waitlist;
by recip_id;
run;
proc sort data=liveranalysis3;
by recip_id;
run;
data HepCwaitlist;
merge liveranalysis3 waitlist;
by recip_id;
if mdy(01,01,2000)<=adate_on<mdy(01,01,2015);
run;
data HepCwaitlist2;
set HepCwaitlist;
if endstat in('D','DA','DS') or pcensor=1 then pcenslisting=1;
else pcenslisting=0;
run;
data HepCwaitlist3;
set HepCwaitlist2;
if psurvival=>0 and rwtime=>0 then survivaltime=psurvival + rwtime;
if psurvival=>0 and suwtime=>0 and rwtime=. then
survivaltime=psurvival+suwtime;
if rwtime=>0 and psurvival=. then survivaltime=rwtime;
if suwtime=>0 and psurvival=. then survivaltime=suwtime;
run;
data HepCwaitlist4;
set HepCwaitlist3;
if pcenslisting=1 and survivaltime>1826.25 then pcens10=0 and
survivaltime=1826.25;
else pcens10=pcenslisting;
if survivaltime>1826.25 then survivaltime=1826.25;
run;
data HepCwaitlist5;
set HepCwaitlist4;
survival10=survivaltime/365.25;
if hepatitis=1 then hepatitisTx=3;
if hepatitis=0 then hepatitisTx=2;
if hepatitis=. then hepatitisTx=1;
run;

proc lifetest data=HepCwaitlist5 notable plots=(S,LLS);
time survivaltime*pcens10(0);
strata hepatitisTx;
where hepatitisTx in (1,3);
run;

/*Thom data*/

data donoroffer;
set standard.donors;
if mdy(10,01,2015)<=ddate<mdy(11,01,2015);
run;

/*Kidney recipients from HCV donors*/
data kidney;
set standard.kidney_tx;
if mdy(01,01,2000)<=tx_date<mdy(01,01,2015);
if dtype in (1,2);
run;
data donorskidney;
set standard.donors;
run;
data donorskidneyHCV;
set donorskidney;
if HBCAB=2;
if sod=1;
run;

proc sort data=kidney;
by donor_id;
run;
proc sort data=donorskidney;
by donor_id;
run;
data kidneydonorinformation;
merge kidney donorskidney;
by donor_id;
if recip_id=. then delete;
run;

proc freq data=kidneydonorinformation;
table HCV;
run;
data kidneydonorinformation2;
set kidneydonorinformation;
if HCV=2 then hepatitis=2;
if HCV=1 then hepatitis=1;
if HCV in (3,4,5,6,7,8,9) then hepatitis=3;
run;
data Missing;
set kidneydonorinformation2;
if psurv=.;
run;
proc sort data=missing;
by recip_id;
run;
data all;
```

```
set standard.kidney_tx;
run;
proc sort data=all;
by recip_id;
run;
data Allmissing;
merge missing all;
by recip_id;
if hepatitis=. then delete;
run;
data Missing2;
set allmissing;
if psurv=. then delete;
rename tx_date=first_tx_date psurv=Patientdays
pcens=patientsurvival;
keep recip_id tx_date psurv pcens;
run;
proc sort data=missing2;
by recip_id;
run;
data missing3;
merge missing missing2;
by recip_id;
run;

data missing4;
set missing3;
if tx_date>first_tx_date then duration=tx_date-first_tx_date;
run;
data missing5;
set missing4;
if patientdays=>duration then psurvfinal=patientdays-duration;
run;
proc sort data=missing5;
by recip_id;
run;
proc sort data=kidneydonorinformation2;
by recip_id;
run;
data Kidneyall;
merge kidneydonorinformation2 missing5;
by recip_id;
run;

data Analysis;
set kidneyall;
if psurv=. then psurv=psurvfinal;
if pcens=. then pcens=patientsurvival;
run;
proc freq data=analysis;
table pcens;
run;
data analysis2;
set analysis;
if psurv=>3650 then psurvival=3650;
else psurvival=psurv;
if gsurv=>3650 then gsurvfinal=3650;
else gsurvfinal=gsurv;
if psurv=>3650 and pcens=1 then pcensor=0;
else pcensor=pcens;
if gsurv=>3650 and gcens=1 then gcensor=0;
else gcensor=gcens;
if rage>40 then rage_grp=2;
else recip_age_grp=1;
if dage>40 then dage_grp=2;
else donor_age_grp=1;
run;
data analysis3;
set analysis2;
ptsurv= psurvival/365.25;
grsurv=gsurvfinal/365.25;
if dethnic=1 then ethnic=1;
else ethnic=2;
if rethnic=1 then recip_ethnic=1;
else recip_ethnic=2;
if graft_no=1 then Tx=1;
if graft_no=2 then Tx=2;
if graft_no>2 then Tx=3;
if crf_tx>85 then sensitised=1;
else sensitised=0;
if txcountry='UNITED KINGDOM';
if pcensor=. then delete;
if gcensor=. then delete;
if past_diabetes=1 then diabetes=1;
if past_diabetes=2 then diabetes=2;
if past_diabetes in (7,8) then diabetes=3;
if past_hypertension=1 then hypertension=1;
if past_hypertension=2 then hypertension=2;
if past_hypertension in (7,8) then hypertension=3;
if past_cardio_disease=1 then cardio=1;
if past_cardio_disease=2 then cardio=2;
if past_cardio_disease in (7,8) then cardio=3;
if past_alcohol_abuse=1 then alcohol=1;
if past_alcohol_abuse=2 then alcohol=2;
if past_alcohol_abuse in (7,8) then alcohol=3;
if past_liver_disease=1 then liver=1;
if past_liver_disease=2 then liver=2;
if past_liver_disease in (7,8) then liver=3;
if past_drug_abuse=1 then drug=1;
if past_drug_abuse=2 then drug=2;
if past_drug_abuse in (7,8) then drug=3;
run;
data recipientinfo;
set database.recipient;
rename HCV=RHCV;
run;
proc sort data=recipientinfo;
by recip_id;
run;
```

```
proc sort data=analysis3;
by recip_id;
run;
data analysis4;
merge analysis3 recipientinfo;
by recip_id;
if donor_id=. then delete;
if RHCV=2 and hepatitis=2 then HCVmatch=1;
if RHCV=2 and hepatitis=1 then HCVMatch=2;
if RHCV=1 and hepatitis=2 then HCVMatch=3;
if RHCV=1 and hepatitis=1 then HCVmatch=4;
if RHCV in(.,3,4,5,6,7,8,9) and hepatitis=2 then HCVmatch=5;
if RHCV in (.,3,4,5,6,7,8,9) and hepatitis=1 then HCVmatch=6;
if RHCV=2 and hepatitis=3 then HCVmatch=7;
if RHCV in (1,.,3,4,5,6,7,8,9) and hepatitis=3 then HCVMatch=8;
run;
data analysisX;
set analysis4;
if hepatitis=2;
run;

proc freq data=analysis4;
table hcvmatch;
run;

proc lifetest data=analysis4 notable plots=(S,LLS);
time ptsurv*pcensor(0);
strata Hcvmatch;
where HCVmatch in (1,2,4);
run;
proc lifetest data=kidneydonorinformation2 notable plots=(S,LLS);
time gsurv*gcens(0);
strata Hepatitis;
run;

proc univariate data=analysis4;
class hcvmatch;
var dage;
where hcvmatch in (1,2);
run;
/*Heart Tx HCV donors*/

data heart;
set standard.cardio_tx;
if mdy(01,01,2000)<=tx_date<mdy(01,01,2015);
if dtype in (1,2);
if txcountry='UNITED KINGDOM';
run;
proc sort data=heart;
by donor_id;
run;
proc sort data=donorskidney;
by donor_id;0
run;
data heartHCV;
merge heart donorskidney;
by donor_id;
if recip_id=. then delete;
run;
proc freq data=heartHCV;
table HCV;
where tx_type=30;
run;



/*data for lnes*/

data HCV;
set standard.donors;
if HCV in (2,3);
if dcountry='UNITED KINGDOM';
if dtype in (1,2);
if mdy(01,01,2010)<=ddate<mdy(01,01,2015);
run;
data HCV2;
set HCV;
if sod=1;
run;
data HCV3;
set HCV2;
if utilised=1;
run;

/*not utilised*/
data HCV4;
set HCV;
if sod=0;
run;
data unused;
set database.unused_organ;
run;
proc sort data=unused;
by donor_id;
run;
proc sort data=HCV4;
by donor_id;
run;
data HCVunused;
merge HCV4 unused;
by donor_id;
if sod=. then delete;
run;
data HCVunusedWhy;
set HCVunused;
if primary_reason=86;
run;
proc sort data=HCVunusedWhy nodupkey;
by donor_id;
```

```
run;

/*differences between groups*/

proc ttest data=HCV;

class sod;

var dage;

run;

proc freq data=HCV;

table sod*dtype/chisq;

run;

proc freq data=HCV;

table sod*dsex/chisq;

run;


proc print data=Hcv3;

title 'Organs Utilised for SOT from HCV positive Donors';

var donor_id ddate dregion hospname organs_ofd organs_txd kidtxd
livtxd hrttxd lngtxd pantxd dtype;

run;

proc print data=HCV4;

title 'Organs Not Utilised for SOT from HCV positive Donors';

var donor_id ddate dregion hospname organs_ofd organs_txd kidtxd
livtxd hrttxd lngtxd pantxd dtype;

run;
```

1.51 Appendix 6: Ligature asphyxiation code

```
data risk;
set standard.donors;
if dtype in (1,2);
if dcountry='UNITED KINGDOM';
if mdy(01,01,2003)<=ddate<mdy(01,01,2017);
run;
proc freq data=risk;
table T_cruzi;
run;

data hanging;
set risk;
if donor_id in
(100272,100303,100318,100357,100462,100469,100670,100683,1008
83,100938,101006,101034,101056,101111,101113,101134,101204,
101475,101667,101670,101771,101944,101995,102026,102226,1023
18,102320,102343,102625,102676,102753,102780,
102891,102995,103230,103258,103267,103312,103428,103435,1035
81,103995,104121,104184,104397,104599,104735,
104834,104842,104843,104898,104924,104942,104964,105101,1051
75,105255,105629,105276,105561,105652,105702,
105815,105968,106061,106070,106134,106286,106425,106531,1068
85,107144,107421,107507,107604,107617,107652,
107727,107829,107907,107955,108043,108130,108136,108188,1081
90,108263,108299,108310,108340,108393,108509,
108528,108557,108739,108989,109335,109368,109493,109642,1096
89,109836,109905,109918,109989,109995,110060,
110124,110345,110662,111012,111034,111070,111229,111268,1113
73,111388,111448,111535,111546,111554,111572,
111634,111642,111649,111770,111837,111913,111916,112067,1120
70,112203,112220,112492,112512,112576,112707,
112729,112742,112765,112799,112810,112980,113108,113128,1131
76,113188,113285,113300,113302,113339,113396,
113405,113882,113899,113909,113997,114077,114201,114224,1142
95,114350,114365,114416,114624,114914,114983,114985,
115156,115199,115258,115305,115331,115382,115387,115523,1155
24,115553,115610,115654,115665,115798,115857,115858,
115947,116072,116229,116271,116347,116356,116376,116380,1163
86,116635,116647,116659,116718,116721,116759,
116867,116938,116954,116991,117004,117022,117129,117262,1173
30,117601,117671,117680,117896,117900,117918,
38608,40084,40107,41752,41813,42531,43134,43495,44551,44602,4
4659,45491,45922,45986,46161,46212,46280,46300,46549,46714,46
822,46897,47171,47273,47460,47494,47691,
47821,49613,49638,49914,49994,50096,50454,51051,51207,51512,5
1887,51927,51972,51974,52389,52602,52630,
52682,52762,52841,52910,52946,53057,53770,53827,53997,54083,5
4234,54384,54783,54895,54963,55118,55149,
55187,55326,55424,55499,55628,55629,56095,56340,56749,56775,5
6802,56946,57332,57666,58287,58462,58471,
58807,58828,59000,59669,60118,60649,60740,6076161555,61586,61
810,61927,61956,62023,62151,62178,62532,
62581,62721,62730,62942,63228,63240,63388,63557,63664,63899,6
4313,64315,64600,64864,65133,65269,65294,
65314,66249,66559,66961,67124,67254,67329,67370,67531,67575,6
7682,67745,68158,68166,68181,68747,69182,
69431,69451,69684,70185,70358,70463,70710,70914,71006,71266,7
1333,71650,71710,71988,72054,72138,
72394,72448,72606,72666,72985,73209,73434,73508,73533,73552,7
3912,74077,74114,74142,74209,74231,74306,
74770,74841,74914,74969,75325,75490,75544,75554,75697,75725,7
5804,76032,76102,76184,76237,76259,
76316,76424,76481,76575,76628,76742,76744,76772,76844,76869,7
7088,77218,77360,77372,77662,77718,77832,
77896,77897,77916,77948,78028,78227,78530,78618,78869,78953,7
9149,79219,79320,79380,79577,79615,79649,79679,
79917,79940,80070,80135,80185,80212,80379,80404,80670,80681,8
0834,80921,81047,81086,81111,81244,81281,
81533,81557,81646,82081,82213,82215,82239,82463,82470,82619,8
2776,83111,83234,83395,83689,83784,83793,
83825,83952,84065,84135,84256,84298,84325,84647,84715,84824,8
4920,85081,85695,85806,85895,85903,85978,86066,
86122,86369,86885,86952,87036,87042,87441,87750,88046,88116,8
8246,88294,88305,88322,88513,88714,88771,88839,89139,89175,
89195,89242,89258,89323,89477,89538,89685,89694,89912,89999,9
0121,90461,90634,90680,90730,90853,91058,
91239,91269,91377,91395,91457,91458,91653,91675,91731,91762,9
1792,91959,91971,92038,92084,92166,92298,
92301,92339,92607,92626,92779,92785,92823,92918,93046,93238,9
3459,93568,93783,93820,93949,93965,93971,94108,94183,
94210,94219,94245,94416,94448,94534,94721,94963,95014,95058,9
5119,95128,95153,95303,95373,95450,95484,95678,
95709,95832,95834,95866,96093,96382,96439,96559,96685,96920,9
6962,97040,97053,97434,97580,97614,97623,
97667,97731,97855,97885,97935,97969,98044,98070,98087,98188,9
8189,98222,98306,98480,98515,98685,98687,98741,
98778,98806,99553,99814,99851,99970,100035,100082,100140,1001
97,100222,100303,100318,100357,100428,100462,
100469,100670,100883,100938,101006,101034,101056,101111,1011
13,101204,101307,101475,101667,101670,101771,
101944,101948,101995,102026,102226,102318,102320,102343,1026
25,102669,102676,102714,102753,102780,102781,
102891,102995,103138,103230,103258,103267,103312,103428,1035
81,103995,104121,104184,104303,104397,104467,
104599,104735,104834,104842,104843,104898,104924,104942,1049
64,105101,105175,105255,105269,105276,105561,
105652,105656,105702,105751,105815,105968,106061,106070,1061
34,106286,106425,106531,106546,106885,107144,
117947,118017,118023,118024,118120,118200,118355,118466,1184
94,118598,118634,118677,118836,118868,118936,119070,
119506,119512,119645,119691,119716,120078,120082,120289,1203
44,120424,120448,120498,120622,120623,
120695,121010,121028,121135,121168,121304,121578,121592,1216
49,121663,121999,122122,122462,122696,
122744,122766,122773,123027,123215,123315,123346,123399,1234
77,123521,123553,123795,123883,124018)
then hanging=1;
run;
proc freq data=hanging;table hanging*sod;run;

/*downing and CO inhlation data*/

data drowning;
set hanging;
if donor_id in
(62682,65352,68864,72173,72576,74355,76514,76996,77261,80239,8
0368,80486,81268,81352,82141,
82162,83827,85759,86392,86573,94114,94191,95033,95478,97118,9
7870,101091,103710,106802,107470,107755,111178,112259,113653,
115124,
26601,27103,33531,40607,40844,41730,41952,42688,42785,43116,4
3549,45519,45831,46152,
46249,46678,47218,47243,47990,49550,49612,49623,49647,49774,4
9782,50272,50463,50510,50908,51792,52715,53216,53611,54097,54
293,55432,55457,
55655,55813,59067,60964,62334,62682,62824,63537,63846,63923,6
5352,65591,66951,68864,69180,70402,70420,72173,72576,72694,74
355,74809,74839,76474,
76514,76916,76918,76996,77139,77261,77374,79647,80239,80368,8
0486,81268,81352,81712,82141,82162,83827,85556,85759,86296,86
392,86573,89365,
91407,91555,92070,93905,94114,94191,95033,95391,95478,96989,9
7118,97226,97362,97870,98064,99359,101091,103641,103688,10371
0,104230,104620,106802)
then drown=1;
run;
data CO;
set drowning;
if donor_id in
(62314,63907,64516,69609,73844,83350,88360,89184,94009,94996,9
6335,97877,100065,103306,107544,110267,116716,
32097,36339,39141,41226,41333,43407,44188,45527,46367,47033,4
7064,47368,47750,47825,50227,50653,51811,53231,53988,54164,55
144,55299,56368,56742,
57195,58116,58548,61861,61957,62314,62315,63543,63659,63744,6
4007,64035,64516,64592,64748,64828,66942,69609,73844,78207,79
604,83350,
88244,88360,89194,92508,93667,94009,94776,94996,95414,95681,9
6335,97877,101293,101382,101734,101735,101740,102601,103009,1
03306,105766)
then CO=1;
run;
data year;
set CO;
donation_year=year(ddate);
run;
data year2;set year;
if donation_year=2000 then dyear='2000';
if donation_year=2001 then dyear='2001';
if donation_year=2002 then dyear='2002';
if donation_year=2003 then dyear='2003';
if donation_year=2004 then dyear='2004';
if donation_year=2005 then dyear='2005';
if donation_year=2006 then dyear='2006';
if donation_year=2007 then dyear='2007';
if donation_year=2008 then dyear='2008';
if donation_year=2009 then dyear='2009';
if donation_year=2010 then dyear='2010';
if donation_year=2011 then dyear='2011';
if donation_year=2012 then dyear='2012';
if donation_year=2013 then dyear='2013';
if donation_year=2014 then dyear='2014';
if donation_year=2015 then dyear='2015';
if dethnic=1 then ethnic=1;
else ethnic=2;
if past_diabetes=1 then diabetes=1;if past_diabetes=2 then
diabetes=2;if past_diabetes in (3,4,5,6,7,8,9,.) then diabetes=3;
if past_hypertension=1 then hypertension=1;if past_hypertension=2
then hypertension=2;if past_hypertension in (3,4,5,6,7,8,9,.) then
hypertension=3;
if past_cardio_disease=1 then cardio=1;if past_cardio_disease=2 then
cardio=2;if past_cardio_disease in (3,4,5,6,7,8,9,.) then cardio=3;
if past_alcohol_abuse=1 then alcohol=1;if past_alcohol_abuse=2 then
alcohol=2;if past_alcohol_abuse in (3,4,5,6,7,8,9,.) then alcohol=3;
if past_liver_disease=1 then liver=1;if past_liver_disease=2 then
liver=2;if past_liver_disease in (3,4,5,6,7,8,9,.) then liver=3;
if past_drug_abuse=1 then drug=1;if past_drug_abuse=2 then
drug=2;if past_drug_abusee in (3,4,5,6,7,8,9,.) then drug=3;
```

```
if hcv=1 then hepC=1;if hcv=2 then hepC=2;if hcv in (3,4,5,6,7,8,.) then
hepc=3;
if past_smoker=1 then smoker=1;if past_smoker=2 then smoker=2;if
past_smoker in (3,4,5,6,7,8,9,.) then smoker=3;
if donor_id in
(101134
101307
103138
104467
110060
111070) then hanging=.;
run;
proc freq data=year2;
table hanging*sod;run;
data year3;set year2;if hanging=1 and dtype=2 then hangdcd=1;if
hanging=1 and dtype=1 then
hangdcd=2;if hanging=. then hanging=0;run;
proc freq data=year3;table hangdcd*sod/chisq;run;
data year4;set year3; if sod=1;run;
proc univariate data=year4;
class hangdcd;
var dage;
run;
proc npar1way data=year3;
class hangdcd;
var dage;
run;

data hypoxicx; set year3; if hangdcd=. then hangdcd=0;run;
/*add in warm ischsaemic time for dcd donors*/
/*try dcsd_donor_data + dcsd_donor_kidney*/
data perfusion;
set database.dcsd_donor_kidney;
keep donor_id perfusion_start_date;
run;
data cardiac;
set standard.dcd_data;
keep donor_id atw_cert_death;
run;
proc sort data=perfusion;
by donor_id;
run;
proc sort data=cardiac;
by donor_id;
run;
data warming;
merge perfusion cardiac;
by donor_id;
run;
data warming2;
set warming;
perfusion_time=timepart(perfusion_start_date);
aystole=timepart(atw_cert_death);
warm_isch= perfusion_start_date-atw_cert_death ;
warm_isch2=perfusion_start_date-atw_cert_death;
run;
data warming3;
set warming2;
                wit=warm_isch/60;
                run;
proc freq data=warming3;
table wit;
run;
proc sort data=warming3;
by donor_id;
run;

                proc sort data=hypoxicx;
                by donor_id;
                run;

data hypoxic;
                merge hypoxicx warming3;
                by donor_id;
                if hangdcd=. then delete;
                run;
proc sort data=hypoxic nodupkey;
                by donor_id;
                                run;
proc freq data=hypoxic;
table wit;
run;

/*from dcd_data*/
data warm;
set standard.dcd_data;
run;
data warm2;
set warm;
perfusion_time=timepart(aortic_perfusion);
aystole=timepart(atw_cert_death);
warm_isch= aortic_perfusion-atw_cert_death ;
warm_isch2=perfusion_start_date-atw_cert_death;
run;
data warm3;set warm2;time1=warm_isch;label time1="time with time8.
format";
format warm_isch time8.;run;
data warm4;set warm3;time2=warm_isch2;label time2="time with
time8. format";
format warm_isch2 time8.;run;
data warm5;
set warm4;
wit=time1/60;
                keep warm_isch wit time1 donor_id;
                run;
                proc sort data=warm5;
                by donor_id;
                run;

                proc sort data=hypoxicx;
                by donor_id;
                run;

data hypoxic;
                merge hypoxicx warm5;
                by donor_id;
                if hangdcd=. then delete;
                run;
proc freq data=hypoxic;
table warm_isch*dtype;
run;
/*draw new bar chart*/
data barchart;
                set hypoxic;
                                if hanging=0;
                run;
proc freq data=barchart;
                table dtype*kiddonor*dyear;
                                run;



proc freq data=hypoxic; table hanging*utilised/chisq;
where sod=1;
run;

proc freq data=hypoxic;
table hangdcd*dyear;
run;


/*utilised from sod*/
data hypoxicused;
set hypoxic;
if sod=1;
if dtype=2;
run;
proc univariate data=hypoxicused;
class hangdcd;
var organs_txd;
run;

proc npar1way data=hypoxicused;class hangdcd;
var organs_txd;
run;
proc freq data=hypoxicused;
table hangdcd*ethnic/chisq;
run;
/*compare proceeding rates DCD vs. DBD*/
proc freq data=hypoxic;
table hypertension*diabetes/chisq;
run;

/*Now compare DBD and DCD kidney donor characteristics*/
   /*first do DBD*/ /*new table saved as Table 1 kidney donor*/
      /*remember hangdcd=1 is DCD*/
       /*separate by kiddonor=1 or kiddonor=0 in place of sod*/
proc freq data=hypoxic;
table kiddonor*hanging/chisq;
where dtype=2;
run;

data hypoxic2;
set hypoxic;
if dtype=1;if kiddonor=1;
run;
proc univariate data=hypoxic2;
class hangdcd;
var dage;
run;
proc  npar1way data=hypoxic2;
class hangdcd;
var dage;
run;
proc freq data=hypoxic2;
table hangdcd*dsex/chisq;
run;
proc freq data=hypoxic2;
table hangdcd*dethnic/chisq;
run;
proc freq data=hypoxic2;
table hangdcd*hypertension/chisq;
run;
proc freq data=hypoxic2;
table hangdcd*cardio/chisq;
run;
proc freq data=hypoxic2;
table hangdcd*diabetes/chisq;
run;
proc freq data=hypoxic2;
table hangdcd*smoker/chisq;
run;
```

```
data tests;
set database.dcsd_organ_donor_ue;
run;
proc sort data=tests;
by donor_id;
run;
proc sort data=hypoxic2;
by donor_id;
run;

data hypoxictests;
merge hypoxic2 tests;
by donor_id;
if hangdcd=. then delete;
run;
proc sort data=hypoxictests;
by donor_id descending creatinine;
run;
data htests;
set hypoxictests;
by donor_id;
if first. donor_id;
if sod=1;
run;
proc freq data=htests;
table hangdcd*sod;
run;

proc univariate data=htests;
class hangdcd;
var creatinine;
run;
proc npar1way data=htests;
    class hangdcd;
                var creatinine;
                run;


/*remove missing data for logistic regression analysis*/
proc univariate data=hypoxic;
var dage;
run;
proc freq data=hypoxic;
table hypertension*diabetes;
run;

data remove;
set hypoxic;
if hypertension=3 then hypertension=.;
if diabetes=3 then diabetes=.;
if cardio=3 then cardio=.;
if smoker=3 then smoker=.;
if dage<40 then age_grp=1;
if 40<=dage<53 then age_grp=2;
if 53<=dage<64 then age_grp=3;
if dage=>64 then age_grp=4;
run;
proc freq data=remove;
table diabetes;
run;

/*checking*/
data check;
set remove;if diabetes=. then delete;
if hypertension=. then delete;
run;
proc freq data=remove;
table dtype;
run;



/*attempt at multiple imputation for missing variables*/
proc mi data=remove out=mi_mvn1 nimpute=20 seed=7654321;
class kiddonor diabetes hypertension cardio dtype hanging smoker
ethnic;
fcs nbiter=5 discrim(Diabetes/details) discrim(Hypertension/details)
discrim(Cardio/details) discrim(smoker/details);
var kiddonor diabetes hypertension cardio dtype hanging smoker ethnic
dage;
run;
proc logistic data=mi_mvn1 descending;
class hanging(ref='0') dtype(ref='2') hypertension(ref='1')
diabetes(ref='1') ethnic (ref='1') smoker(ref='1') cardio (ref='1');
model kiddonor= diabetes hypertension cardio dtype hanging smoker
ethnic dage  dage;
by _imputation_;
ods output parameterestimates=lgsparms
                                        CovB=lgscovb;
                run;
proc mianalyze parms(classvar=classval)=lgsparms ;
class dtype hanging hypertension diabetes ethnic smoker cardio;
modeleffects intercept dage dtype hanging hypertension diabetes
ethnic smoker cardio;
ods output ParameterEstimates=parms2;
run;
data  exponentional;
set parms2;
OR=exp(estimate);
UCI=exp(UCLMean);
LCI=exp(LCLmean);
run;

data expo2;
set exponentional;
keep parm dage dtype hanging hypertension diabetes ethnic smoker
cardio probt OR UCI LCI;
run;



proc logistic data=remove descending;
class hanging(ref='0') dtype(ref='2')hypertension (ref='1')
diabetes(ref='1') ethnic (ref='1') smoker (ref='1') cardio (ref='1')
HepC(ref='1');
model kiddonor=dage dtype hanging hypertension diabetes ethnic
smoker cardio ;
run;
proc logistic data=remove descending;
class hanging(ref='0') age_grp(ref='2') dtype(ref='2')hypertension
(ref='1') diabetes(ref='1') ethnic (ref='1') smoker (ref='1') cardio (ref='1')
HepC(ref='1');
model kiddonor=age_grp dtype hanging diabetes smoker cardio ethnic
hypertension/selection=stepwise;
run;

data temp1;
a=1-CDF('CHISQUARE',14249.050 - 14240.125 ,1);
put a;
run;


/*new logistic regression for reviewers*/
                /*first only including hanging donors*/
                                /*reviewers wanted increased risk behaviour
added in*/



data remove2;
set remove;
if hanging=1;
if donor_id in
(115653, 114819, 114136, 113244,
112746,111880,111572,103242,109999,108539,107940,107896,
107849,107794,107722,106546,105751,100500,103558,102676,1005
66,114819,114509,113104,111880,
111522,107940,107129,106178,105751,104542,103242,101459,1151
76,114914,59285,60885,61131,64452,
67161,71186,77320,79519,80637,82199,83710,84762,85674,85793,8
6693,87348,89139,91848,93337,
93810,97175,97653,97756,99346,101459,103242,104542,105751,106
411,107129,107794,107940,
107995) then HRSB=1;
if donor_id in
(117081,114581,114528,113303,113109,112934,112724,112152,1119
33,111411,110559,110334,108118,
107661,106679,106218,105697,105372,103592,103309,100703,1010
56,77195,80869,92742,99921,
59736,62488,63081,63167,63602,64498,65325,66680,66727,66875,6
8083,69664,70386,72500,
72799,73146,73381,74724,74914,76083,77196,77218,78059,81437,8
2709,83910,84948,85603,
85707,87151,87669,88203,90161,90392,90960,91959,92742,93127,9
3656,94862,95205,95478,95968,
96216,96492,97332,99921,100060,100375,100703,101056,101843,10
1994,103309,103592,104542,105372,
105634,105697,106218,106679,107661
) then HRSB=2;
if donor_id in
(117857,110250,100375,60864,65391,68140,68929,80495,92918,933
82,94416,95615,100064,100375,
100500,106178) then HrsB=3;
if donor_id in
(108989,106611,103899,87004,95478,100566,101759,
103899) then HrsB=4;
if donor_id in
(117391,112783,109881,109142,106279,104587,100319,72941,80501
,83817,98976,100319,104587,
106279,106839) then HrsB=5;
run;
data IVDUnew;
set remove2;
if donor_id in
(117907,117881,117857,117685,117646,117601,117526,117473,1174
22,116954,116950,116936,116717,
116476,116402,116017,115643,115616,115524,115523,115382,1151
67,115102,114912,114804,114676,
114648,114535,114480,114364,114322,114239,114156,113996,1136
15,113324,113303,113228,113192,
113114,112807,112699,112430,112276,112152,111830,111819,1118
01,111604,111230,110087,110713,
110608,110461,110345,110343,109999,109917,109887,109493,1093
20,108996,108972,108757,108667,
108572,108526,108441,108305,108043,108029,107995,107994,1078
49,107809,107794,107652,107279,
106939,106931,106841,106715,106456,106425,106265,106178,1060
98,105786,105109,105106,105059,
104842,104749,104467,104273,104253,104204,104080,104037,1038
00,103535,103259,103211,103066,
```

```
102995,102676,102590,102291,102225,102100,102056,101759,1015
17,101408,101270,100702,100597,
100521,60623,62721,65651,66117,66214,70439,72753,73451,73860,
76439,77166,77787,78912,79509,
81805,81990,83005,83150,85331,85631,85687,86122,86198,86715,8
7414,87676,88380,90424,90999,
91090,91458,91630,92145,92768,92771,94331,94944,95352,95459,9
6238,96250,97295,97316,97558,
100014,100105,100702,101270,101517,101548,57586,91569
94602
82390
77389)
then IVDU=1;
if donor_id in
(117428,117330,116530,116361,116210,115749,115556,115356,1153
05,114938,114890,114869,114833,
114578,114299,114176,114011,113912,113414,112390,111762,1117
26,111535,111388,111264,111034,
110768,110378,110346,109836,109321,109163,108618,108156,1071
07,106489,106340,106244,106213,
105698,105201,105187,104989,104964,104941,104659,104410,1040
97,102506,102305,102253,101769,
101599,101548,101197,100730,100500,100272,100161,58665,58916,
59101,59445,60540,60569,60580,
61844,63033,64020,64695,64909,66131,67989,68289,68717,69134,7
0590,70842,71094,71358,73154,
73286,73290,73473,75084,75086,76102,76447,78089,78844,79485,7
9906,80537,80863,80981,81688,
81785,82184,82291,82345,83698,84327,84744,85053,85081,85450,8
5545,86681,87648,88076,88730,
90766,91468,91678,92169,93679,93756,93919,94423,95126,95286,9
6390,97187,97216,98377,98928,
99003,99321,99401,100272,100377,100521,101006,101197,101577,1
01599,69302,94075,114353,88713,
90532,102640,65083,89928,62081,72094,78609,97155)
then IVDU=2;
run;
proc freq data=IVDU;table IVDU;run;
data prisonnew;
set IVDUnew;
if donor_id in
(117877,116676,115957,115675,115643,115638,115523,115287,1152
52,115167,115069,115061,114833,
114827,114739,114256,114194,114176,114011,113149,112807,1127
46,112683,112430,112408,112152,
111916,111893,111765,111604,111572,111189,110776,110662,1105
02,110378,109907,109407,109380,
109233,109189,109045,109039,108747,108247,108134,108029,1071
27,106931,106839,106698,106429,
106411,106316,106016,105914,105682,105221,104749,104499,1043
99,104275,103726,103592,103511,
103066,102753,102225,101994,101474,100457,100105,61620,61348,
60947, 63529, 63474, 60947
63989,64365,64403,65845,67094,67652,68140,68405,69684,72979,7
3565,73809,74789,76548,
76751,78028,79050,79519,79940,80085,80240,81533,82169,83082,8
4433,84589,86693,87032,
87112,87441,88333,88771,89139,89740,90429,90495,90635,90677,9
0918,91377,91524,91915,
92031,92166,92946,93808,94219,94265,94527,94627,95114,96246,9
6356,96671,96986,97154,
97246,97787,97885,98806,99069,100161,100462,101177,101204,101
408,101873,102056,102291,
102590,102696,103278,103726,103995,104068,104143,105059,1058
41,106546,106699,106931,107127,
107279,107652,107794,107809,107995
108009)
then prison=1;
if donor_id in
(117907,117896,117526,117422,116954,116867,115699,115654,1155
24,115102,114912,114018,113285,
113176,112810,112384,111864,111535,111393,111268,111230,1110
88,110947,110345,110296,109989,
109989,109261,108667,108009,107995,107940,107849,107809,1077
94,107652,107557,106546,106061,
105841,105059,104143,104068,103995,103278,102696,102590,1022
91,102069,102056,101873,101408,
101303,101263,101204,101177,100597,100462,100161,61639,63907,
63482,64118,66352,73563,
74914,75055,75381,75697,76254,78149,78407,79589,80869,82145,8
2199,82842,83959,85344,85793,
85857,86798,87368,88067,89464,90212,90520,92723,93182,93186,9
3379,93558,93571,93587,93884,
93964,94057,94086,94947,95015,95153,95342,95373,96072,96285,9
6692,96946,97313,97557,97751,
97887,98543,98636,99258,99272,99515,99866,100597,101263,10147
4,102225,102753,103066,103511,
104399,104499,104749,105221,105682,106016,106316,106429,1066
11,106698,106839
107557,83682)
then prison=2;
if ivdu=. then ivdu=0;
run;
data format;
set prisonnew;
if ivdu in (1,2) then drugs=1;else drugs=0;
if prison in (1,2) then prisoner=1;else prisoner=0;
run;
proc freq data=format;
table prisoner*hanging;
run;

proc logistic data=format descending;
class dtype(ref='2')hypertension(ref='1') drugs(ref='0') alcohol
(ref='1')prisoner(ref='0') diabetes(ref='1') ethnic (ref='1') smoker (ref='1')
cardio (ref='1') HepC(ref='1');
model kiddonor=dage dtype ethnic smoker  drugs prisoner alcohol;
run;

data format



/*assess role of downtime*/
   /*mport dataset of ligature donors wit hanging time and downtime*/
      /*first will do descriptive statistics and then will analyse its role*/
---------------------------------------------------------------------- */

DATA WORK.hanging_down_times_for_paper;
   LENGTH
      Donor_id          8
      'Hanging time'n    8
      downtime          8 ;
   FORMAT
      Donor_id        F12.
      'Hanging time'n  BEST12.
      downtime        BEST12. ;
   INFORMAT
      Donor_id        BEST12.
      'Hanging time'n  BEST12.
      downtime        BEST12. ;
   INFILE 'E:\SASWork\_TD8664_MSVSAS01_\#LN00024'
      LRECL=15
      ENCODING="WLATIN1"
      TERMSTR=CRLF
      DLM='7F'x
      MISSOVER
      DSD ;
   INPUT
      Donor_id        : BEST32.
      'Hanging time'n  : BEST32.
      downtime        : BEST6. ;
RUN;

data downtime;
set WORK.hanging_down_times_for_paper;
timedown=1;
if donor_id in
(101134
101307
103138
104467
110060
111070)then delete;
run;
proc sort data=downtime;
by donor_id;
run;
proc freq data=downtime;
table 'Hanging time'n ;
run;
proc univariate data=downtime;
var 'Hanging time'n ;
run;
proc sort data=hypoxic;
by donor_id;run;

/*merge data together*/
data hypoxictime;
merge hypoxic downtime;
by donor_id;
run;

/*now remove those who didnt proceed*/
  /*first check how they aligned*/
data hangtimes;
set hypoxictime;
if hanging=1;
run;
proc freq data=hangtimes;table 'Hanging time'n ;
run;


/*subanalysis of only those with recorded downtimes*/
data hypoxiatimes;
set hangtimes;
if downtime=. then delete;
if downtime<15 then dt=1;
if 15<=downtime<25 then dt=2;
if 25<=downtime<40 then dt=3;
if 40<=downtime then dt=4;
run;
proc univariate data=hypoxiatimes;
class dtype;
var downtime;
run;
proc npar1way data=hypoxiatimes;
class dtype;
var downtime;
run;
data tests;
set database.dcsd_organ_donor_ue;
```

```
run;
proc sort data=tests;
by donor_id;
run;
proc sort data=hypoxiatimes;
by donor_id;
run;

data hypoxictests;
merge hypoxiatimes tests;
by donor_id;
if hangdcd=. then delete;
run;
proc sort data=hypoxictests;
by donor_id descending creatinine;
run;
data htests;
set hypoxictests;
by donor_id;
if first. donor_id;
run;
proc freq data=htests;
table dt*dtype/chisq;
run;
ods graphics on;
proc corr data=htests plots=all;
var creatinine downtime;
run;
ods graphics off;

proc gplot data=htests;
plot creatinine*downtime;
run;


proc univariate data=htests;
class hangdcd;
var creatinine;
run;
proc npar1way data=htests;
    class hangdcd;
                var creatinine;
                run;



/*new table DCD first and next DBD*/
Data hypoxic2;
set hypoxic;
if dtype=2;
if sod=1;
if organs_Txd=>3 then used=3;
else used=organs_txd;
run;
proc univariate data=hypoxic2;
class hangdcd;
var organs_txd;
run;
proc npar1way data=hypoxic2;
class hangdcd;
var organs_txd;
run;

proc freq data=hypoxic2;
table hangdcd*used/chisq;
run;

/*dcd only comparisons*/
proc univariate data=hypoxic2;
class hangdcd;
var dage;
run;
proc npar1way data=hypoxic2;
class hangdcd;
var dage;
run;
proc freq data=hypoxic2;
table hangdcd*diabetes/chisq;
run;

/*now compare DBD*/
Data hypoxic3;
set hypoxic;
if dtype=1;
if sod=1;
run;

proc univariate data=hypoxic3;
class hangdcd;
var organs_txd;
run;
proc npar1way data=hypoxic3;
class hangdcd;
var organs_txd;
run;
/*dcd only comparisons*/
proc univariate data=hypoxic3;
class hangdcd;
var dage;
run;
proc npar1way data=hypoxic3;
class hangdcd;
var dage;
run;
proc freq data=hypoxic3;
table hangdcd*diabetes/chisq;
run;

/*combine with pre-donation blood tests*/

/*Checking reason for decline*/
proc sort data=hypoxic;
by donor_id;run;

data unused;
set database.unused_organ;
run;
proc sort data=unused;by donor_id;run;
data notes;
set database.unused_organ_note;
run;
proc sort data=notes;by donor_id;run;

data unusedhypoxic;
merge hypoxic unused notes;
by donor_id;
if hangdcd=. then delete;
if organ_type in (10,11,12) then organ='Kidney';
if organ_type in (40,41,42,45,46,47) THEN ORGAN='Liver';
if organ_type in (50,51,52,53,130) then organ='Pancreas/SPK';
if organ_type in (60,61,62,63,64,65,66,67,68,69) then organ='Lung';
if organ_type=30 then organ='Heart';
run;
proc sort data=unusedhypoxic nodupkey;by donor_id;run;

data unusedhypoxickidney;
set unusedhypoxic;
if organ='Kidney';
run;
proc freq data=unusedhypoxickidney;
table hangdcd;
run;

proc freq data=unusedhypoxickidney;table
NOTE_TEXT*hangdcd;where hangdcd in (1,2);run;
data unusedhypoxicsod;set unusedhypoxic;if sod=0;run;

PROC FREQ DATA=UNUSEDHYPOXICsod;TABLE
PRIMARY_REASON*organ;RUN;

DATA UNUSEDHYPOXIC2;
SET UNUSEDHYPOXICkidney;
If hangdcd in (1,2);
keep donor_id primary_reason sod hangdcd dtype note_text;
RUN;
proc sort data=unusedhypoxic2;
by donor_id;
run;
DATA KIDNEYDBD;
SET UNUSEDHYPOXIC2;
RUN;
PROC FREQ DATA=unusedhypoxickidney;
TABLE PRIMARY_REASON*hangdcd;
where dtype=2;
RUN;
PROC SORT DATA=KIDNEYDBD NODUPKEY;
BY DONOR_ID;
RUN;
DATA KIDNEYDBD2;
SET KIDNEYDBD;
IF pRIMARY_REASON=98;
keep donor_id primary_reason note_text;
RUN;
PROC FREQ DATA=KIDNEYdbd2;
TABLE DONOR_ID*NOTE_TEXT;
RUN;
proc freq data=kidneydbd2;
table note_text*hangdcd;
run;

PROC SORT DATA=KIDNEYDBD2 NODUPKEY;
BY DONOR_ID;
RUN;

/*offer refusals*/
data offers;
set standard.current_offers;
run;
proc sort data=offers;
by donor_id;
run;
proc sort data=unusedhypoxic;
by donor_id;
run;
data refusedoffers;
merge unusedhypoxic2 offers;
by donor_id;
if hangdcd=. then delete;
KEEP DONOR_ID ORG_TYPE FINAL_oFFER REASON1 REASON2
SOD;
run;
data refused;
```

```
set refusedoffers;
if org_type in (10,11,12) then organ='Kidney';
if org_type in (40,41,42,45,46,47) THEN ORGAN='Liver';
if org_type in (50,51,52,53,130) then organ='Pancreas/SPK';
if org_type in (60,61,62,63,64,65,66,67,68,69) then organ='Lung';
if org_type=30 then organ='Heart';
run;
data refused2;
set refused;
if organ='Kidney';
proc freq data=refused;
table reason1*organ;
run;
proc sort data=refused2 nodupkey;
by donor_id;
run;
data donorsnotes;
set database.donor_comment;
run;
proc sort data=donorsnotes;
by donor_id;
run;
proc sort data=unusedhypoxic2;
by donor_id;
run;
data haningnotes;merge unusedhypoxic2 donorsnotes;
by donor_id;
if hangdcd=. then delete;
run;
data unusedhypoxiccheck;
set unusedhypoxic;
if sod=0;
run;
data names;
set database.donor_basics;
run;
proc sort data=unusedhypoxiccheck;
by donor_id;
run;
proc sort data=names;
by donor_id;
run;
data all;
merge unusedhypoxiccheck names;
by donor_id;
if hangdcd=. then delete;
run;

/*differe reasons*/
data unused2;
set unusedhypoxic;
                if sod=0;
                IF PRIMARY_REASON=11;
                run;
proc freq data=unused2;table note_text;run;
proc sort data=unused2 NODUPKEY ;by donor_id;run;

/*kidneys refused*/
data unused3;
set unused2;
if organ_type in (60,61,62,63,64,65,66,67,68,69);
run;
proc freq data=unused3;
table primary_REASON;
RUN;
DATA UNUSED4;
SET UNUSED3;
IF PRIMARY_REASON=12;
RUN;
proc freq data=unused2;table organ_type*note_text;where organ_type
in (50,51,63,70);run;

/*Blood tests of donors pre-donation*/
/*DCD first*/
/*U and E's*/
data tests;
set database.dcsd_organ_donor_ue;
run;
proc sort data=tests;
by donor_id;
run;
proc sort data=hypoxic3;
by donor_id;
run;
data hypoxictests;
merge hypoxic3 tests;
by donor_id;
if hangdcd=. then delete;
run;
proc sort data=hypoxictests;
by donor_id descending creatinine;
run;
data htests;
set hypoxictests;
by donor_id;
if first. donor_id;
if sod=1;
run;
proc freq data=htests;
table hangdcd*sod;
run;

proc univariate data=htests;
class hangdcd;
var creatinine;
run;
proc npar1way data=htests;
    class hangdcd;
                var creatinine;
                run;

/*LFT's*/
data LFT;
 set database.donor_liver_function;
  run;
proc sort data=LFT;by donor_id;run;
proc sort data=hypoxic3;by donor_id;run;
data hypoxicLFT;
   merge hypoxic3 LFT;
   by donor_id;
   if hANGDCD=. then delete;
   run;
proc sort data=hypoxiclft;
by donor_id descending Amylase;
run;
data hLFT;
set hypoxiclft;
by donor_id;
if first. donor_id;
if sod=1;
run;
proc univariate data=hlft;
    class hANGDCD;
                var Amylase;
                run;
proc npar1way data=hlft;
    class hANGDCD;
                var Amylase;
                run;

/*check outcomes*/

/*Kidney*/
proc sort data=hypoxic;by donor_id;run;
data kidney;set standard.kidney_tx;if
mdy(01,01,2003)<=tx_date<mdy(01,01,2017);
if txcountry='UNITED KINGDOM';if dcountry='UNITED KINGDOM';if
dtype in (1,2);if Tx_type in (10,11,12,13,14);run;
proc sort data=kidney;by donor_id;run;
data kidneyrisk;merge hypoxic kidney;by donor_id;if recip_id=. then
delete;
run;

/*Find missing patient survival data*/
proc freq data=kidneyrisk;table pcens;run;
data donors;set standard.donors;run;
proc sort data=kidneyrisk;by donor_id;run;
proc sort data=donors;by donor_id;run;
data kidneyrisk2;set kidneyrisk; if psurv=.;run;
proc sort data=kidneyrisk2;by recip_id;run;
data all;set standard.kidney_tx;run;
proc sort data=all;by recip_id;run;
data Allmissing;merge kidneyrisk2 all;
by recip_id;if hangdcd=. then delete;run;
data Missing2;set allmissing;if psurv=. then delete;
rename tx_date=first_tx_date psurv=Patientdays
pcens=patientsurvival;
keep recip_id tx_date psurv pcens;
run;
proc sort data=missing2;by recip_id;run;
data missing3;merge kidneyrisk2 missing2;by recip_id;run;
data missing4;set missing3;if tx_date>first_tx_date then
duration=tx_date-first_tx_date;
run;
data missing5;set missing4;if patientdays=>duration then
psurvfinal=patientdays-duration;
run;
proc sort data=missing5;by recip_id;run;
proc sort data=kidneyrisk;by recip_id;run;
data Kidneyall;merge kidneyrisk missing5;by recip_id;run;
proc freq data=kidneyall;table hangdcd;run;
data Analysis;set kidneyall;if psurv=. then psurv=psurvfinal;if pcens=.
then pcens=patientsurvival;
run;
proc freq data=analysis;table pcens;run;
proc freq data=analysis;table hangdcd;run;

/*46 graft surviva;l missing, 33 patient survival deleted*/

/*Censor to 10 years graft and patient survival*/

data analysis2;set analysis;
if psurv=>3650 then psurvival=3650;else psurvival=psurv;
if gsurv=>3650 then gsurvfinal=3650;else gsurvfinal=gsurv;
if psurv=>3650 and pcens=1 then pcensor=0;else pcensor=pcens;
if gsurv=>3650 and gcens=1 then gcensor=0;else gcensor=gcens;
if rage>40 then rage_grp=2;else recip_age_grp=1;
if dage>40 then dage_grp=2;else donor_age_grp=1;
if pcensor=. then delete;
run;
proc lifetest data=analysis2 notable plots=survival;
time psurvival*pcensor(0);
```

```
strata hangdcd;
run;
proc freq data=analysis2;
table /chisq;
run;

/*dbd vs hang dbd*/
data analysisdbd;
set analysis2;
if dtype=1;
if dgf in (4,5,6,7,8,9,.) then DeGF=4;
else DeGF=DGF;
run;

proc freq data=analysisdbd;
table pcens;
run;

ods graphics on;
proc logistic data=analysis2 descending plots=all;
class hanging(ref='0') hypertension (ref='1') HLA_GRP rec_unit tx_yr;
model degf= dage rage hangdcd hypertension cld_isch rec_unit tx_yr ;
run;


data KidneyFinal;set analysis2;
if rethnic=1 then recip_ethnic=1;else recip_ethnic=2;
if graft_no=1 then Tx=1;if graft_no=2 then Tx=2;if graft_no>2 then
Tx=3;
if crf_tx>85 then sensitised=1;else sensitised=0;
if txcountry='UNITED KINGDOM';if pcensor=. then delete;if gcensor=.
then delete;
if rhcv=1 then rhepc=1;if rhcv=2 then rhepc=2;if rhcv in (3,4,5,6,7,8,9,.)
then rhepc=3;
if prd in (210,211,212,213,214,215,216,217,219) then renal=1;
if prd in (220,221,222,223,224,225,229) then renal=2;
if prd in (241,242) then renal=3;
if prd in (280,281) then renal=4;
if dgf in (3,4,5,6,7,8,9,.) then DGrF=3;
else DGrf=DGF;
if hanging=. then hanging=0;

run;

/*new basrcharts for AJT paper*/
data kidneybarchart;
set kidneyfinal;
if hanging=1;
run;

/*check for time effect*/
data kidneyfinaltime;
set kidneyfinal2;
if mdy(01,01,2003)<=tx_date<mdy(01,01,2010) then time=1;
if mdy (01,01,2010)<=tx_date<mdy(01,01,2017) then time=2;run;

/*do time 1 first*/
data first;
set kidneyfinaltime;
if time=2;
run;

%macro
survival(data,surv,cens,period,end,end1,var,survival,yaxis,cgm);
ods listing;
/*READS IN YOUR DATASET AND CHANGES THE SURVIVAL
VARIABLES READY FOR USE*/
/*ALSO CHANGES THE DATA TO YEARS OR MONTHS OR DAYS*/
data surv;
set &data;
if &surv <0 then delete;
cens = &cens;
/*survival analysis-Initially all High risk behaviour together*/
/*Survival macro used*/
if lowcase("&period") = "months" then surv = &surv / 30.44;
if lowcase("&period") = "years" then surv = &surv / 365.25;
if lowcase("&period") = "days" then surv = &surv / 1;
if surv > &end then do; surv = &end; cens = 0; end;
fup = 0;
if surv = &end or cens ne 0 then fup = 1;
run;

/*GETS THE COUNT FOR EACH STRATA*/
proc freq data = surv noprint; table &var / out = num; run;

/*GETS THE COUNT FOR FOLLOW UP*/
proc freq data = surv noprint; table &var * fup / out = fup; run;

/*OPENS THE FILE TO SAVE THE PLOT*/
filename gsasfile "&file.\&cgm..emf";

/*RUNS THE LIFETEST PROCEDURE TO OUTPUT THE DATA
NEEDED FOR THE PLOT*/
ODS OUTPUT homtests=homtests;
proc lifetest data=surv plots=(s) outsurv=surv1;
time surv*cens(0); strata &var;
run;
quit;

/*SORTS OUT THE LAYOUT OF THE PLOT AND CHOOSES
COLOURS FOR THE LINES*/
goptions reset=all reset=symbol htext=1.8 cback=white colours=(black)
/*ftext=HWCGM005*/ ftext='Arial/bold'
noborder hsize=8.5 vsize=9.5 Gaccess=GSASFILE;run;
axis1 minor=none order=&yaxis to 100 by 10 label=(ANGLE=90 "%
&survival survival");
axis2 minor=none order=0 to &end by &end1 label=("&period post-
transplant");
symbol;
symbol1 c=CXFF6600 i=steplj w=4 l=1 v=none;
symbol2 c=CX99CCFF i=steplj w=4 l=1 v=none;
symbol3 c=CXFFCC00 i=steplj w=4 l=1 v=none;
symbol4 c=CX339966 i=steplj w=4 l=1 v=none;
symbol5 c=black    i=steplj w=4 l=1 v=none;
symbol6 c=CXFF6600 i=steplj w=4 l=2 v=none;
symbol7 c=CX99CCFF i=steplj w=4 l=2 v=none;
symbol8 c=CXFFCC00 i=steplj w=4 l=2 v=none;
symbol9 c=CX339966 i=steplj w=4 l=2 v=none;
symbol10 c=black   i=steplj w=4 l=2 v=none;

                LEGEND1 ACROSS=1
                POSITION=(BOTTOM INSIDE CENTER)
                MODE=SHARE
                OFFSET=(0,1.5)
                SHAPE=SYMBOL(5,1)
                                        CBORDER=Black
                LABEL=(POSITION=(TOP)
                JUSTIFY=CENTER H=1.2 "&var")
                                        VALUE=(H=1.2);

/*PRODUCES THE PLOT*/
data splot1; set surv1; retain lag_s; drop=lag_s; if survival=. then
survival=lag_s;
lag_s=survival; run;
data splot2; set splot1; survival=survival*100;
proc gplot data=splot2; plot survival * surv = &var /legend=legend1
noframe vaxis=axis1 haxis=axis2;
title ' '; run; quit;

/*USES THE DATA TO OBTAIN THE SURVIVAL ESTIMATES FOR
THE STRATA*/
data surv2; set surv1; if _censor_ = 0; run;
proc sort data = surv2; by &var survival; run;
proc sort data = surv2 nodupkey; by &var; run;

data surv3; set surv2; surv = (survival*100); lcl = (sdf_lcl*100); ucl =
(sdf_ucl*100);
format surv lcl ucl 10.1; run;

data surv4; merge surv3 num; by &var; run;

/*OBTAINS THE P-VALUE FOR THE STRATA*/
data _null_;
set homtests;
where test = 'Log-Rank';
call symput ("logrank",trim(left(put(ProbChiSq,PVALUE6.4))));
run;

/*PRINTS THE ESTIMATES, COUNT AND P-VALUE FOR THE
DATA*/
title1"&survival survival by &var p=&logrank";
proc print data = surv4; var &var count surv lcl ucl;  run;
%mend survival;

/*MACRO VARIABLES REQUIRED*/
/*%survival(data,surv,cens,time,end,end1,censor,var,survival,period,cg
m);*/
/*WHERE     data=dataset with survival variables
                surv=name of survival variable - eg gsurv
                cens=name of censoring variable - eg
gcens
                period=years, months, days
                end=put 10 if wanting 10 year survival, 12
for 12 month survival, 30 for 30 day survival
                end1=how big you want your x-label gap eg
1 if you want 10 years by 1 year
                var=variable you want to strata by - eg
centre
                survival=either graft, patient or transplant
                yaxis=point at which you want the yaxis to
start, 40 is standard
                emf=name of emf file you want to save
*/

%survival(kidneyfinal2,gsurv,gcens,Years,5,1,hanging,graft,0,HR_g);
%survival(kidneyfinal2,psurv,pcens,Years,5,1,hanging,patient,0,HR_p);


/*for figures*/
data kidneyfinal4;
set kidneyfinal3;run;

data kidneyfinal2;
set kidneyfinal;
if dtype=2 and hanging=0 then Hangtype=3;
if dtype=1 and hanging=0 then Hangtype=4;
else hangtype=hangdcd;
if rsex in (3,4,5,6,7,8,9,.) then recip_sex=3;
else recip_sex=rsex;
if dgf in (4,5,6,7,8,9,.) then DeGF=4;
else DeGF=DGf;
if dgf in (1,3) then delayed=0;
```

```
if dgf=2 then delayed=1;
if dgf=3 then pnf=1;if dgf in (1,2) then pnf=0;
if 0<cld_isch<12 then cit=1;
if 12<=cld_isch<18 then cit=2;
if 18<=cld_isch<24 then cit=3;
if cld_isch=>24 then cit=4;
transplant_year=year(tx_date);
IF PRD=888 THEN RENAL=6;
run;


proc freq data=kidneyfinal2;
table PRD;
run;

data kidneyfinal3;
set KidneyFinal2;
if delayed=. then delayed=2;
if pnf=. then pnf=2;
if  transplant_year=2000 then tyear='2000';
if  transplant_year=2001 then tyear='2001';
if  transplant_year=2002 then tyear='2002';
if  transplant_year=2003 then tyear='2003';
if  transplant_year=2004 then tyear='2004';
if transplant_year=2005 then tyear='2005';
if  transplant_year=2006 then tyear='2006';
if  transplant_year=2007 then tyear='2007';
if transplant_year=2008 then tyear='2008';
if  transplant_year=2009 then tyear='2009';
if transplant_year=2010 then tyear='2010';
if  transplant_year=2011 then tyear='2011';
if  transplant_year=2012 then tyear='2012';
if  transplant_year=2013 then tyear='2013';
if  transplant_year=2014 then tyear='2014';
if transplant_year=2015 then tyear='2015';
if transplant_year=2016 then tyear='2016';
IF RENAL=. THEN RENAL=5;
run;
proc freq data=kidneyfinal2;
table hangtype*tx_type/chisq;
run;



proc univariate data=kidneyfinal3;
var psurv;
where tyear='2016';
run;
proc freq data=kidneyfinal3;
table hangtype*wit/chisq;where dtype=2;
run;
proc univariate data=kidneyfinal3;
class hangtype;
var wit;
where dtype=2;
run;


/*logistic regression of DGF and PNF*/
  /*start with DGF-missing data put into dummy missing variable*/
data kidneyfinal4;
set kidneyfinal3;
if pnf in (0,1);
run;
proc freq data=kidneyfinal3;
table dgf*pnf/chisq;
run;

data kidneydcdonly;
set kidneyfinal3;
if dtype=2;
logwarm=log(wit);
run;


/*attempt at multiple imputation for missing variables*/
proc mi data=kidneyfinal4 out=MII nimpute=20 seed=7654321;
class pnf hanging dtype hypertension HLA_GRP diabetes renal
REC_UNIT TYEAR ;
fcs discrim(Diabetes=dage rage cld_isch dweight);

FCS discrim(Hypertension=dage rage cld_isch dweight);

FCS logistic(HLA_GRP=dage rage hanging dtype hypertension
diabetes renal rec_unit tyear cld_isch dweight);

FCS reg(cld_isch= dage rage hanging dtype hypertension HLA_GRP
diabetes renal rec_unit tyear  dweight);
FCS reg(dweight= dage rage hanging dtype hypertension HLA_GRP
diabetes renal rec_unit tyear);
var dage rage pnf hanging dtype hypertension HLA_GRP diabetes
renal rec_unit tyear cld_isch dweight;
run;
proc logistic data=mil descending;
class hanging(ref='0') dtype(ref='2') hypertension(ref='1')rec_unit
diabetes(ref='1') RENAL(ref='1') TYEAR HLA_GRP(REF='2') dbg rbg;
model pnf= dage rage hanging dtype hypertension HLA_GRP diabetes
renal tyear cld_isch dweight dbg rbg;
by _imputation_;
ods output parameterestimates=DGFPARM
                                        CovB=lgscovb;
                run;
proc mianalyze parms(classvar=classval)= DGFPARM ;
class hanging dtype hypertension rec_unit diabetes RENAL TYEAR
HLA_GRP dbg rbg;
modeleffects intercept dage rage hanging dtype hypertension
HLA_GRP diabetes renal rec_unit dbg rbg tyear cld_isch dweight;
ods output ParameterEstimates=combined;
;
run;
data  exponential;
set combined;
HR=exp(estimate);
UCI=exp(UCLMean);
LCI=exp(LCLmean);
run;
data exponentional3;
set exponential;
keep parm dage rage hanging dtype hypertension HLA_GRP diabetes
renal rec_unit dbg rbg tyear cld_isch dweight probt HR UCI LCI;
run;

/*attempt at multiple imputation for missing variables-now just DCD
donors therefore includes warm ischaemic time*/
proc mi data=kidneydcdonly out=MII nimpute=20 seed=7654321;
class delayed hanging hypertension HLA_GRP diabetes renal
REC_UNIT TYEAR ;
fcs discrim(Diabetes=dage rage cld_isch dweight);

FCS discrim(Hypertension=dage rage cld_isch dweight);

FCS logistic(HLA_GRP=dage rage hanging hypertension diabetes
renal rec_unit tyear cld_isch dweight);

FCS reg(cld_isch= dage rage hanging  hypertension HLA_GRP
diabetes renal rec_unit tyear  dweight);
FCS reg(dweight= dage rage hanging  hypertension HLA_GRP
diabetes renal rec_unit tyear);
FCS reg(logwarm= dage rage hanging  dweight cld_isch hypertension
HLA  GRP diabetes renal rec  unit tyear);
var dage rage delayed hanging logwarm hypertension HLA_GRP
diabetes renal rec_unit tyear cld_isch dweight;
run;
proc logistic data=mil descending;
class hanging(ref='0') hypertension(ref='1')rec_unit diabetes(ref='1')
RENAL(ref='1') TYEAR HLA_GRP(REF='2') dbg rbg;
model delayed= dage rage hanging logwarm hypertension HLA_GRP
diabetes renal tyear cld_isch dweight dbg rbg;
by _imputation_;
ods output parameterestimates=DGFPARM
                                        CovB=lgscovb;
                run;
proc mianalyze parms(classvar=classval)= DGFPARM ;
class hanging hypertension rec_unit diabetes RENAL TYEAR
HLA_GRP dbg rbg;
modeleffects intercept dage rage hanging logwarm hypertension
HLA_GRP diabetes renal rec_unit dbg rbg tyear cld_isch dweight;
ods output ParameterEstimates=combined;
;
run;
data  exponential;
set combined;
HR=exp(estimate);
UCI=exp(UCLMean);
LCI=exp(LCLmean);
run;
data exponentional3;
set exponential;
keep parm dage rage hanging logwarm hypertension HLA_GRP
diabetes renal rec_unit dbg rbg tyear cld_isch dweight probt HR UCI
LCI;
run;


data kidneydcdonly2;
set kidneydcdonly;
if pnf in (1,0);
run;


proc logistic data=kidneydcdonly2 descending plots=all;
class hanging(ref='0') hanging(ref='0') hypertension(ref='1')
HLA_GRP(ref='2') diabetes(ref='1') renal(ref='5') cit_hrs rec_unit tyear;
model pnf=  hanging;
run;

proc logistic data=kidneyfinal4 descending plots=all;
class hanging(ref='0') hanging(ref='0') hypertension(ref='1')
HLA_GRP(ref='2') diabetes(ref='1') renal(ref='5') cit_hrs rec_unit tyear;
model delayed= hanging hypertension dage HLA_GRP diabetes renal
rec_unit tyear cld_isch dweight;
run;
/*compare DCD first*/
proc univariate data=kidneyfinal2;
class hangtype;
var rage;
run;
proc npar1way data=kidneyfinal2;
class hangdcd;
where dtype=1;
var rage;
run;
```

```
proc freq data=kidneyfinal2;
table hangTYPE;
run;
data check;
set kidneyfinal2;
if hangtype=.;
run;

proc freq data=kidneyfinal2;
table hangtype*recip_ethnic/chisq;
where dtype=1;
run;
proc freq data=kidneyfinal2;
table hangdcd*hla_grp/chisq;
where dtype=2;
run;
proc freq data=kidneyfinal2;
table hangdcd*renal/chisq;
where dtype=1;
run;


data MVAdata;
set kidneyfinal3;
if gsurv > (5*365.25) then gsurv5=(5*365.25);
else gsurv5=gsurv;
if gsurv > (5*365.25) then gcens5=0;
else gcens5=gcens;

if gsurv > (1*365.25) then gsurv1=365.25;
else gsurv1=gsurv;
if gsurv > (1*365.25) then gcens1=0;
else gcens1=gcens;


if psurv > (5*365.25) then psurv5=5;
else psurv5=psurv/365.25;
if psurv > (5*365.25) then pcens5=0;
else pcens5=pcens;

if psurv > (1*365.25) then psurv1=365.25;
else psurv1=psurv;
if psurv > (1*365.25) then pcens1=0;
else pcens1=pcens;

if gsurv=0 and gcens=1 then pnf1=1;
else pnf1=0;
if diabetes=3 then diabetes=.;
if hypertension=3 then hypertension=.;
if graft_no=1;

run;

/*dcd on its own*/
data kidneydcdonly;
SET MVADATA;
IF DTYPE=2;
logwarm=log(wit);
RUN;
proc phreg data=kidneydcdonly;
class hanging(ref='0') ;
model psurv5*pcens5(0)= hanging;
hazardratio hanging/diff=ref;
run;


proc freq data=mvadata;
table cld_isch;
run;
proc mi data=kidneydcdonly out=five nimpute=20 seed=7654321;
class hanging  hypertension HLA_GRP diabetes renal REC_UNIT
TYEAR ;
fcs discrim(Diabetes=dage rage cld_isch dweight);

FCS discrim(Hypertension=dage rage cld_isch dweight);

FCS logistic(HLA_GRP=dage rage hanging  hypertension diabetes
renal rec_unit tyear cld_isch dweight);

FCS reg(cld_isch= dage rage hanging hypertension HLA_GRP
diabetes renal rec_unit tyear  dweight);
FCS reg(dweight= dage rage hanging hypertension HLA_GRP
diabetes renal rec_unit tyear);
fcs reg(logwarm=dage rage hanging hypertension HLA_GRP diabetes
renal rec_unit tyear);
var dage rage  hanging logwarm hypertension HLA_GRP diabetes
renal rec_unit tyear cld_isch dweight;
run;

proc phreg data=five outest=imputed covout;
class hanging(ref='0') hanging(ref='0') hypertension(ref='1')
HLA_GRP(ref='2') diabetes(ref='1') renal(ref='5')  rec_unit tyear;
model Gsurv5*Gcens5(0)= dage hanging logwarm rage hypertension
diabetes hla_grp cld_isch dweight tyear renal/covb;
by _imputation_;
random rec_unit;
run;
PROC MIANALYZE DATA=IMPUTED;
MODELEFFECTS dage rage  HANGING1 LOGWARM  diabetes2
hypertension2  HLA_GRP1 HLA_GRP3 HLA_GRP4 renal1 renal2
renal3 renal4 renal6 cld_isch dweight tyear2003 tyear2004 tyear2005
tyear2006 tyear2007 tyear2008 tyear2009 tyear2010 tyear2011
tyear2012 tyear2013 tyear2014 tyear2015;
;
ODS OUTPUT PARAMETERESTIMATES=SURVIVE;
RUN;
proc mianalyze PARMS(CLASSVAR=FULL)=imputed;
class hanging1 hypertension2 diabetes2 HLA_GRP1 HLA_GRP3
HLA_GRP4 renal1 renal2 renal3 renal4 renal6 tyear2003 tyear2004
tyear2005 tyear2006 tyear2007 tyear2008 tyear2009 tyear2010
tyear2011 tyear2012 tyear2013 tyear2014 tyear2015;
modeleffects  dage rage  HANGING1 LOGWARM  diabetes2
hypertension2  HLA_GRP1 HLA_GRP3 HLA_GRP4 renal1 renal2
renal3 renal4 renal6 cld_isch dweight tyear2003 tyear2004 tyear2005
tyear2006 tyear2007 tyear2008 tyear2009 tyear2010 tyear2011
tyear2012 tyear2013 tyear2014 tyear2015;
ods output Parameterestimate=survival;
run;
data  HR;
set survive;
HR=exp(estimate);
UCI=exp(UCLMean);
LCI=exp(LCLmean);
run;
data exponentional3;
set HR;
keep parm dage rage hanging dtype hypertension HLA_GRP diabetes
renal rec_unit dbg rbg tyear cld_isch dweight probt HR UCI LCI;
run;

proc mianalyze DATA=IMPUTED;
modeleffects  dage rage hanging1 diabetes2 hypertension2
HLA_GRP1 HLA_GRP3 HLA_GRP4 renal1 renal2 renal3 renal4 renal6
cld_isch dweight tyear2003 tyear2004 tyear2005 tyear2006 tyear2007
tyear2008 tyear2009 tyear2010 tyear2011 tyear2012 tyear2013
tyear2014 tyear2015;
ods output Parameterestimate=survival;
run;
data  survival2;
set survival;
HR=exp(estimate);
UCI=exp(UCLMean);
LCI=exp(LCLmean);
run;
data exponentional3;
set exponential;
keep parm dage rage hanging LOGWARM hypertension HLA_GRP
diabetes renal rec_unit dbg rbg tyear cld_isch dweight probt HR UCI
LCI;
run;



proc phreg data=mvadata;
class hanging(ref='0') hanging(ref='0') hypertension(ref='1')
HLA_GRP(ref='2') diabetes(ref='1') renal(ref='5')  rec_unit
tyear/param=ref;
model gsurv1*gcens1(0)= dage hanging hla_grp cld_isch  rec_unit
tyear renal;
random rec_unit;
hazardratio hanging/diff=ref;
run;


proc phreg data=kidneyfinal3;
class hanging(ref='0')/param=reference;
model gsurvfinal*gcensor(0)=  hanging;
hazardratio hanging/diff=ref;
run;
proc phreg data=kidneyfirst2;
class dtype (ref='1')
hanging(ref='0')hypertension(ref='1')hla_grp(ref='2')renal(ref='5')/param
=ref;
model firstfive*gfive(0)=  hanging dtype hypertension dage rage renal
hla_grp cit;
hazardratio hanging/diff=ref;
run;

/*data first graft survival*/
data kidneyfinalfirst;
set kidneyfinal2;
if graft_No=1;
if gsurv=>1826.25 then firstfive=1826.25;else firstfive=gsurv;
run;
data kidneyfirst2;
set kidneyfinalfirst;if gcens=1 and gsurv=>1826.25 then gfive=0;else
gfive=gcens;run;


/*impact of hanging on delayed graft function and primary non-
function*/
proc logistic data=kidneyfinal2 descending;
class;
;*%mend;*);*';*";**/;
run;


/*CREATININE 1 YEAR*/
```

```
DATA CREATININE;
SET STANDARD.KID_SERUM_CREATININE;
RUN;

PROC SORT DATA=CREATININE;
BY TX_ID;
RUN;
PROC SORT DATA=kidneyDCDONLY;
BY TX_ID;
RUN;

DATA KIDNEYCREATININE;
MERGE kidneyDCDONLY CREATININE;
BY TX_ID;
IF hangdcd=. THEN DELETE;
RUN;
proc freq data=kidneycreatinine;
table serum12;
run;

DATA camcreat;
SET KIDNEYCREATININE;
if SERUM12 ne . and RAGE ne . and Rsex ne . and Rethnic ne 9 then
do;
    * non-black males *;
    if Rsex=1 and Rethnic ne 3 then do;
        mdrd =round((186*((SERUM12/88.4)**(-1.154))*(Rage**(-
0.203))));
    end;
    * black males *;
    if RSex=1 and Rethnic=3 then do;
        mdrd =round((186*((SERUM12/88.4)**(-1.154))*(Rage**(-
0.203))*1.210));
    end;
    * non-black females *;
    if Rsex=2 and Rethnic ne 3 then do;
        mdrd =round((186*((SERUM12/88.4)**(-1.154))*(Rage**(-
0.203))*0.742));
    end;
    * black females *;
    if Rsex=2 and Rethnic=3 then do;
        mdrd =round((186*((SERUM12/88.4)**(-1.154))*(Rage**(-
0.203))*0.742*1.210));
    end;
end;
RUN;

ods graphics on;
proc npar1way data=camcreat plots=all;
class hangtype;
var MDRD;
run;
ods graphics off;

proc mi data=CAMCREAT out=five nimpute=20 seed=7654321;
class hanging  hypertension HLA_GRP diabetes renal REC_UNIT
TYEAR ;
fcs discrim(Diabetes=dage rage cld_isch dweight);

FCS discrim(Hypertension=dage rage cld_isch dweight);

FCS logistic(HLA_GRP=dage rage hanging  hypertension diabetes
renal rec_unit tyear cld_isch dweight);

FCS reg(cld_isch= dage rage hanging  hypertension HLA_GRP
diabetes renal rec_unit tyear  dweight);
FCS reg(dweight= dage rage hanging  hypertension HLA_GRP
diabetes renal rec_unit tyear);
FCS reg(logwarm=dage rage hanging  hypertension HLA_GRP
diabetes renal rec_unit tyear);
var dage rage  hanging logwarm hypertension HLA_GRP diabetes
renal rec_unit tyear cld_isch dweight MDRD;
run;
PROC GLM DATA=FIVE;
BY _IMPUTATION_;
CLASS
hanging(ref='0')hypertension(ref='1')hla_grp(ref='2')renal(ref='5')
DIABETES REC_UNIT tyear;
MODEL MDRD=dage rage  hanging  hypertension HLA_GRP diabetes
renal rec_unit tyear cld_isch dweight/SOLUTION;
random rec_unit;
ODS output ParameterEstimates=PARMS_GLM;
RUN;

run;
PROC FREQ DATA=CAMCREAT;
TABLE MDRD;RUN;
PROC GLM DATA=CAMCREAT;
CLASS  hanging(ref='0');
MODEL MDRD= hanging /SOLUTION CLPARM;
ODS output ParameterEstimates=PARMS_GLM;
RUN;

run;
DATA PARMS_GLM2;
SET PARMS_GLM;
IF PARAMETER NE 'INTERCEPT' THEN DO;
FIRSTLEVEL=SCAN(PARAMETER,1,' ');
LEVELSPOS=INDEXW(PARAMETER,FIRSTLEVEL);
LEVELSLIST=SUBSTR(PARAMETER,LEVELSPOS);
PARAMETER='P'||COMPRESS(LEVELSLIST);
END;
RUN;

PROC SORT DATA=PARMS_GLM;
BY PARAMETER _IMPUTATION_;
RUN;

proc mianalyze PARMS=PARMS_GLM2;
modeleffects  PHANGING1 ;
ods OUTPUT ParameterEstimates=PARMS_GLM3;
run;
data  HR;
set survive;
HR=exp(estimate);
UCl=exp(UCLMean);
LCl=exp(LCLmean);
run;
data exponentional3;
set exponential;
keep parm dage rage hanging dtype hypertension HLA_GRP diabetes
renal rec_unit dbg rbg tyear cld_isch dweight probt HR UCl LCl;
run;

proc univariate data=camcreat;
class hangtype;
var GFR;
run;

proc glm


/*Liver*/
proc sort data=hypoxic;by donor_id;run;
data liver;set standard.liver_tx;if
mdy(01,01,2003)<=tx_date<mdy(01,01,2017);
if txcountry='UNITED KINGDOM';if dtype in (1,2);run;
proc sort data=liver;by donor_id;run;
data liverrisk;merge hypoxic liver;by donor_id;if recip_id=. then delete;
run;
proc freq data=liverrisk;table hang;
run;

/*Find missing patient survival data*/
proc freq data=liverrisk;table pcens;run;
data donors;set standard.donors;run;
proc sort data=liverrisk;by donor_id;run;
proc sort data=donors;by donor_id;run;
data liverrisk2;set liverrisk; if psurv=.;run;
proc sort data=liverrisk2;by recip_id;run;
data total;set standard.liver_tx;run;
proc sort data=total;by recip_id;run;
data totalmissing;merge liverrisk2 total;
by recip_id;if hangdcd=. then delete;run;
data LiverMissing2;set totalmissing;if psurv=. then delete;
rename tx_date=first_tx_date psurv=Patientdays
pcens=patientsurvival;
keep recip_id tx_date psurv pcens;
run;
proc sort data=Livermissing2;by recip_id;run;
data Livermissing3;merge liverrisk2 livermissing2;by recip_id;run;
data Livermissing4;set livermissing3;if tx_date>first_tx_date then
duration=tx_date-first_tx_date;
run;
data Livermissing5;set livermissing4;if patientdays=>duration then
psurvfinal=patientdays-duration;
run;
proc sort data=livermissing5;by recip_id;run;
proc sort data=liverrisk;by recip_id;run;
data liverall;merge liverrisk livermissing5;by recip_id;run;
proc freq data=liverall;table hangdcd;run;
data liverAnalysis;set liverall;if psurv=. then psurv=psurvfinal;if pcens=.
then pcens=patientsurvival;
run;
proc freq data=liveranalysis;table hangdcd;run;

/*5 year censor for Liver analysis*//*104 patients deleted due to no
survival information=1%of data*/

data liveranalysis2;set liveranalysis;
if psurv=>3650 then psurvival=3650;else psurvival=psurv;
if gsurv=>3650 then gsurvfinal=3650;else gsurvfinal=gsurv;
if psurv=>3650 and pcens=1 then pcensor=0;else pcensor=pcens;
if gsurv=>3650 and gcens=1 then gcensor=0;else gcensor=gcens;
if rage>40 then rage_grp=2;else recip_age_grp=1;
if dage>40 then dage_grp=2;else donor_age_grp=1;
if pcensor=. then delete;
if pld= 424 then liverd=1;if pld=419 then liverd=2; if pld in
(428,430,431,432,435,436,437,438,439,471,472,473,474,475,476,477,
478,479,480,481,482)then liverd=3;
run;



proc lifetest data=liveranalysis2 notable plots=(S,LLS);
time psurvival*pcensor(0);
strata hangdcd;run;
proc freq data=liveranalysis2;
table hypoxic;
run;
```

```
/*Data Tables Liver*/
data LiverFinal;set Liveranalysis2;
if rethnic=1 then recip_ethnic=1;else recip_ethnic=2;
if graft_no=1 then Tx=1;if graft_no=2 then Tx=2;if graft_no>2 then
Tx=3;
if crf_tx>85 then sensitised=1;else sensitised=0;
if txcountry='UNITED KINGDOM';if pcensor=. then delete;if gcensor=.
then delete;
if dcountry='UNITED KINGDOM';
if rhcv=1 then rhepc=1;if rhcv=2 then rhepc=2;if rhcv in (3,4,5,6,7,8,9,.)
then rhepc=3;if liverd=. then liverd=4;
if dtype=2 and hangdcd=0 then Hangtype=3;
if dtype=1 and hangdcd=0 then Hangtype=4;
else hangtype=hangdcd;
if rsex in (3,4,5,6,7,8,9,.) then recip_sex=3;
else recip_sex=rsex;
if renal=. then renal=5;
run;

proc freq data=liverfinal;
table hangdcd;
run;
data livercheck;
set liverfinal;
if dtype=2;
run;
proc freq data=livercheck;
table hangdcd;
run;

proc lifetest data=liverfinal notable plots=(S,LLS);
time gsurv*gcens(0);
strata hangtype;run;

proc freq data=liverfinal;
table rec_unit*cof;
where hangdcd in (1,2);
run;



%survival(liverfinal,gsurvfinal,gcensor,Years,5,1,hangtype,graft,0,HR_g
);
%survival(liverfinal,psurvival,pcensor,Years,5,1,hangtype,patient,0,HR
_p);

proc phreg data=liverfinal plots=survival;
class hanging(ref='0') hypertension smoker (ref='1')
liverd(ref='4')/param=ref ;
model psurv*pcens(0)= dage rage hanging hypertension dbmi smoker
liverd;
hazardratio hanging/diff=ref;
run;

proc phreg data=liverfinal plots=survival;
class hanging(ref='0') hypertension smoker (ref='1')
liverd(ref='4')/param=ref ;
model gsurv*gcens(0)= dage rage hanging hypertension dbmi smoker
liverd;
hazardratio hanging/diff=ref;
run;


/*dcd liver only*/
data liverfinal2;
set liverfinal;
if dtype=2;
run;
/*dbd liver only*/
data liverfinal3;
set liverfinal;
if dtype=1;
run;

/*liver tables*/
proc freq data=liverfinal;
table hangtype;
run;
proc univariate data=liverfinal;
class hangtype;
var rage;
run;
proc npar1way data=liverfinal3;
class hangtype;
var rage;
run;
proc freq data=liverfinal2;
table hangtype*livpd_grp/chisq;
run;
proc univariate data=liverfinal;
class hangtype;
var ukeld;
run;
proc npar1way data=liverfinal3;
class hangtype;
var ukeld;
run;


/*Cardiothoracic*/

/*Heart*/
proc sort data=hypoxic;by donor_id;run;
data heart;set standard.cardio_tx;if
mdy(01,01,2000)<=tx_date<mdy(01,01,2016);
if txcountry='UNITED KINGDOM';if dtype in (1,2);run;
proc sort data=heart;by donor_id;run;
data heartrisk;merge hypoxic heart;by donor_id;if recip_id=. then
delete;
run;

/*Find missing patient survival data*/
proc freq data=heartrisk;table pcens;run;
data donors;set standard.donors;run;
proc sort data=heartrisk;by donor_id;run;
proc sort data=donors;by donor_id;run;
data heartrisk2;set heartrisk; if psurv=.;run;
proc sort data=heartrisk2;by recip_id;run;
data complete;set standard.cardio_tx;run;
proc sort data=total;by recip_id;run;
data completemissing;merge heartrisk2 complete;
by recip_id;if hangdcd=. then delete;run;
data heartMissing2;set completemissing;if psurv=. then delete;
rename tx_date=first_tx_date psurv=Patientdays
pcens=patientsurvival;
keep recip_id tx_date psurv pcens;
run;
proc sort data=heartmissing2;by recip_id;run;
data heartmissing3;merge heartrisk2 heartmissing2;by recip_id;run;
data heartmissing4;set heartmissing3;if tx_date>first_tx_date then
duration=tx_date-first_tx_date;
run;
data heartmissing5;set heartmissing4;if patientdays=>duration then
psurvfinal=patientdays-duration;
run;
proc sort data=heartmissing5;by recip_id;run;
proc sort data=heartrisk;by recip_id;run;
data heartall;merge heartrisk heartmissing5;by recip_id;run;
proc freq data=heartall;table hangdcd;run;
data heartAnalysis;set heartall;if psurv=. then psurv=psurvfinal;if
pcens=. then pcens=patientsurvival;
run;
proc freq data=heartanalysis;table hangdcd*tx_type;run;

/*censor data at 5 years*/

data heartanalysis2;set heartanalysis;
if psurv=>3650 then psurvival=3650;else psurvival=psurv;
if gsurv=>3650 then gsurvfinal=3650;else gsurvfinal=gsurv;
if psurv=>3650 and pcens=1 then pcensor=0;else pcensor=pcens;
if gsurv=>3650 and gcens=1 then gcensor=0;else gcensor=gcens;
if rage>40 then rage_grp=2;else recip_age_grp=1;
if dage>40 then dage_grp=2;else donor_age_grp=1;
if pcensor=. then delete;
run;
proc freq data=heartanalysis2;
table hypoxic*tx_type;
run;
data heartanalysis3;
set heartanalysis2;
if hypoxic=1;
run;

/*Data Tables heart*/
data heartFinal;set heartanalysis2;
if rethnic=1 then recip_ethnic=1;else recip_ethnic=2;
if graft_no=1 then Tx=1;if graft_no=2 then Tx=2;if graft_no>2 then
Tx=3;
if crf_tx>85 then sensitised=1;else sensitised=0;
if txcountry='UNITED KINGDOM';if pcensor=. then delete;
if dcountry='UNITED KINGDOM';
if rhcv=1 then rhepc=1;if rhcv=2 then rhepc=2;if rhcv in (3,4,5,6,7,8)
then rhepc=3;
run;
proc freq data=heartfinal;
table hypoxic*tx_type;
run;
data lungsurvival;
set heartfinal;
if tx_type in (60,63,70);
if hanging=1 then hypo=1;
if drown=1 then hypo=2;
if Co=1 then hypo=3;
if hypoxic=0 then hypo=4;
if psurvival >365 then psurvfinal=365;else psurvfinal=psurvival;
if  psurvival >365 and pcensor=1 then pcensored=0;else
pcensored=pcensor;
run;

/*coding for primary lung disease*/
data lungsurvival2;
set lungsurvival;
if pcd=327 then plungd=1;
if pcd=322 then plungd=2;
if pcd=323 then plungd=3;
if pcd=325 then plungd=4;
if past_smoker=1 then smoker=1;
if past_smoker=2 then smoker=2;
if past_smoker in (3,4,5,6,7,8,9,.) then smoker=3;
run;
proc freq data=lungsurvival2;
table plungd;
```

```
run;
data test;set lungsurvival2;if plungd=. then plungd=5;run;


proc lifetest data=lungsurvival notable plots=(S,LLS);
time psurvival*pcensor(0);
strata hangdcd;run;

%survival(lungsurvival,gsurvfinal,gcensor,Years,3,0.25,hypoxic,graft,0,
HR_g);
%survival(lungsurvival,psurvival,pcensor,Years,1,0.25,hypoxic,patient,
0,HR_p);

/*multivariate analysis*/
ods graphics on;
proc phreg data=test plots= survival;
class hangdcd(ref='0') smoker(ref='1')plungd(ref='2')/param=ref ;
model psurvival*pcensored(0)= dage rage hangdcd smoker plungd;
hazardratio hangdcd/diff=ref;
run;

proc phreg data=test;


/*Lung cause of death*/
data lungdeath;
set lungsurvival;
if hangdcd=1;if pcens=1;
keep rcod rdod cof recip_id hangdcd psurv pcens;
run;
proc sort data=lungdeath;by recip_id;run;
data recipient2;set database.recipient_note;run;
proc sort data=recipient2;by recip_id;run;
data together;merge lungdeath recipient2;by recip_id;if hangdcd=1;run;

proc freq data=together;table rcof;run;

/*effect of downtime*/

data donorsall;
set standard.donors;
if donor_id in
(100272,100303,100318,100357,100462,100469,100670,100683,1008
83,100938,101006,101034,101056,101111,101113,101134,101204,
101475,101667,101670,101771,101944,101995,102026,102226,1023
18,102320,102343,102625,102676,102753,102780,
102891,102995,103230,103258,103267,103312,103428,103435,1035
81,103995,104121,104184,104397,104599,104735,
104834,104842,104843,104898,104924,104942,104964,105101,1051
75,105255,105629,105276,105561,105652,105702,
105815,105968,106061,106070,106134,106286,106425,106531,1068
85,107144,107421,107507,107604,107617,107652,
107727,107829,107907,107955,108043,108130,108136,108188,1081
90,108263,108299,108310,108340,108393,108509,
108528,108557,108739,108989,109335,109368,109493,109642,1096
89,109836,109905,109918,109989,109995,110060,
110124,110345,110662,111012,111034,111070,111229,111268,1113
73,111388,111448,111535,111546,111554,111572,
111634,111642,111649,111770,111837,111913,111916,112067,1120
70,112203,112220,112492,112512,112576,112707,
112729,112742,112765,112799,112810,112980,113108,113128,1131
76,113188,113285,113300,113302,113339,113396,
113405,113882,113899,113909,113997,114077,114201,114224,1142
95,114350,114365,114416,114624,114914,114983,114985,
115156,115199,115258,115305,115331,115382,115387,115523,1155
24,115553,115610,115654,115665,115798,115857,115858,
115947,116072,116229,116271,116347,116356,116376,116380,1163
86,116635,116647,116659,116718,116721,116759,
116867,116938,116954,116991,117004,117022,117129,117262,1173
30,117601,117671,117680,117896,117900,117918,
38608,40084,40107,41752,41813,42531,43134,43495,44551,44602,4
4659,45491,45922,45986,46161,46212,46280,46300,46549,46714,46
822,46897,47171,47273,47460,47494,47691,
47821,49613,49638,49914,49994,50096,50454,51051,51207,51512,5
1887,51927,51972,51974,52389,52602,52630,
52682,52762,52841,52910,52946,53057,53770,53827,53997,54083,5
4234,54384,54783,54895,54963,55118,55149,
55187,55326,55424,55499,55628,55629,56095,56340,56749,56775,5
6802,56946,57332,57666,58287,58462,58471,
58807,58828,59000,59669,60118,60649,60740,6076161555,61586,61
810,61927,61956,62023,62151,62178,62532,
62581,62721,62730,62942,63228,63240,63388,63557,63664,63899,6
4313,64315,64600,64864,65133,65269,65294,
65314,66249,66559,66961,67124,67254,67329,67370,67531,67575,6
7682,67745,68158,68166,68181,68747,69182,
69431,69451,69684,70185,70358,70463,70710,70914,71006,71266,7
1333,71650,71710,71988,72054,72138,
72394,72448,72606,72666,72985,73209,73434,73508,73533,73552,7
3912,74077,74114,74142,74209,74231,74306,
74770,74841,74914,74969,75325,75490,75544,75554,75697,75725,7
5804,76032,76102,76184,76237,76259,
76316,76424,76481,76575,76628,76742,76744,76772,76844,76869,7
7088,77218,77360,77372,77662,77718,77832,
77896,77897,77916,77948,78028,78227,78530,78618,78869,78953,7
9149,79219,79320,79380,79577,79615,79649,79679,
79917,79940,80070,80135,80185,80212,80379,80404,80670,80681,8
0834,80921,81047,81086,81111,81244,81281,
81533,81557,81646,82081,82213,82215,82239,82463,82470,82619,8
2776,83111,83234,83395,83689,83784,83793,
83825,83952,84065,84135,84256,84298,84325,84647,84715,84824,8
4920,85081,85695,85806,85895,85903,85978,86066,
86122,86369,86885,86952,87036,87042,87441,87750,88046,88116,8
8246,88294,88305,88322,88513,88714,88771,88839,89139,89175,
89195,89242,89258,89323,89477,89538,89685,89694,89912,89999,9
0121,90461,90634,90680,90730,90853,91058,
91239,91269,91377,91395,91457,91458,91653,91675,91731,91762,9
1792,91959,91971,92038,92084,92166,92298,
92301,92339,92607,92626,92779,92785,92823,92918,93046,93238,9
3459,93568,93783,93820,93949,93965,93971,94108,94183,
94210,94219,94245,94416,94448,94534,94721,94963,95014,95058,9
5119,95128,95153,95303,95373,95450,95484,95678,
95709,95832,95834,95866,96093,96382,96439,96559,96685,96920,9
6962,97040,97053,97434,97580,97614,97623,
97667,97731,97855,97885,97935,97969,98044,98070,98087,98188,9
8189,98222,98306,98480,98515,98685,98687,98741,
98778,98806,99553,99814,99851,99970,100035,100082,100140,1001
97,100222,100303,100318,100357,100428,100462,
100469,100670,100883,100938,101006,101034,101056,101111,1011
13,101204,101307,101475,101667,101670,101771,
101944,101948,101995,102026,102226,102318,102320,102343,1026
25,102669,102676,102714,102753,102780,102781,
102891,102995,103138,103230,103258,103267,103312,103428,1035
81,103995,104121,104184,104303,104397,104467,
104599,104735,104834,104842,104843,104898,104924,104942,1049
64,105101,105175,105255,105269,105276,105561,
105652,105656,105702,105751,105815,105968,106061,106070,1061
34,106286,106425,106531,106546,106885,107144);
keep donor_id;
run;

/*down time and hanging time*/
data donorinfo;
set database.donor_comment;
if donor_id in
(100272,100303,100318,100357,100462,100469,100670,100683,1008
83,100938,101006,101034,101056,101111,101113,101134,101204,
101475,101667,101670,101771,101944,101995,102026,102226,1023
18,102320,102343,102625,102676,102753,102780,
102891,102995,103230,103258,103267,103312,103428,103435,1035
81,103995,104121,104184,104397,104599,104735,
104834,104842,104843,104898,104924,104942,104964,105101,1051
75,105255,105629,105276,105561,105652,105702,
105815,105968,106061,106070,106134,106286,106425,106531,1068
85,107144,107421,107507,107604,107617,107652,
107727,107829,107907,107955,108043,108130,108136,108188,1081
90,108263,108299,108310,108340,108393,108509,
108528,108557,108739,108989,109335,109368,109493,109642,1096
89,109836,109905,109918,109989,109995,110060,
110124,110345,110662,111012,111034,111070,111229,111268,1113
73,111388,111448,111535,111546,111554,111572,
111634,111642,111649,111770,111837,111913,111916,112067,1120
70,112203,112220,112492,112512,112576,112707,
112729,112742,112765,112799,112810,112980,113108,113128,1131
76,113188,113285,113300,113302,113339,113396,
113405,113882,113899,113909,113997,114077,114201,114224,1142
95,114350,114365,114416,114624,114914,114983,114985,
115156,115199,115258,115305,115331,115382,115387,115523,1155
24,115553,115610,115654,115665,115798,115857,115858,
115947,116072,116229,116271,116347,116356,116376,116380,1163
86,116635,116647,116659,116718,116721,116759,
116867,116938,116954,116991,117004,117022,117129,117262,1173
30,117601,117671,117680,117896,117900,117918,
38608,40084,40107,41752,41813,42531,43134,43495,44551,44602,4
4659,45491,45922,45986,46161,46212,46280,46300,46549,46714,46
822,46897,47171,47273,47460,47494,47691,
47821,49613,49638,49914,49994,50096,50454,51051,51207,51512,5
1887,51927,51972,51974,52389,52602,52630,
52682,52762,52841,52910,52946,53057,53770,53827,53997,54083,5
4234,54384,54783,54895,54963,55118,55149,
55187,55326,55424,55499,55628,55629,56095,56340,56749,56775,5
6802,56946,57332,57666,58287,58462,58471,
58807,58828,59000,59669,60118,60649,60740,6076161555,61586,61
810,61927,61956,62023,62151,62178,62532,
62581,62721,62730,62942,63228,63240,63388,63557,63664,63899,6
4313,64315,64600,64864,65133,65269,65294,
65314,66249,66559,66961,67124,67254,67329,67370,67531,67575,6
7682,67745,68158,68166,68181,68747,69182,
69431,69451,69684,70185,70358,70463,70710,70914,71006,71266,7
1333,71650,71710,71988,72054,72138,
72394,72448,72606,72666,72985,73209,73434,73508,73533,73552,7
3912,74077,74114,74142,74209,74231,74306,
74770,74841,74914,74969,75325,75490,75544,75554,75697,75725,7
5804,76032,76102,76184,76237,76259,
76316,76424,76481,76575,76628,76742,76744,76772,76844,76869,7
7088,77218,77360,77372,77662,77718,77832,
77896,77897,77916,77948,78028,78227,78530,78618,78869,78953,7
9149,79219,79320,79380,79577,79615,79649,79679,
79917,79940,80070,80135,80185,80212,80379,80404,80670,80681,8
0834,80921,81047,81086,81111,81244,81281,
81533,81557,81646,82081,82213,82215,82239,82463,82470,82619,8
2776,83111,83234,83395,83689,83784,83793,
83825,83952,84065,84135,84256,84298,84325,84647,84715,84824,8
4920,85081,85695,85806,85895,85903,85978,86066,
86122,86369,86885,86952,87036,87042,87441,87750,88046,88116,8
8246,88294,88305,88322,88513,88714,88771,88839,89139,89175,
89195,89242,89258,89323,89477,89538,89685,89694,89912,89999,9
0121,90461,90634,90680,90730,90853,91058,
91239,91269,91377,91395,91457,91458,91653,91675,91731,91762,9
1792,91959,91971,92038,92084,92166,92298,
92301,92339,92607,92626,92779,92785,92823,92918,93046,93238,9
3459,93568,93783,93820,93949,93965,93971,94108,94183,
```

```
94210,94219,94245,94416,94448,94534,94721,94963,95014,95058,9
5119,95128,95153,95303,95373,95450,95484,95678,
95709,95832,95834,95866,96093,96382,96439,96559,96685,96920,9
6962,97040,97053,97434,97580,97614,97623,
97667,97731,97855,97885,97935,97969,98044,98070,98087,98188,9
8189,98222,98306,98480,98515,98685,98687,98741,
98778,98806,99553,99814,99851,99970,100035,100082,100140,1001
97,100222,100303,100318,100357,100428,100462,
100469,100670,100883,100938,101006,101034,101056,101111,1011
13,101204,101307,101475,101667,101670,101771,
101944,101948,101995,102026,102226,102318,102320,102343,1026
25,102669,102676,102714,102753,102780,102781,
102891,102995,103138,103230,103258,103267,103312,103428,1035
81,103995,104121,104184,104303,104397,104467,
104599,104735,104834,104842,104843,104898,104924,104942,1049
64,105101,105175,105255,105269,105276,105561,
105652,105656,105702,105751,105815,105968,106061,106070,1061
34,106286,106425,106531,106546,106885,107144);

keep donor_id note_text;
run;
proc sort data=donorinfo;
by donor_id;
run;

data check;
set donorinfo;
if donor_id in
(64864
67370
62730
67531
72394
72448
73533
74969
75490
75725
1179 47
118017
118023
118024
118120
118200
118355
118466
118494
118598
118634
118677
118836
118868
118936
119070
119506
119512
119645
119691
119716
120078
120082
120289
120344
120424
120448
120498
120622
120623
120695
121010
121028
121135
121168
121304
121578
121592
121649
121663
121999
122122
122462
122696
122744
122766
122773
123027
123215
123315
123346
123399
123477
123521
123553
123795
123883
124018) then delete;
run;
proc freq data=kidneyfinal2;
table hanging*recip_id;
where hanging=1;
run;

proc sort data=kidneyfinal2;
by recip_id;
run;

data check;
set kidneyfinal2;
if recip_id=48113;
run;
/* attempt at propensity score matching*/
proc logistic data=kidneyfinal3 descending;
class dtype hypertension HLA_GRP  renal tyear;
        model hanging=dage rage dtype hypertension HLA_GRP
renal cld_isch dweight tyear;
        output out=study pred=ps xbeta=logit_ps;
        run;

proc univariate data=study;
        class hanging;
                var ps;
                run;



proc freq data=study;
table hanging*ps;
where hanging=1;
run;
data study2;
set study;
if ps=. then delete;
if dtype=2;
run;
data prop_score_treated prop_score_untreated;
set study2;
if hanging=1 then output prop_score_treated;
else if hanging=0 then output prop_score_untreated;
run;
proc univariate data=study;
class hanging;
var ps;
run;


%psmatch_multi(subj_dsn = prop_score_treated,
subj_idvar = RECIP_id,
subj_psvar = ps,
cntl_dsn = prop_score_untreated,
cntl_idvar = RECIP_id,
cntl_psvar = ps,
match_dsn = matched_pairs1,
match_ratio = 1,
score_diff = 0.01
);

data matching;
set matched_pairs1;
rename subj_idvar=recip_id;
rename cntl_idvar=matched_recip_id;
run;

proc sort data=matching nodupkey;
by recip_id;
run;


proc univariate data=matching;
var cntl_score;
run;



/*import matched data to assess how well matched post propensity
score matching*/

DATA WORK.porpensity_score_matched_data;
   LENGTH
      recip_id          8
      matched_recip_id   8
      subj_score         8
      cntl_score         8 ;
   FORMAT
      recip_id         F12.
      matched_recip_id F12.
      subj_score       BEST12.
      cntl_score       BEST12. ;
   INFORMAT
      recip_id         BEST12.
      matched_recip_id BEST12.
      subj_score       BEST12.
      cntl_score       BEST12. ;
   INFILE 'E:\SASWork\_TD37152_MSVSAS01_\#LN00057'
      LRECL=53
      ENCODING="WLATIN1"
      TERMSTR=CRLF
      DLM='7F'x
      MISSOVER
      DSD ;
   INPUT
      recip_id         : BEST32.
      matched_recip_id : BEST32.
```

```
      subj_score      : BEST32.
      cntl_score      : BEST32. ;
RUN;
data propmatch;
set WORK.porpensity_score_matched_data;
run;
proc univariate data=propmatch;
var cntl_score;
run;



proc sort data=matching;

proc univariate data=matching;
var

%psmatch_multi(

%macro psmatch_multi(subj_dsn =, /* Data set with subject data */
subj_idvar=,  /* Subject ID variable in
&SUBJ_DSN */
subj_psvar=,  /* Propensity Score variable in
&SUBJ_DSN */
cntl_dsn=,    /* Data set with control data  */
cntl_idvar=,  /* Control ID variable in data set
&CNTL_DSN */
cntl_psvar=,  /* Propensity Score variable in
&CNTL_DSN */
match_dsn=,   /* Output data set */
match_ratio=, /* Number of matches per subject  */
score_diff=,  /* Maximum allowable absolute
differences between propensity
scores*/
opt=none,     /* Type of matching optimization --
by number of matches( = num),
by closeness ( = close),
or default none ( = none) */
seed=1234567890); /* Optional seed for random number
generator */
/*********************************************************************/
/*  Delete final matched pairs dataset, if exists from a prior run
/*********************************************************************/
PROC DATASETS nolist;
delete __final_matched_pairs;
run;
quit;
/*********************************************/
/*  Make all internal macro variables local
/*********************************************/
%local __dsid __varnum __cntl_type __rc __num;
/*********************************************/
/* Control ID variable (numeric or character)
/*********************************************/
%let __dsid      = %sysfunc(open(&cntl_dsn,i));
%let __varnum    = %sysfunc(varnum(&__dsid, &cntl_idvar));
%let __cntl_type = %sysfunc(vartype(&__dsid, &__varnum));
%let __rc        = %sysfunc(close(&__dsid));
%put &__cntl_type;
/************************/
/*  Subject Matching Data
/************************/
DATA __subjmatch (keep = &subj_idvar &subj_psvar);
set &subj_dsn;
run;
/************************/
/*  Control Matching Data
/************************/
DATA __contmatch (keep = &cntl_idvar &cntl_psvar);
set &cntl_dsn;
run;
/*********************************************************************/
/*  Find all possible matches between subjects and controls
/*  Propensity scores must match within +/- &match (radius)
/*********************************************************************/
PROC SQL;
create table __matches0 as
select
s.&subj_idvar as subj_idvar,
c.&cntl_idvar as cntl_idvar,
s.&subj_psvar as subj_score,
c.&cntl_psvar as cntl_score,
abs(s.&subj_psvar - c.&cntl_psvar) as diff_score
from __subjmatch s left join __contmatch c
on abs(s.&subj_psvar - c.&cntl_psvar) <= &score_diff
order by subj_idvar;
quit;
/*************************************/
/*  Data set of all possible matches
/*************************************/
DATA __possible_matches;
set __matches0;
/*-------------------------------------------*/
/*  Create a random number for each match
/*-------------------------------------------*/
call streaminit(&seed);
rand_num = rand('uniform');
/*-------------------------------------------------*/
/*  Remove subjects who had no possible matches
/*-------------------------------------------------*/
%if &__cntl_type = C %then %do;
if cntl_idvar ^= '';
%end;
%else %if &__cntl_type = N %then %do;
%end;
if cntl_idvar ^= .;
/*-------------------------------------------*/
/*  Round DIFF_SCORE to an order of magnitude
/*-------------------------------------------*/
%if &opt = close %then %do;
if . < diff_score < .000000001 then
sort_diff_score = .000000001;
else if .000000001 <= diff_score < .00000001 then
sort_diff_score = round(diff_score, .000000001);
else if .00000001 <= diff_score < .0000001 then
sort_diff_score = round(diff_score, .00000001);
else if .0000001 <= diff_score < .000001 then
sort_diff_score = round(diff_score, .0000001);
else if .000001 <= diff_score < .00001 then
sort_diff_score = round(diff_score, .000001);
else if .00001 <= diff_score < .0001 then
sort_diff_score = round(diff_score, .00001);
else if .0001 <= diff_score < .001 then
sort_diff_score = round(diff_score, .0001);
else if .001 <= diff_score < .01 then
sort_diff_score = round(diff_score, .001);
else if .01 <= diff_score < .1 then
sort_diff_score = round(diff_score, .01);
else if diff_score >= .1 then
sort_diff_score = round(diff_score, .1);
%end;
/*--------------------------*/
/*  Create a dummy variable
/*--------------------------*/
n = 1;
run;
/*********************************************************************/
/*  Find the number of potential control matches for each subject
/*********************************************************************/
PROC FREQ data=    possible  matches noprint;
tables subj_idvar / out=__matchfreq (keep = subj_idvar count);
run;
DATA __matches_freq;
merge __possible_matches
__matchfreq;
by subj_idvar;
/*-------------------------------------------------------------*/
/*  Only keep subjects with minimum number of possible matches
/*-------------------------------------------------------------*/
if count >= &match_ratio;
run;
PROC DATASETS nolist;
delete __matches0;
run;
quit;
/*********************************************************************/
/*  Count the number of entries in the file of possible matches
/*********************************************************************/
%let __dsid = %sysfunc(open(__matches_freq,i));
%let __num = %sysfunc(attrn(&__dsid,nobs));
%let __rc = %sysfunc(close(&__dsid));
%do %while (&__num >= 1);
PROC SORT data=__matches_freq;
by %if &opt = num %then %do;
count
%end;
%else %if &opt = close %then %do;
sort_diff_score
%end;
rand_num subj_idvar;
run;
/*********************************************************************/
/*  Get first randomly selected subject
/*  For options, with either the least number of matches or
/*   the closest match
/*********************************************************************/
DATA __first_subj_idvar (keep = subj_idvar);
set __matches_freq;
by n;
if first.n;
run;
/*************************************/
/*  Get all matches for that subject
/*************************************/
PROC SORT data=__matches_freq;
by subj_idvar %if &opt = num %then %do;
count
%end;
%else %if &opt = close %then %do;
sort_diff_score
%end;
rand_num;
run;
DATA __all_first_id;
merge __matches_freq
__first_subj_idvar (in=i);
by subj_idvar;
if i;
num + 1;
run;
DATA __new_matched_pairs (keep = subj_idvar cntl_idvar
                                 subj_score cntl_score);
```

```
                set __all_first_id;
label subj_idvar =
"Subject ID, original variable name &subj_idvar"
cntl_idvar =
"Matched Control ID, original variable name &cntl_idvar"
subj_score =
"Subject Propensity Score, original var name &subj_psvar"
cntl_score =
"Matched Control Propensity Score, orig var &cntl_psvar"
;
if num <= &match_ratio;
run;
/*********************************************/
/*  Remove subjects with matched controls
/*********************************************/
PROC SORT data=__new_matched_pairs (keep = subj_idvar)
out=__new_matched_subj nodupkey;
by subj_idvar;
run;
DATA __match_remove_subj;
merge __possible_matches
__new_matched_subj (in=id);
by subj_idvar;
if ^id;
run;
/*****************************************************************/
/*  Remove all matched pairs that include selected controls
/*****************************************************************/
PROC SORT data=__new_matched_pairs (keep = cntl_idvar)
out=__remove_cont;
by cntl_idvar;
run;
PROC SORT data=__match_remove_subj;
by cntl_idvar;
run;
DATA __match_remove_cont;
merge __match_remove_subj
__remove_cont (in=id);
by cntl_idvar;
if ^id;
run;
PROC SORT data=__match_remove_cont out=__possible_matches;
by subj_idvar;
run;
/*****************************************************************/
/*  Add new matched pairs to set of final matched pairs
/*****************************************************************/
PROC APPEND base=__final_matched_pairs
data=__new_matched_pairs;
run;
/*****************************************************************/
/*  Find the number of potential control matches for each subject
/*****************************************************************************/
PROC FREQ data=__possible_matches noprint;
tables subj_idvar / out=__matchfreq (keep = subj_idvar count);
run;

DATA __matches_freq;
merge __possible_matches
__matchfreq;
by subj_idvar;
/*-------------------------------------------------------------*/
/*  Only keep subjects with the minimum number of matches
/*-------------------------------------------------------------*/
if count >= &match_ratio;
run;
/*****************************************************/
/*  Determine number of remaining possible matched pairs
/*****************************************************/
%let __dsid = %sysfunc(open(__matches_freq,i));
%let __num = %sysfunc(attrn(&__dsid,nobs));
%let __rc = %sysfunc(close(&__dsid));
%end;  /*  of " %do %while (&__num >= 1);  */
/*****************************************************************************/
/*  Create final output data set with one observation for each
/*  original subject.
/*
/*  Variable names in output data set are:
/*    SUBJ_IDVAR, SUBJ_SCORE, CNTL_IDVAR, CNTL_SCORE
/*
/*  If no match for subject ID (SUBJ_IDVAR), then CNTL variables
/*    (CNTL_IDVAR, CNTL_SCORE) are missing.
/*****************************************************************/
PROC SORT data=__final_matched_pairs;
by subj_idvar subj_score;
run;
DATA __subjmatch_orig;
set __subjmatch (rename= (&subj_idvar = subj_idvar
&subj_psvar = subj_score));
run;
PROC SORT data=__subjmatch_orig;
by subj_idvar subj_SCORE ;
run;
DATA &match_dsn (label="Final Matched Pairs for PS Matching");
merge __final_matched_pairs
__subjmatch_orig;
by subj_idvar subj_score;
run;
/*****************************************************/
/*  Delete all temporary datasets created by macro
/*****************************************************/
PROC DATASETS nolist;
delete __contmatch __final_matched_pairs __matches_freq0
__matches_freq __match_pair0 __matchfreq
__match_remove_cont __match_remove_subj
__new_matched_pairs __subjmatch __subjmatch_orig
__possible_matches __remove_cont
__first_subj_idvar __all_first_id
__new_matched_subj;
run;
quit;
%mend psmatch_multi;

/*checking differenc in propensity scores*/


/*assess impact of macthed cohort on outcomes*/
data kidneypropatched;
set kidneyfinal3;
if recip_id in
(3085          164323
6686           117384
run;

proc sort data=kidneypropatched nodupkey;
by recip_id;
run;

data kidneypropDCD;
set kidneyfinal3;
if recip_id in
run;

data kidneypropmatchDCD2;
set kidneypropDCD;
run;
data propmatch;
set kidneypropatched;
run;
proc freq data=propmatch;
table hanging*graft_no;
run;
proc npar1way data=propmatchdcd;
class hanging;
var dage;
run;
proc freq data=propmatch;
table dtype*hanging/chisq;
run;

proc logistic data=propmatchdcd;
model pnf=hanging;
where pnf in (1,0);
run;

proc lifetest data=propmatch2dcd plots=(S,LLS);
time gsurv5*gcens5(0);
strata hanging;run;



data propmatch2dcd;
set propmatchdcd;
if gsurv > (5*365.25) then gsurv5=(5*365.25);
else gsurv5=gsurv;
if gsurv > (5*365.25) then gcens5=0;
else gcens5=gcens;

if gsurv > (1*365.25) then gsurv1=365.25;
else gsurv1=gsurv;
if gsurv > (1*365.25) then gcens1=0;
else gcens1=gcens;


if psurv > (5*365.25) then psurv5=5;
else psurv5=psurv/365.25;
if psurv > (5*365.25) then pcens5=0;
else pcens5=pcens;

if psurv > (1*365.25) then psurv1=365.25;
else psurv1=psurv;
if psurv > (1*365.25) then pcens1=0;
else pcens1=pcens;

if gsurv=0 and gcens=1 then pnf1=1;
else pnf1=0;
if diabetes=3 then diabetes=.;
if hypertension=3 then hypertension=.;
run;


proc lifetest data=propmatch2 atrisk plots=survival(cb);
time gsurv1*gcens1(0);
strata hanging;
run;

proc phreg data=propmatch2dcd;
model psurv1*pcens1(0)=hanging;
hazardratio hanging/diff=ref;
run;

proc sgplot data=propcheck;
```

```
                loess x= gsurv1 y=schres/clm;
run;


/*CREATININE 1 YEAR*/
DATA CREATININE;
SET STANDARD.KID_SERUM_CREATININE;
RUN;

PROC SORT DATA=CREATININE;
BY TX_ID;
RUN;
PROC SORT DATA=propmatch2dcd;
BY TX_ID;
RUN;

DATA KIDNEYCREATININEPSdcd;
MERGE propmatch2dcd CREATININE;
BY TX_ID;
IF hangdcd=. THEN DELETE;
RUN;
proc freq data=kidneycreatinine;
table serum12;
run;

DATA camcreatpsdcd;
SET KIDNEYCREATININEpsdcd;
if SERUM12 ne . and RAGE ne . and Rsex ne . and Rethnic ne 9 then
do;
    * non-black males *;
    if Rsex=1 and Rethnic ne 3 then do;
        mdrd =round((186*((SERUM12/88.4)**(-1.154))*(Rage**(-
0.203))));
    end;
    * black males *;
    if RSex=1 and Rethnic=3 then do;
        mdrd =round((186*((SERUM12/88.4)**(-1.154))*(Rage**(-
0.203))*1.210));
    end;
    * non-black females *;
    if Rsex=2 and Rethnic ne 3 then do;
        mdrd =round((186*((SERUM12/88.4)**(-1.154))*(Rage**(-
0.203))*0.742));
    end;
    * black females *;
    if Rsex=2 and Rethnic=3 then do;
        mdrd =round((186*((SERUM12/88.4)**(-1.154))*(Rage**(-
0.203))*0.742*1.210));
    end;
end;
RUN;

ods graphics on;
proc univariate data=camcreatps;
class hanging;
var MDRD;
run;
ods graphics off;

PROC GLM DATA=camcreatpsdcd;
CLASS  hanging(ref='0');
MODEL MDRD=hanging;
RUN;

run;
PROC FREQ DATA=CAMCREAT;
TABLE MDRD;RUN;

proc npar1way data=camcreatps;
class hanging;
var mdrd;
run;


PROC GLM DATA=CAMCREATps;
CLASS  hanging(ref='0');
MODEL MDRD= hanging /SOLUTION CLPARM;
ODS output ParameterEstimates=PARMS_GLM;
RUN;

run;
```

1.52 Appendix 7: Risk Variation code

```
data kidney;
set standard.kidney_tx;
if mdy(01,01,2006)<=tx_date<mdy(01,01,2016);
if txcountry='UNITED KINGDOM';If dtype in (1,2);if rage=>18;
if dcountry='UNITED KINGDOM';if tx_type in (10,11,12,13,14);if
dage=>10;
if recip_id=>0 then id=1;
run;

/*missing death data*/
proc freq data=kidney;table pcens;run;
data donors;set standard.donors;run;
proc sort data=kidney;by donor_id;run;
proc sort data=donors;by donor_id;run;
data kidney2;set kidney; if psurv=.;run;
proc sort data=kidney2;by recip_id;run;
data all;set standard.kidney_tx;run;
proc sort data=all;by recip_id;run;
data Allmissing;merge kidney2 all;
by recip_id;if id=. then delete;run;
data Missing2;set allmissing;if psurv=. then delete;
rename tx_date=first_tx_date psurv=Patientdays
pcens=patientsurvival;
keep recip_id tx_date psurv pcens;
run;
proc sort data=missing2;by recip_id;run;
data missing3;merge kidney2 missing2;by recip_id;run;
data missing4;set missing3;if tx_date>first_tx_date then
duration=tx_date-first_tx_date;
run;
data missing5;set missing4;if patientdays=>duration then
psurvfinal=patientdays-duration;
run;
proc sort data=missing5;by recip_id;run;
proc sort data=kidney;by recip_id;run;
data Kidneyall;merge kidney missing5;by recip_id;run;
proc freq data=kidneyall;table id;run;
data Analysis;set kidneyall;if psurv=. then psurv=psurvfinal;if pcens=.
then pcens=patientsurvival;
run;
proc freq data=analysis;table pcens;run;

/*checking Guys survival*/
data Guys;
set analysis;
if mdy(01,01,2006)<=tx_date<mdy(01,01,2010)then group=1;
if mdy(01,01,2010)<=tx_date<mdy(01,01,2016) then group=2;
run;
data guys2;
set guys;
if graft_no=1;
run;



proc lifetest data=guys notable plots=survival;
time gsurv*gcens(0);
strata group;
run;



/*own attempt at doing survival form listing over set period*/
data history;set standard.kidwait; if
mdy(01,01,2006)<=adate_on<mdy(01,01,2016);run;
data history2; set history;surv=d_date-adate_on;if endstat in ('DA','DS',
'D', 'DR') then died=1;if endstat='L' then delete;run;
data history3;set history2;if surv=>0 then died=1;run;
data history4;set history3;if died=. then newtimes=mdy(01,01,2016)-
adate_on;run;
proc freq data=history4;table died;run;
proc sort data=history4;by recip_id;run;
proc sort data=analysis;by recip_id;run;

data allhistory;merge analysis history4;by recip_id; if adate_on=. then
delete;if mdy(01,01,2006)<=adate_on<mdy(01,01,2016);run;
proc sort data=allhistory;by recip_id rsex tx_date;run;
data allhistory allhistory2;
  set allhistory;
  by recip_id rsex tx_date;
  if last.rsex then output allhistory;
  else output allhistory2;
run;
data allhistorycheck;
set allhistory;
keep recip_id adate_on;
run;


data ahistory4;set allhistory;time=tx_date-adate_on;run;
data ahistory5;set ahistory4;timing=time+psurv;run;
data ahistory6;set ahistory5;if pcens=1 then died=1;if donor_id=. then
txd=0;else txd=1;run;
proc freq data=ahistory6;table txd*tx_date;run;
data ahistory7;set ahistory6;if died=1;times=surv;run;
data ahistory8;set ahistory6;if txd=1 then times=timing;
run;
data ahistory9;set ahistory6;if txd=0 and died=. then
times=newtimes;run;
proc sort data=ahistory7;by recip_id;run;
proc sort data=ahistory8;by recip_id;run;
proc sort data=ahistory9;by recip_id;run;
data aallhistory;merge ahistory7 ahistory8;by recip_id;run;
data aallhistory2; merge ahistory9 aallhistory; by recip_id;run;
proc sort data=analysis;by recip_id;run;
proc sort data=ahistory9;by recip_id;run;
data aallhistory;merge ahistory9 analysis;by recip_id;if adate_on=. then
delete;run;
data sorting;set aallhistory; run;
data sorting2; set sorting;newtimes=tx_date-adate_on;run;
data sorting3; set sorting2;timelisting=psurvfinal+newtimes;run;
data sorting4; set sorting3;if timelisting=. then timelisting=surv;run;
data sorting5; set sorting4; if timelisting=. then timelisting=times;run;
data sorting6; set sorting5;if timelisting=. then timelisting=wait_time +
psurvfinal;run;
data sorting7;set sorting6;if timelisting=. then timelisting=wait_time +
psurv;run;
data sorting8;set sorting7; listingcentre=tx_cent;
if dcountry='OVERSEAS' then delete;
if tx_cent in ('Z0201','Z0206','Z0209','Z0220',
'Z0223','Z0227','Z0235','Z0298','Z0399','Z0405',
'Z0406','Z0607','Z0612','Z0612')
then delete;
if tx_cent in ('G0501','G1501', 'G1403','G1401') THEN
LISTINGcENTRE='G1501';
if tx_cent in ('H1305', 'H1202') then listingcentre='H1202';
if died=. then died=0;run;
proc sort data=sorting8; by  listingcentre;run;
proc lifetest data=sorting8 notable plots=s;
time timelisting*died(0);
strata txd;
run;


/*import risk score data*/

DATA WORK.Book4;
   LENGTH
      Rec_Unit         $ 5
      Score1            8
      Score1b           8
      Score1c           8
      Score2a           8
      Score2b           8
      Score2c           8
      EarlyScore1a      8
      Earlyscore1b      8
      Earlyscore1c      8
      Earlyscore2a      8
      Earlyscore2b      8
      Earlyscore2c      8
      Latescore1a       8
      Latescore1b       8
      Latescore1c       8
      Latescore2a       8
      Latescore2b       8
      Latescore2c       8 ;
   FORMAT
      Rec_Unit         $CHAR5.
      Score1           BEST12.
      Score1b          BEST12.
      Score1c          BEST12.
      Score2a          BEST12.
      Score2b          BEST12.
      Score2c          BEST12.
      EarlyScore1a     BEST12.
      Earlyscore1b     BEST12.
      Earlyscore1c     BEST12.
      Earlyscore2a     BEST12.
      Earlyscore2b     BEST12.
      Earlyscore2c     BEST12.
      Latescore1a      BEST12.
      Latescore1b      BEST12.
      Latescore1c      BEST12.
      Latescore2a      BEST12.
      Latescore2b      BEST12.
      Latescore2c      BEST12. ;
   INFORMAT
      Rec_Unit         $CHAR5.
      Score1           BEST12.
      Score1b          BEST12.
      Score1c          BEST12.
      Score2a          BEST12.
      Score2b          BEST12.
      Score2c          BEST12.
      EarlyScore1a     BEST12.
```

```
      Earlyscore1b    BEST12.
      Earlyscore1c    BEST12.
      Earlyscore2a    BEST12.
      Earlyscore2b    BEST12.
      Earlyscore2c    BEST12.
      Latescore1a     BEST12.
      Latescore1b     BEST12.
      Latescore1c     BEST12.
      Latescore2a     BEST12.
      Latescore2b     BEST12.
      Latescore2c     BEST12. ;
   INFILE 'E:\SASWork\_TD6264_MSVSAS01_\#LN00023'
      LRECL=86
      ENCODING="WLATIN1"
      TERMSTR=CRLF
      DLM='7F'x
      MISSOVER
      DSD ;
   INPUT
      Rec_Unit        : $CHAR5.
      Score1          : BEST32.
      Score1b         : BEST32.
      Score1c         : BEST32.
      Score2a         : BEST32.
      Score2b         : BEST32.
      Score2c         : BEST32.
      EarlyScore1a    : BEST32.
      Earlyscore1b    : BEST32.
      Earlyscore1c    : BEST32.
      Earlyscore2a    : BEST32.
      Earlyscore2b    : BEST32.
      Earlyscore2c    : BEST32.
      Latescore1a     : BEST32.
      Latescore1b     : BEST32.
      Latescore1c     : BEST32.
      Latescore2a     : BEST32.
      Latescore2b     : BEST32.
      Latescore2c     : BEST32. ;
RUN;


data riskscores;
set work.book4;
if rec_unit='O2020' then rec_unit='02020';
run;
data riskscores2;
set riskscores;
listingcentre=rec_unit;
run;
proc sort data=riskscores;
by rec_unit;
run;
proc sort data=guys;
by rec_unit;
run;

data all;
merge guys riskscores;
by rec_unit;
run;
proc univariate data=all;
var score1;
run;

data model;
set all;
if prd in (210,211,212,213,214,215,216,217,219) then renal=1;
if prd in (220,221,222,223,224,225,229) then renal=2;
if prd in (241,242) then renal=3;
if prd in (280,281) then renal=4;
if score1<20 then risky=1;
if 20<=score1<25 then risky=2;
if 25<=score1<30 then risky=3;
if score1=>32 then risky=4;
if score1b<48.5 then risky1b=1;
if 48.5<=score1b<60 then risky1b=2;
if 60<=score1b<75.0 then risky1b=3;
if score1b=>75 then risky1b=4;
if score1c<52 then risky1c=1;
if 52<=score1c<66.5 then risky1c=2;
if 66.5<=score1c<83.5 then risky1c=3;
if score1c=>83.5 then risky1c=4;
if score2a<90 then risky2a=1;
if 90<=score2a<111 then risky2a=2;
if 111<=score2a<160 then risky2a=3;
if score2a=>160 then risky2a=4;
if score2b<216 then risky2b=1;
if 216<=score2b<269 then risky2b=2;
if 269<=score2b<389.5 then risky2b=3;
if score2b=>389.5 then risky2b=4;
if score2c<237 then risky2c=1;
if 237<=score2c<291.5 then risky2c=2;
if 291.5<=score2c<438.5 then risky2c=3;
if score2c=>438.5 then risky2c=4;
if tx=. then tx=0;
if removed=. then removed=0;
run;
data model2;
set model;
if renal=. then renal=5;
run;

proc  freq data=model2;
table renal;
run;
proc phreg data=model2;
class renal(ref='5') risky(ref='2')tx_yr graft_no (ref='1');
model psurv*pcens(0)=renal  rage wait_time risky tx_yr;
hazardratio risky/diff=ref;
run;
proc freq data=model2;
table rec_unit;
run;


proc freq data=all;
table listingcentre;
run;

data all2;
set all;
if dcountry='OVERSEAS' then delete;
if tx_cent in ('Z0201','Z0206','Z0209','Z0220',
'Z0223','Z0227','Z0235','Z0298','Z0399','Z0405',
'Z0406','Z0607','Z0612','Z0612', 'T0101')
then delete;

if died=1 or pcens=1 or patientsurvival=1 then death=1;else death=0;
if reg_age<18 then delete;run;
DATA ;
prOC UNIVARIATE DATA=ALL2;VAR score1;run;
proc sort data=all2;
by reg_age;
run;


data all3;
set all2;
if score1=>30 then risky=4;
if score1<20 then risky=1;
if 20<=score1<25 then risky=2;
if 25<=score1<30 then risky=3;
run;
PROC FREQ DATA=ALL3;
TABLE DEATH*txd;
RUN;

data all4;set all3;if  donor_id=. then txde=0;else txde=1;run;
proc freq data=all4;table txdE;run;

data all5;set all4;run;

proc freq data=all3;table risky*death;run;

data external;set all5;if txde=0;run;
proc sort data=external;by recip_id;run;

data death;
set database.recip_ext_agency_death;
run;
proc sort data=death;by recip_id;run;

data externaldeath;merge external death;by recip_id;if txde=. then
delete;run;
data new; set externaldeath; keep recip_id death death_date;run;
proc freq data=new;table death;run;
data new2;set new;if death=1 then deadly=1;run;
data new3;set new2;if death_date=>0 then deadly=1;run;
proc freq data=new3;table deadly;run;
proc sort data=all5; by recip_id;run;
proc sort data=new3;by recip_id;run;

data alldeath;merge all5 new3;by recip_id;run;
data alldeath2;set alldeath; if death=1 and deadly=. then deadly=1;run;

data alldeath3;set alldeath2;if deadly=. then deadly=0;run;
proc freq data=alldeath3;table listingcentre*risky;run;

data alldeath4;set alldeath3;
rec_unit=listingcentre;new_time=timelisting;if recip_id=. then
real=0;else real=1;run;
proc freq data= alldeath4;table new_time;run;

data alldeathnow;set alldeath4;if new_time=. then
new_time=wait_time+psurv;run;
proc freq data=alldeathnow;table new_time;run;
data checking;set alldeathnow;if new_time=.;run;
data checking2;set checking; format death_time date9. ;run;


data checking3;set checking2; new_time=death_time-adate_on;run;

data checking4;set checking3; if new_time=. then new_time=wtime;run;
proc sort data=checking4;by recip_id;run;
proc sort data=alldeath4;by recip_id;run;
proc freq data=alldeath4;table deadly;run;
data alldeath5;merge alldeath4 checking4;by recip_id;run;
proc freq data=alldeath5;table new_time;run;

/*If tx=1*/
data info;
set alldeath5;
if txd=1 ;
```

```
run;
data info2;
set info;
survival=psurv + wtime;
run;
proc freq data=info2;
table survival;
run;

/*if tx=0*/
data infox;
set alldeath5;
if txd=0 ;
run;
data infox2;
set infox;
if deadly=1;
run;
data infox3;
set infox2;
survival= d_date-adate_on;
run;

/*tx=0 and deadly=0*/
data infoxx;
set alldeath5;run;
data infoxx2;
set infoxx;
if deadly=0;
if txd=0;
run;
proc freq data=infoxx2;
table new_time;
run;
data infoxx3;
set infoxx2;
if tx_date=>0 and tx_date<mdy(01,01,2016) then txde=1 and
survival=psurv + wtime;
run;
data infoxx4;
set infoxx3;
if txde=1;
if tx_type=130 or tx_type=150 then delete;
run;
data infoxx5;
set infoxx3;
if txde=0;
survival=new_time;
run;


proc sort data=infoxx4;by recip_id;run;
data kidneyall;set standard.kidney_tx;run;
proc sort data=kidneyall;by reciP_id;run;
data sense; merge infoxx4 kidneyall;by recip_id;if txde=. then delete;
if dage<10 then delete;if txcountry='UNITED KINGDOM';if rage=<18
then delete;if tx_date<=mdy(01,01,2006);run;
data sense2;set sense;survival=psurv+wtime;run;

proc sort data=infoxx4;by recip_id;run;
proc sort data=kidney; by recip_id;run;
data infoxkidney;merge infoxx4 kidney; by recip_id; if txde=. then
delete;run;


/*combine all*/
proc sort data=info2; by recip_id;run;
proc sort data=infox3; by recip_id;run;
data together; merge info2 infox3; by recip_id;run;
proc sort data=infoxx5;by recip_id; run;
proc sort data=together;by recip_id;run;
data together2; merge together infoxx5; by recip_id;run;
proc sort data=sense2;by recip_id;run;
proc sort data=together2;by recip_id;run;
data together3;merge together2 sense2;by recip_id;
;run;
proc freq data=together3;table survival;run;
data news;set together3;if survival=. then delete;run;
data letsee;set together3;if survival=.  ;death=datepart(death_date);run;
data letsee2;set letsee;date1=death;label date1="DATE with DATE9.
format";
format death date9.;run;
data letsee3;set letsee2;survival2=death-adate_on;run;

proc sort data=letsee3;by recip_id;run;
proc sort data=news;by recip_id;run;
data news2;merge letsee3 news;by recip_id;run;
proc freq data=news2;table survival2;run;
data news3;set news2;if survival2=. then surviving=survival;else
surviving=survival2;if listingcentre=. then listingcentre=tx_cent;
if tx_cent in ('G0501','G1501', 'G1403','G1401') THEN
LISTINGcENTRE='G1501';
if tx_cent in ('H1305', 'H1202') then listingcentre='H1202';run;
proc freq data=news3;table surviving;run;
proc freq data=news3;table listingcentre;run;
data keep;
set news3;
keep recip_id listingcentre rec_unit tx_cent score1 score1b;
run;
data keep2;
set keep;
if listingcentre=.;
run;

/*checking negative times*/
data checking;
set together2;
if new_time<0 then delete;
run;
proc freq data=checking;
table new_time2;
run;

proc univariate data=alldeath5;
class risky;
var wait_time;
run;

proc npar1way data=alldeath5;
class risky;
var wait_time;
run;
ods graphics on;
proc logistic data=news3 descending plots=all;
class risky(ref='3')/param=ref;
model txd=risky;
run;


proc lifetest data=news3 notable plots=survival;
time surviving*deadly(0);
strata txd;
run;
data alldeath6;
set alldeath5;
if risky in (1,3);
run;

/*Overall time period-Risk scores*/
proc univariate data=news3;
var score1b;
run;
data checking2;
set news3;
if score1b<48.5 then risky1b=1;
if 48.5<=score1b<57.5 then risky1b=2;
if 57.5<=score1b<75.0 then risky1b=3;
if score1b=>75 then risky1b=4;
if score1c<52 then risky1c=1;
if 52<=score1c<66.5 then risky1c=2;
if 66.5<=score1c<83.5 then risky1c=3;
if score1c=>83.5 then risky1c=4;
if score2a<89 then risky2a=1;
if 89<=score2a<111 then risky2a=2;
if 111<=score2a<160 then risky2a=3;
if score2a=>160 then risky2a=4;
if score2b<216 then risky2b=1;
if 216<=score2b<269 then risky2b=2;
if 269<=score2b<389.5 then risky2b=3;
if score2b=>389.5 then risky2b=4;
if score2c<237 then risky2c=1;
if 237<=score2c<291.5 then risky2c=2;
if 291.5<=score2c<438.5 then risky2c=3;
if score2c=>438.5 then risky2c=4;
run;
proc freq data=checking2;table score2c;run;
data how;
set checking2;
if score2c=.;
run;

libname library 'F:\Stats & Audit\Shared\All\Temporary\Paddy';
data library.checking2;
set checking2;
run;

/*early time period graft and patient survival*/
data checkingearly;
set news3;
if mdy(01,01,2006)<adate_on<mdy(01,01,2010);
run;
proc univariate data=checkingearly;
var EarlyScore2c;
run;
data checkingearly2;
set news3;
if earlyscore1a<17 then early1a=1;
if 17<=earlyscore1a<23 then early1a=2;
if 23<=earlyscore1a<28 then early1a=3;
if earlyscore1a=>28 then early1a=4;
if earlyscore1b<39.5 then early1b=1;
if 39.5<=earlyscore1b<53.0 then early1b=2;
if 53.0<=earlyscore1b<68.5 then early1b=3;
if earlyscore1b=>68.5 then early1b=4;
if earlyscore1c<45.5 then early1c=1;
if 45.5<=earlyscore1c<59.5 then early1c=2;
if 59.5<=earlyscore1c<73.5 then early1c=3;
if earlyscore1c=>73.5 then early1c=4;
if earlyscore2a<75 then early2a=1;
if 75<=earlyscore2a<114 then early2a=2;
if 114<=earlyscore2a<143 then early2a=3;
if earlyscore2a=>143 then early2a=4;
```

```
if earlyscore2b<147.5 then early2b=1;
if 147.5<=earlyscore2b<273.5 then early2b=2;
if 273.5<=earlyscore2b<362.0 then early2b=3;
if earlyscore2b=>362.0 then early2b=4;
if earlyscore2c<191 then early2c=1;
if 191<=earlyscore2c<305 then early2c=2;
if 305<=earlyscore2c<381.5 then early2c=3;
if earlyscore2c=>381.5 then early2c=4;
run;

/*Late score time period*/
data checkinglate;
set news3;
if mdy(01,01,2010)<=adate_on<mdy(01,01,2016);
run;
proc freq data=checkinglate;
table latescore1a;
run;
proc univariate data=checkingearly;
var lateScore2c;
run;
data checkinglate2;
set checkinglate;
if latescore1a<21 then late1a=1;
if 21<=latescore1a<24 then late1a=2;
if 24<=latescore1a<32 then late1a=3;
if latescore1a=>32 then late1a=4;
if latescore1b<51.5 then late1b=1;
if 51.5<=latescore1b<62.0 then late1b=2;
if 62.0<=latescore1b<72.0 then late1b=3;
if latescore1b=>72.0 then late1b=4;
if latescore1c<55 then late1c=1;
if 55<=latescore1c<64 then late1c=2;
if 64<=latescore1c<84.5 then late1c=3;
if latescore1c=>84.5 then late1c=4;
if latescore2a<114 then late2a=1;
if 114<=latescore2a<161 then late2a=2;
if 161<=latescore2a<174 then late2a=3;
if latescore2a=>174 then late2a=4;
if latescore2b<221 then late2b=1;
if 221<=latescore2b<277 then late2b=2;
if 277<=latescore2b<367 then late2b=3;
if latescore2b=>367 then late2b=4;
if latescore2c<257.5 then late2c=1;
if 257.5<=latescore2c<309.5 then late2c=2;
if 309.5<=latescore2c<426.5 then late2c=3;
if latescore2c=>426.5 then late2c=4;
run;



%macro
survival(data,surv,cens,period,end,end1,var,survival,yaxis,cgm);
ods listing;
/*READS IN YOUR DATASET AND CHANGES THE SURVIVAL
VARIABLES READY FOR USE*/
/*ALSO CHANGES THE DATA TO YEARS OR MONTHS OR DAYS*/
data surv;
set &data;
if &surv <0 then delete;
cens = &cens;
/*survival analysis-Initially all High risk behaviour together*/
/*Survival macro used*/
if lowcase("&period") = "months" then surv = &surv / 30.44;
if lowcase("&period") = "years" then surv = &surv / 365.25;
if lowcase("&period") = "days" then surv = &surv / 1;
if surv > &end then do; surv = &end; cens = 0; end;
fup = 0;
if surv = &end or cens ne 0 then fup = 1;
run;

/*GETS THE COUNT FOR EACH STRATA*/
proc freq data = surv noprint; table &var / out = num; run;

/*GETS THE COUNT FOR FOLLOW UP*/
proc freq data = surv noprint; table &var * fup / out = fup; run;

/*OPENS THE FILE TO SAVE THE PLOT*/
filename gsasfile "&file.\&cgm..emf";

/*RUNS THE LIFETEST PROCEDURE TO OUTPUT THE DATA
NEEDED FOR THE PLOT*/
ODS OUTPUT homtests=homtests;
proc lifetest data=surv plots=(s) outsurv=surv1;
time surv*cens(0); strata &var;
run;
quit;

/*SORTS OUT THE LAYOUT OF THE PLOT AND CHOOSES
COLOURS FOR THE LINES*/
goptions reset=all reset=symbol htext=1.8 cback=white colours=(black)
/*ftext=HWCGM005*/ ftext='Arial/bold'
noborder hsize=8.5 vsize=9.5 Gaccess=GSASFILE;run;
axis1 minor=none order=&yaxis to 100 by 10 label=(ANGLE=90 "%
&survival survival");
axis2 minor=none order=0 to &end by &end1 label=("&period post-
transplant");
symbol;
symbol1 c=CXFF6600 i=steplj w=4 l=1 v=none;
symbol2 c=CX99CCFF i=steplj w=4 l=1 v=none;
symbol3 c=CXFFCC00 i=steplj w=4 l=1 v=none;
symbol4 c=CX339966 i=steplj w=4 l=1 v=none;
symbol5 c=black    i=steplj w=4 l=1 v=none;
symbol6 c=CXFF6600 i=steplj w=4 l=2 v=none;
symbol7 c=CX99CCFF i=steplj w=4 l=2 v=none;
symbol8 c=CXFFCC00 i=steplj w=4 l=2 v=none;
symbol9 c=CX339966 i=steplj w=4 l=2 v=none;
symbol10 c=black   i=steplj w=4 l=2 v=none;

                LEGEND1 ACROSS=1
                POSITION=(BOTTOM INSIDE CENTER)
                MODE=SHARE
                OFFSET=(0,1.5)
                SHAPE=SYMBOL(5,1)
                                                CBORDER=Black
                LABEL=(POSITION=(TOP)
                JUSTIFY=CENTER H=1.2 "&var")
                                                VALUE=(H=1.2);

/*PRODUCES THE PLOT*/
data splot1; set surv1; retain lag_s; drop=lag_s; if survival=. then
survival=lag_s;
lag_s=survival; run;
data splot2; set splot1; survival=survival*100;
proc gplot data=splot2; plot survival * surv = &var /legend=legend1
noframe vaxis=axis1 haxis=axis2;
title ' '; run; quit;

/*USES THE DATA TO OBTAIN THE SURVIVAL ESTIMATES FOR
THE STRATA*/
data surv2; set surv1; if _censor_ = 0; run;
proc sort data = surv2; by &var survival; run;
proc sort data = surv2 nodupkey; by &var; run;

data surv3; set surv2; surv = (survival*100); lcl = (sdf_lcl*100); ucl =
(sdf_ucl*100);
format surv lcl ucl 10.1; run;

data surv4; merge surv3 num; by &var; run;

/*OBTAINS THE P-VALUE FOR THE STRATA*/
data _null_;
set homtests;
where test = 'Log-Rank';
call symput ("logrank",trim(left(put(ProbChiSq,PVALUE6.4))));
run;

/*PRINTS THE ESTIMATES, COUNT AND P-VALUE FOR THE
DATA*/
title1"&survival survival by &var p=&logrank";
proc print data = surv4; var &var count surv lcl ucl;  run;
%mend survival;

/*MACRO VARIABLES REQUIRED*/
/*%survival(data,surv,cens,time,end,end1,censor,var,survival,period,cg
m);*/
/*WHERE          data=dataset with survival variables
                                surv=name of survival variable - eg
gsurv
                                cens=name of censoring variable -
eg gcens
                                period=years, months, days
                                end=put 10 if wanting 10 year
survival, 12 for 12 month survival, 30 for 30 day survival
                                end1=how big you want your x-label
gap eg 1 if you want 10 years by 1 year
                                var=variable you want to strata by -
eg centre
                                survival=either graft, patient or
transplant
                                yaxis=point at which you want the
yaxis to start, 40 is standard
                                emf=name of emf file you want to
save
*/

%survival(guys,psurv,pcens,Years,5,1,group, graft,0,HR_g);
%survival(checkinglate2,surviving,deadly,Years,5,1,late1a,patient,0,HR
_p);

proc freq data=checking2;table listingcentre;run;
data why;
set checking2;
if endstat in ('RS', 'R', 'S', 'RA') or deadly=1 then removed=1;else
removed=0;
run;
proc freq data=why;
table removed;
run;

proc freq data=why;
table listingcentre;
run;


data guysdeath;
set alldeath5;
if listingcentre='G1501';
if tx_date<mdy(01,01,2010)then group=1;
else group=0;
run;
```

```
proc freq data=guysdeath;
table group;
run;
data guysdeath2;
set guysdeath;
if group=0;
run;


proc phreg data=alldeath5;
class risky(ref='1')/param=ref;
model new_time*deadly(0)=risky rage;
hazardratio risky/diff=ref;
run;
```