



# THE UNIVERSITY *of* EDINBURGH

This thesis has been submitted in fulfilment of the requirements for a postgraduate degree (e. g. PhD, MPhil, DClinPsychol) at the University of Edinburgh. Please note the following terms and conditions of use:

- This work is protected by copyright and other intellectual property rights, which are retained by the thesis author, unless otherwise stated.
- A copy can be downloaded for personal non-commercial research or study, without prior permission or charge.
- This thesis cannot be reproduced or quoted extensively from without first obtaining permission in writing from the author.
- The content must not be changed in any way or sold commercially in any format or medium without the formal permission of the author.
- When referring to this work, full bibliographic details including the author, title, awarding institution and date of the thesis must be given.

Marginal Donor Characteristics and Outcomes After  
Liver Transplantation

Miss Amanda Roebuck

MScR Thesis

University of Edinburgh

2023

# Abstract

## Introduction

Liver Transplantation across the globe has a supply and demand issue. Ever-advancing improvements in road safety and medical care mean a reduced pool of “ideal donors” and the population age is increasing rapidly over time. There is a growing need for donor livers as the number of critically unwell recipients awaiting liver transplantation increases. The extended criteria donor liver has been increasingly utilised in an attempt to balance the equation. There are many studies looking at combinations of variables associated with complications, graft survival and recipient survival but no universal consensus on how to define the limits for each of these variables when choosing a donor. Matching these marginal liver grafts with an appropriate recipient adds another challenge in the quest to deliver the best outcomes for patients. Increasing donor age and donation after cardiac death (DCD) liver transplantations are variables that are widely studied and reported in the literature to negatively affect graft and recipient survival outcomes and are the focus of this analysis. The aim of this study was to determine the impact of these variables on outcomes and to establish whether other variables as confounders enhanced or limited these effects.

## Methods

A retrospective analysis of NHSBT (National Health Service Blood and Transplant service) whole liver transplantation data was performed using R studio version 4.1.1. Donor and recipient demographics were scrutinised. Recipients <18 years old and living donors were actively removed from the dataset. Univariable analysis with logistic regression for graft and recipient survival outcomes and Kaplan Meier survival curves for time to event analysis was used to identify variables of interest to pass to multivariable analysis. Consideration was then given to variables that should be included or excluded on the basis of literature and clinical grounds. Missing data analysis was performed, and data filtered to include transplantation between 2000-2015. Multivariable analysis was performed using a Cox proportional hazards model. Primary explanatory variables of interest were donor age and DCD transplantation

and other variables resulting in significant difference to graft and recipient survival were noted. Variables with significance but not widely reported in the literature were excluded and those with low or no significance were still included if they were felt of importance in the literature.

## Results

Both increasing donor age >60 years old (HR 1.29, CI 1.09-1.53,  $p=0.004$ ) and DCD liver transplantation (when compared to donation after brainstem death transplantation, HR 1.69, CI 1.40-2.04,  $p<0.001$ ) negatively impacted graft survival at both univariable and multivariate analysis. Other variables after adjusting for confounders to negatively impact on graft survival include Hepatitis C positive recipient status (HR 1.47, CI 1.27-1.71,  $p<0.001$ ), recipient inpatient status pre-transplant (HR 1.17, CI 1.01-1.36,  $p=0.032$ ), "suboptimal" donor organ appearance (HR 1.32, CI 1.16-1.51,  $p<0.001$ ) and increasing CIT >8 hours (HR 1.23, CI 1.05-1.45,  $p=0.009$ ). For recipient survival increasing donor age caused poorer recipient survival on both univariable (HR 1.23, CI 1.08-1.40,  $p=0.002$ ) and multivariate analysis (HR 1.25, CI 1.06-1.46,  $p=0.007$ ). For DCD transplantations there was no statistically significant difference in recipient survival on univariable or multivariable analysis (HR 1.09, CI 0.89-1.34,  $p=0.400$ ). Other variables correlating with poorer recipient survival after adjustment for confounding factors in the cox proportional hazards model include HCV positive recipients (HR 1.37, CI 1.20-1.57,  $p<0.001$ ) and recipient inpatient status pre-op (HR 1.32, CI 1.14-1.52,  $p<0.001$ ).

## Discussions

Donor livers utilised from >60 year olds were more likely to be transplanted to a recipient in better clinical condition when considering variables such as ventilation status, renal support, blood group compatibility and lifestyle scores to indicate fitness. This correlates with many studies which suggest careful recipient characteristic selection to avoid further host stress to the graft. This was also evident in DCD liver transplantations. Older donor livers were also more likely to be CMV positive, to have died from intracranial haemorrhage (rather than trauma causes in younger donors) and were more likely DCD grafts all compounding the risks of

poorer outcomes. The arbitrary cut-off chosen for the older group of donors was >60 years and this corresponded with the median in the literature and as a result this study demonstrated similar outcomes. It is possible that choosing an older cohort or cut-off would have resulted in a more significant negative impact on survival.

In DCD liver transplantation it was evident that these grafts less likely to be transplanted to Hepatitis C virus positive recipients or to recipients with poorer clinical state pre-transplantation as with older donors, again all in an effort it seems to reduce increased host stress on a graft already exposed to some ischaemic reperfusion injury. Care was taken when designing statistical analysis to choose variables which were either significant on univariable analysis or important in the literature to allow a condensed model to be chosen and to optimise the fit and predictive power for survival outcomes. It was worth noting the relationships that naturally occurred between variables, such as CMV status as this was more likely positive in older donors. This means these were difficult to separate in cause and effect analysis.

Future work to enhance this study could include development of a more complete or robust dataset and data recording strategies to eliminate the large volume of missing data. A warm ischaemic time variable would be an essential addition to fully explore the effects of DCD transplantation, but as there are now machine and normothermic regional perfusion techniques that are well established and have developed a good evidence base this has become less relevant.

## Conclusions

In this study, increasing donor age was found to adversely affect both graft and recipient survival outcomes. DCD transplantation resulted in poorer outcomes for graft survival but had no significant impact on recipient survival. This correlated with much of the wider literature in this field, although the range of analytic methods and strategies across multiple studies makes it difficult to standardise a universal consensus on how to limit these negative outcomes. These extended donor characteristics are the focus of many donor-recipient matching protocols to limit these effects on survival. Machine perfusion and normothermic perfusion procedures help to limit the impact of these donors and are now the focus of the next stage of

development of techniques to bridge the waiting list gaps for liver transplantation in the United Kingdom.

# Lay Abstract

## Introduction

There are many people around the world on waiting lists to have a liver transplant but there are not enough organ donors (patients who give up their organs after death) to allow everyone to have their liver replaced when needed. In the past, organ donors would often be younger and would be patients who had an accident or injury leaving them with brain death in intensive care. The organs that would be donated would have a good blood supply and of better condition as the donors were healthy before these events causing brain death. In more recent years, these accidents particularly on the roads are much less common, there are less of these types of donors available and so waiting list for transplantation are longer. To prevent death whilst waiting with liver failure, it is now more common for donors to be older, or to die with a condition that their heart stops beating before organ donation (DCD or donation after cardiac death donors) and to have other features which mean the liver graft may not be as good quality. This study aims to review these features of donors who may not provide such good quality grafts to determine how this changes outcomes for the recipients of a liver transplantation.

## Methods

An organisation called the National Health Service Blood and Transfusion service (NHSBT) keep a record of all organ transplantations that occur in the United Kingdom and were able to provide a large database containing anonymous details of liver transplantations from the groups that we were of interest in this study. A computer software that allows analysis of the statistics called R was used to study the large group of patients . The aim was to determine which characteristics, in particular the age of the liver donor and the donors who had their heart stop beating prior to giving their liver for donation, would either improve or inhibit the survival of the liver transplant of the patient receiving this. Research papers describing many studies internationally were reviewed to gather background information about the characteristics of interest, donor age and DCD liver transplantation, and to determine which other characteristics were important. In this large database there were many

pieces of information missing and this was reviewed and the transplantations between 2000-2015 were chosen to analyse to prevent results being affected by this. Statistical tests were used to look at these characteristics individually in the database and compare these to the survival of the liver transplant or the recipient. Further tests were then performed to determine whether these characteristics affected each other and which were the most important to predict the outcomes.

## Results

Donor age above 60 years old was related to a lower rate of the transplanted liver surviving, and also a lower rate of the recipient surviving. The statistical tests used determined that this result was reliable and this also matched the majority of research studies reviewed before looking at our data. Donation after cardiac death liver transplantations also resulted in poorer survival of the liver graft, but the survival of the recipient overall was no different to transplantations where the donor had brain death (Donation after brainstem death or DBD) prior to transplantation. Other characteristics that caused poorer liver graft survival included recipients who had viral infections with Hepatitis C, who were already staying in hospital before their transplantation due to ill health, and in those where the liver had been labelled as of poorer quality by the surgeon performing the transplant. The time taken between the liver organ being put on ice until it was transplanted into the patient is called the cold ischaemic time, and this also caused poorer liver graft outcomes when this time was increased. For recipient survival outcomes the additional characteristics which caused poorer results were viral infections with Hepatitis C and a recipient in hospital before transplantation.

## Discussions

When looking at the older donor livers >60 years it was interesting that these were used in recipients who were more healthy and not as unwell whilst awaiting their liver transplantation. Characteristics such as whether the patient was on any extra life support or machines supporting their kidneys, fitness of the patient before transplantation and whether the blood group of the donor and patient matched well

all seemed to be more favourable in these patients who were given an older donor liver. There are theories that this means the older donor liver that may not work as well in a more unwell recipient. A younger and healthier donor liver will not be put under so much pressure when transplanted if the recipient is healthier beforehand. Donor age >60 was chosen for this study because in the published research this was the most common cut-off age, and although a higher cut off would have made results more striking, it was felt appropriate to stick with the majority of studies approaches from experts in many other departments around the world. Similarly, the other characteristics chosen to study in the statistical tests were all noted to be of most importance when looking at a large number of relevant studies. Some of the characteristics would naturally change together, such as older donors being more likely to have a viral infection called CMV (cytomegalovirus) due to having a longer life to risk being infected with this. As a result some of these factors may well go hand-in hand and are hard to separate as individual causes of poorer outcomes. It is important to consider improvements that can be made and future work in this study could include finding more of the missing values from the dataset and adding some other characteristics results of interest which we did not have access to in this database. Since this study was designed and performed there have been many advanced in the way organs can be falsely given a circulation or blood supply whilst waiting to be transplanted into the recipient and so much of the work going forward will focus on this.

## Conclusions

In this study, older donor livers were linked to poorer survival results for the liver transplanted and the recipient of the transplant surviving. DCD transplantations had poorer survival of the liver graft but did not affect the survival of the recipient. These results widely matched the opinions in many studies around the world looking at results of transplantations in their transplantation hospitals. It is important that studies continue to look at the characteristics that affect outcomes regularly to note patterns and improvements that can be made to ensure the best outcomes for patients. Current advanced in this area are already well established including

techniques to give a circulation to the organs whilst passing between a donor and the recipient to keep the organ healthy and prevent damage.

## Contents

1.0 Introduction .....	11
Aims: .....	12
1.1 Extended Criteria Donors .....	13
1.2.0 Donor age .....	15
1.2.1 Liver Physiology .....	16
1.2.2 Donor age has negative survival impact .....	18
1.2.3 Donor age has no survival impact .....	22
1.2.4 Extremes of Donor Age .....	23
1.3.0 Donation after Cardiac Death (DCD) .....	25
1.3.1 Classification of DCD Type .....	26
1.3.2 Warm Ischaemic time .....	27
1.3.4 Cold ischaemic time .....	29
1.3.5 Matching DCD Graft to Recipient .....	30
1.3.6 DCD LT does not affect graft or recipient survival .....	31
1.3.7 DCD causes poorer graft and recipient survival .....	33
2.0 Methods .....	37
2.1 Data collection .....	37
2.2 Data Analysis .....	38
2.3 Missing Data .....	39
2.4 Donor Age Variable Analysis .....	40
2.5 DCD Variable Analysis .....	42
2.6 Multivariable Analysis .....	43
3.0 Results 1 – Associations between donor Age and Graft and Recipient survival .	44
3.1 Donor demographics: .....	46
3.2 Recipient demographics: .....	49
3.3 Univariate analysis – Graft Survival .....	56
3.4 Univariate analysis – Recipient Survival .....	60
3.5 Graft survival per Donor Age .....	65
3.6 Recipient Survival per Donor Age .....	66
4.0 Data 2 – Donation After Cardiac Death (DCD) .....	68
4.1 Donor demographics per Donor Type .....	68
4.1 Recipient demographics per Donor Type .....	70
4.2 Graft survival DCD vs DBD .....	75
4.3 Recipient Survival DCD vs DBD .....	76
5.0 Data 3 – Multivariable Analysis .....	77

5.1 Multivariable Analysis – Graft Survival .....	77
5.2 Multivariable analysis – Recipient Survival.....	80
6.0 Discussions.....	84
6.1 Donor age – significant demographics .....	84
6.2 Donor age – effect on graft and recipient survival .....	85
6.3 DCD – Significant demographics .....	87
6.4 DCD – effect on graft and recipient survival .....	89
6.5 Univariable analysis showing factors significant in graft and recipient survival	90
6.6 Multivariable analysis .....	92
6.7 Limitations of dataset .....	96
6.8 Missing data.....	97
6.9 Suggestions for Further Work .....	99
7.0 Conclusions .....	101
8.0 References .....	102

## 1.0 Introduction

In the United Kingdom and worldwide there is an ever-increasing number of patients being managed with liver transplantation and as a result there is a continually increasing demand for suitable liver donors. However, this demand is becoming more difficult to meet for a number of reasons including improvements in road safety and advancements in medical care including neurosurgical management of brain injury(1, 2). This results in lower numbers of typical donors classified as brainstem dead to provide organs for donation after brainstem death (DBD) transplantation. Until the 1990s the typical donor was young, male, with a head injury and resultant brainstem death(3).

In recent years various strategies to increase the liver donor pool are essential to meet demand. This includes use of organs from donation after cardiac death (DCD) donors, split liver, domino or living donor grafts, and use of organs from other marginal donors(4). An extended criteria donor (EDC) is an organ donor that may not meet the usual "ideal" donor organ standard with criteria outwith the normally acceptable or traditional reference range. EDC donors can include those of advanced age, with hypernatraemia, use of vasopressor agents, deranged liver enzymes, intensive care unit (ICU) stay, steatotic livers, and uncontrolled non-heart beating donors or cardiac arrest donors(5-7). These factors can all affect the short-term success of liver transplantation and recipient survival(8). Donors with malignancy and hepatitis C are also considered in this marginal category but have implications for recipient morbidity as a long term-risk factor.

The use of extended criteria donor livers for transplantation has been increasing partly due to the need and increased demand but also due to many studies, showing that outcomes can be favourable and are improving(8, 9).

This study was conceived prior to the introduction and mainstream utilisation of machine perfusion and normothermic regional perfusion techniques that now

improve assessment of organs for transplantation and limit the effects of the extended donor criteria.

Aims:

1. To observe donor and recipient characteristics in liver transplantation where donors are >60 years of age and report significant findings
2. To observe donor and recipient characteristics associated with DCD liver transplantation and report significant findings
3. To determine the impact of donor age on graft and recipient survival in the UK
4. To determine the impact of DCD liver transplantation on graft and recipient survival in the UK
5. To determine any other significant variables impacting graft or recipient survival in the UK

## 1.1 Extended Criteria Donors

British Transplant Society (BTS) guidelines define an EDC (Extended Donor Criteria) donor having age >50yrs, overweight Body Mass Index (BMI) or bodyweight >100kg, elevated cold and warm ischaemic times (>8hrs and >20mins respectively), graft steatosis more than 15% and an extended ICU stay greater than 5 days(10). These organs may not be the best option in terms of function and have increased rates of initial poor function or primary non-function, but can delay inevitable mortality of the recipient whilst on the liver transplantation waiting list(6).

Attia and Feng when discussing EDC donors describe broadly 2 categories; those with risk of technical difficulties and graft failure such as DCD transplantation, grafts with poorer condition such as steatosis, older donors and longer warm and cold ischaemic times; and those with risk of longer term morbidity with transmission of disease (such as Hepatitis C Virus, HCV) or malignancy(8, 11). Extended criteria donors in other studies also include hypernatremia, split-liver grafts and living donors (12, 13). In addition to these EDC criteria, Pagano determined additional conditions to be met for donors to be considered in this extended category, including bacterial infection risk, ICU (intensive care unit) stay >7days and prolonged hypotension or dopamine or inotrope use all suggestive of haemodynamic instability(14). Rocha suggests that survival rates for EDC donors are comparable to those of “ideal donor” recipients(5). EDC donors in this study were considered to have serum bilirubin greater than 2mg/dL(34.2umol/L), age over 55, aspartate aminotransferase greater than 150U/L, cardiac arrest (DCD donor), use of high doses of dopamine or other vasoactive drug, serum sodium greater than 150mEq/L(mmol/L), ICU stay over 5 days and moderate to severe macrosteatosis(5). The criteria accepted by clinicians is variable per centre and in another single-centre study by Gruttadauria *et al* the characteristics accepted were age greater than 60, ICU stay >7 days and hypernatraemia with a peak sodium greater than 160 mg/L(7) amongst other standard criteria. There are evidently varying criteria between centres to identify extended donor characteristics to impact on decision making and outcomes.

Sarkut *et al* retrospectively examined 47 liver transplantations of which 15 were considered to be marginal donations and 18 had high donor risk index (DRI) scores(15). This scoring system was established by Feng *et al* and used here to calculate DRI scores for cadaveric donors(16). Feng calculated this score based on several characteristics including height, age, weight, cardiac arrest status, orthotopic liver transplantation (OLT) vs split graft and cold ischaemic time. Rates of early graft dysfunction were comparable (although not statistically significant,  $p=0.71$ ). Those with a donor risk index (DRI) or either  $<1.7$  or  $>1.7$  were also compared and they similarly found no difference in early graft dysfunction between these groups(15). This study was small however and failed to meet statistical significance, and their comments on the mortality of patients receiving either marginal or ideal donor liver transplantation were conflicting.

Extended Donor Criteria (EDC) have different associations with graft and patient survival (17) and as such there are many differences in the “cut-off” values for each. As a result, careful donor and recipient selection is recommended to achieve the best outcomes(8, 16, 17). Although studies aim to try to combine risks of note such as donor age with cold ischaemic time (CIT) by arranging factors into small groups they are on more of a continuous spectrum and so not easy to divide and analyse based on arbitrary values(3).

Merion when discussing the definition of expanded criteria donors splits variables into a dominant group, with donor age, CIT and type of graft (partial/split etc) and then other variables of note separately such as gender (and particularly M:F matching/combinations), race, body mass index (BMI), donor cause of death, DCD, steatosis and hypernatraemia(3). Gender mismatching has been shown to have a detrimental effect with female donor to male recipient liver transplantation resulting in an increased risk of graft failure(6).

Predictably all grafts including transplanted livers have some degree of ischaemic reperfusion injury and some marginal grafts have more sensitivity to this injury and more resultant damage(8). It is suggested that where a donor liver is deemed

marginal that these organs should not be used in an unwell or high risk patient but instead selected to a recipient who is more stable with lower MELD (Modified End-stage Liver Disease) scores, for example(8). Liver transplantation and the subsequent outcome is reliant on a complex interaction between the donor and the recipients' biological systems(18).

In a study by Dutkowski (which excluded DCD) they identified their strongest predictors of graft and recipient survival (including MELD, CIT, recipient and donor age, previous orthotopic liver transplantation and level of life support pre-procurement of donor) to then create the BAR score (Balance of Risks score) to predict outcomes(19). Importantly when considering scoring of extended donors this excluded all DCD transplantations.

### 1.2.0 Donor age

Donor age of more than 60 years old has widely been accepted as the cut off for age when categorising a marginal or expanded criteria donor liver(10, 20). These organs are more widely used as waiting lists increase and supply of healthy or better-quality organs reduces. Liver transplantation is increasingly successful and so more potential recipients are placed on these waiting lists(13). Despite increasing demand for transplantation the donor pool is not expanding and waiting list mortality is increasing. Between 2006 and 2013 in the UK around 20% of patients waiting for a liver transplantation died waiting for a suitable graft(21). It is also highlighted that donor quality has reduced for instance with the dramatic reduction in road traffic accidents in recent years therefore resulting in increased use of marginal donors(13). As donor age increases, for example, the cause of death shifts with less trauma and more cerebrovascular events(3).

Donors aged >50 years were rarely used until 1980s when several studies published on successful use and the upper age limit has steadily increased as a result in subsequent years(22). This upper age limit is variable between studies with a generally defined 50-60 years old seen as an extended criteria donor and donor age

greater than 70 years in some centres will still see the liver rejected(21). In addition to concerns about early poor graft function and failure due to a perceived increase in susceptibility to ischaemic damage, there is also a concern generally about the risk of occult malignancy in the donor liver with increasing age(1, 21). Although donor age is increasing over time, other characteristics in liver transplantation are changing, such as a favourable reduction in HCV positive recipients over time(23).

### 1.2.1 Liver Physiology

The aging liver, in comparison to other organs, has a remarkable capacity to maintain biological and physiological processes. The liver is therefore much more robust in comparison to the kidneys or lungs, for example(24). There is a more limited decline in function across all processes as the host ages and as a result the impact of donor age on a liver transplantation is not necessarily as stark as would be imagined - atrophy of cells and general reduction in the liver volume over time does not see a correlation in the rate of functional decline that would be expected(24). There are several complex processes to allow for this regeneration and maintenance of function in the liver. In cholangiocytes and hepatocytes telomere length remains constant with age and enzyme function does not deteriorate(24).

Although function can be largely maintained there are, however, limitations which increase with regards the liver's ability to heal and repair after damage from external factors(25). The liver parenchyma is more aged and more susceptible to ischaemic reperfusion injury due to fewer hepatocytes overall and a reduced ability to regenerate when damage occurs(11). These include a reduction in volume and blood flow (from around 30 years of age) and bile salt secretion, some limitation of the cytochrome p450 system and more pro-inflammatory cytokines are produced(1, 8, 25). The liver in a young adult constitutes around 2.6% of total body weight but only 1.6% in a nonagenarian(26). Graft steatosis is more likely in an older donor liver due to the increase in fat deposited within the liver and older livers are less able to perform gluconeogenesis(25). Also, older donors have potentially higher incidence of co-morbidities such as obesity, diabetes mellitus and hypertension, all contributing to

steatosis and atherosclerosis with further susceptibility to injury(11). In a study by Rodríguez González et al looking at donors over 60 years old there was significantly higher incidence of moderate to severe microvesicular steatosis, 38% vs 20% in the <60 years old control group ( $p<0.001$ )(27).

Other factors thought to increase the likelihood of liver damage or ischaemic reperfusion injury at the time of transplantation are lower stores ATP and glycogen, telomere shortening in sinusoidal and stellate cells, or decrease cytochrome p450, plus overall reduction of hepatic blood flow by 30-50% in the older donor liver(24). All of these changes occur with time as the body's immune system alters and the liver itself has less regenerative capacity and less ability to maintain homeostasis under stress(1).

Although hepatic function in an older liver is maintained in a healthy subject, the more limited response to a stressed environment such as in ischaemic reperfusion injury (IRI) during transplantation is what contributes in theory to poorer outcomes(1). Older donor liver cells are in a "hyperfunctioning" state perhaps to compensate for a reduction in number(26).

An increased susceptibility to IRI following liver procurement and transplantation is noted in DCD donors which is thought to indicate the involvement of other cell types for example causing ischaemic cholangiopathy(24). Feng *et al* noted higher rates biliary complications and cholestasis in donor age over 60yrs(11).

There are multiple receptors and genetic considerations here which have not been investigated in the scope of this thesis that contribute to changes in liver physiology and function as the host ages.

It is also considered that an older donor liver by nature will have poorer vasculature due to atherosclerosis and might mean a more technically challenging operation and increased incidence of complications such as hepatic artery thrombosis (HAT)(1, 11).

### 1.2.2 Donor age has negative survival impact

There have been studies to evaluate the effect of increasing donor age on the survival of patients and liver grafts with varying results(28). Given that there are many studies that indicate graft survival is impacted by increasing donor age this is a variable taken into account in scoring systems such as the Donor Risk Index (DRI), D-MELD (Donor Age and MELD), the BAR (Balance of Risks) Score and SOFT (Survival Outcome Following liver Transplantation)(19, 28). There are also studies that aim to determine how donor and/or recipient age can be used as an adjunct to recipient scoring systems such as UKELD (the UK validated version of MELD) and MELD scores to improve predictability of graft and patient survival(29). MELD was introduced as a score to stratify where recipients placed on the waiting list as it was found to be an accurate predictor of waiting list mortality(19). Other studies show poor outcomes using this measure and Dutkowski aimed to allow balance of other high-risk characteristics i.e. increased donor age with the high MELD recipient, for example(19).

Several studies show that in specific circumstances donor age outcomes are more significant where other criteria are considered. A study by Grat *et al* which assessed prolonged CIT in association with low, medium or high MELD scores and determined poorer survival outcomes where MELD was at least moderate and CIT >9 hours with donor age >46(30), although methods here looked to have been very selective in the cut off values in order to gain significant results. High MELD scores (25) and increased CIT, hepatitis C positive recipients or highly-urgent transplantations (31) have all been noted in combination with increased donor age to negatively affect survival outcomes. MELD scores were introduced in Poland in 2005 and on review Dudek *et al* concluded that older donor livers could be utilised more successfully where MELD score was lower(32). To fully isolate extended criteria donors to review outcomes, Pagano *et al* focussed on low risk recipients (MELD ≤20, BAR ≤9) and the EDC group had higher risk of graft loss (18% vs 8%, p=0.038) and 1 year mortality (14% vs 4%, p=0.009)(14).

A study in Birmingham in 2003 aimed to develop a scoring system based on CIT to allow prediction of survival outcomes and determined that donor age in combination with graft steatosis allowed classification of whether a donor liver was marginal or not(9). They concluded that CIT was not independently a risk factor in non-marginal donors but was associated with poorer outcomes where a donor was marginal as per this scoring system, including older donors.

Lozanovski *et al* aimed to identify within the EDC which of these were major contributors to poor graft or patient survival and did identify increased donor age (>65 years) as a significant determining factor(17).

A large study in the United States looking at all liver transplantation 1999-2008 found reduced graft survival with increased donor age(33). This effect increased over time from transplant with the worst outcomes for patients aged <1 or ≥65 years old. Donor age was found to be a particularly important risk factor for survival in Hepatitis C virus (HCV) positive patients (risk of death 84% higher in >64 P>0.006 and at 5 years 114%)(28, 33), as it has been shown that fibrosis develops more rapidly in an older donor liver of a HCV positive recipient(28). There has also been demonstration of a strong correlation with HCV and increasing donor age around 40 years and above(11). This combination is thought to result in higher rates of fibrosing cholestatic hepatitis, more rapid fibrosis, and resultant infections and graft failure subsequently increasing mortality(11).

Another large study instead reviewing the Eurotransplant database for liver transplantations between 2000 – 2014 also assessed risk of graft failure according to donor age(31). It was evident that the number of donors >80 year of age increased over time. Kaplan Meier (KM) survival curves and cox-regression analysis showed reduced survival and a higher risk of graft failure with increasing donor age(31) and it was noted that the linearity of the association meant there was no particular “cut-off” age at which survival deteriorated. EDC was considered >65 years of age by Eurotransplant but no study is agreed to determine actual best cut off age. This is

evident in that cut off values when analysing donor age are very variable across papers. Hoofnagle performed a large 3 centre cohort study in the United States and their cut off to determine older donor liver was 50 years of age(22). Older donor livers with associated poorer graft survival persisted after adjusting for many variables using bivariate and multivariate analysis (although it is worth noting the relatively short period of study here looking at just transplantations between 1990-1994). The main factor was quality noted by the harvesting surgeon as good had good outcomes and fair or poor has poor outcomes(22).

In a study by Marino it was shown that donor age above 45 started to show some negative effect on graft failure (34). A further study looking at specifically HCV positive recipients investigated a donor age cut-off even lower at 35 years(35). Although a single centre study in Madrid showed poor mean survival rates when “older” donors were used, they concluded that the threshold predicting poorer recipient survival was a donor age of 30 years and graft survival 25 years(36). With low levels of significance and these very young ages in comparison to literature cannot be deemed “extended criteria” or “old” donors(36).

Pagano *et al* used the cut-off 60yrs(37) although the focus of this study looked more at donor-recipient age mismatch rather than donor age independently and concluded that when adjusted for covariates in MV analysis age-mismatch was independently a risk factor predicting recipient death (HR 2.13, 95% CI 1.1-4.17; p = 0.027) and graft loss (HR 3.86, 95% CI 1.02-15.47; p = 0.046)(37).

Marino in 1995 published results showing comparison between <60yrs and >60yrs donor age groups and the 60-79 year old donor group had significantly lower 2 year graft survival (43% vs 71%, p0.0001) and recipient survival (62% vs 78% p0.037)(38). There were no differences in the quality of donor livers between groups when considering proportions on pressors, CPR (cardio-pulmonary resuscitation) pre-procurement, ICU (Intensive Care Unit) stay length, transaminase levels, cold ischaemic time (CIT), and recipient age or UNOS (United Network for Organ

Sharing) score(38) and so donor age >60 was felt to independently correlate to poor graft and recipient survival.

A review of retrospective data from the Scientific Registry of Transplant Recipients (US) and University HealthSystem Consortium databases looked at <60 and >70 years donor age groups and cut out the 60-70yr donor age group on purpose as <60 years old was deemed “standard” and used as a control group(39). Elderly grafts were less likely to be used in recipients with a MELD score >27 (13.2% vs 23.0%,  $P < 0.001$ )(39), and were more likely to originate from a female donor. Donor age 70 years or older after multivariable analysis for cofounders was associated with small increased in risk of graft failure (hazard ratio(HR) 1.3; 95% confidence interval(CI), 1.08–1.56;  $P = 0.005$ )(39).

The Collaborative Transplant Study rather than specifying a “cut-off” donor age found that donor age had an almost linear negative influence on graft survival, with an increase in graft loss of 0.9% for every year increase in donor age (HR 1.009;  $p < 0.001$ )(23). They also noted strong correlations between HCV positive and alcoholic cirrhosis in the recipient with graft loss. When comparing 80 year old donors at Cox multivariable regression to 20 year old donors there was a 73% risk of graft loss and subsequent years after transplantation an increased risk around 0.92% per year in 80 vs 20 year old groups(23). A review of the UNOS database by Rustgi also showed on multivariable analysis a 1.3% increase in risk of graft loss for each year of additional donor age ( $p < 0.0001$ )(40). The relative risk for graft failure for each decade beyond donor age 50 years was 47.9%, 75.2% and 90.3% increase in likelihood when compared to the <50year old donor age group ( $p < 0.0001$ )(40).

Another large study by Monteno reviewing a retrospective UNOS database (excluding HCV positive recipients) showed graft and recipient survival similar across donor groups on univariable analysis but poorer outcomes in all donor age groups >60 years (60-69, 70-79 and 80+) on multivariable regression analysis(41).

In previous studies reporting either no difference or reduced patient or graft survival with increasing donor age, almost all papers recommended the continued use of livers from older donors with careful selection depending on other donor or recipient factors(12, 25, 31).

### 1.2.3 Donor age has no survival impact

There are many studies to indicate that despite an increasing age in the donor liver pool the overall survival outcomes continue to improve over time(42). Many studies showing no effect of donor age seem to select the recipients very carefully i.e. low MELD scores and Hepatitis C negative recipients(24).

A study by Chapman *et al* looked at a single centre experience of 847 whole orthotopic liver transplantations in adults. This found no difference in patient survival or graft survival when using older donor livers(20). A number of other studies similarly indicated no survival difference when older donor livers were used in transplantation. A Spanish centre analysed 212 recipients who had no significant difference in demographics or operative type and were shown to have similar survival across donor age groups at 3 years (slightly poorer outcomes for 60-69 and >80 groups but similar in <60 and 70-79 groups and p value showed results were not significant) (43). Chedid *et al* analysed a group of 109 donors aged 70-80 years within a group of 780 transplant recipients over 12 years and found no statistically significant differences in long term patient survival ( $p=0.67$ ) or graft ( $p=0.42$ ). However, 7 yrs survival of HCV positive recipients of an older donor liver was half that of recipients receiving a younger donor liver(44). In their matching strategy for donors and recipients they noted that they aimed to pair an older liver with a recipient who was more unwell or more urgently requiring a transplant and also avoided recipients who had risk factors for a longer more difficult surgery and therefore long CIT(44). Hoofnagle *et al* described a cohort study analysing 772 patients from 3 centres between 1990-1994 with older donors defined as >50 years old. The older donors were more commonly women and the organs were more often described as poor or fair rather than good (17% vs 4%  $p<.001$ )(22). Graft survival

less at 3 months(81% vs 91%  $p < .0001$ ), 1year (76% vs 85%  $p = .007$ ), 2 years (71% vs 80%  $p = .005$ ) and patient survival were all similar(22). Faber *et al* performed a retrospective review of 272 OLTs with a 12months follow-up period and Hep C positive recipients were excluded. They noted no increase in primary non-function (PNF) or any difference in surgical complications or LFT (Liver Function Tests) and no significant difference in recipient survival or graft rejection rates(acute rejection did not correlate with donor age)(45).

In Canada survival rates have been maintained over time despite use of marginal donors including increased donor age and DCD use(46). Sela found that these outcomes were maintained due to simultaneous improvement in logistics(46). This is particularly notable in Canada where there is a population spanning an area 768,052 km<sup>2</sup> with only 7 transplant centres, in comparison to the United States, for example, with 127 transplant units covering an area of 192,774 km<sup>2</sup>. In a study looking at DBD liver transplantation only, Dudek studied 505 patients and at 3 year follow-up assessment of survival showed no overall difference in patient or graft survival for older donors(32). A secondary conclusion was that livers from donors aged >60 years can be used where the recipient has a relatively low MELD score(32). In the University Hospital Birmingham in 2005-2015, Schlegel *et al* looked at donor age >60 in DCD liver transplantations and established that other factors similar for donor age groups above and below 60 were CIT, BMI, recipient age, and recipient MELD and BAR scores. Multivariable analysis to determine which factors impacted survival concluded that increasing donor BMI impacted graft loss rates negatively(10) but that donor age had no significant impact.

#### 1.2.4 Extremes of Donor Age

There are some studies that focus on extremes of donor age either >80 years or >90 years. Rabelo performed a retrospective single centre cohort analysis of a small number of >80 year old donors (17 of 312 recipients total). There was no difference between recipient groups demographics, complications (biliary or vascular), repeated surgeries or recipient or graft survival at 6 months post-transplant(47). A very small

Italian case-series of 80-90 year old donor livers utilised (3 in total >90yrs) showed favourable outcomes and all recipients survived to discharge. The same team later reviewed results comparing 1354 liver transplantations between 2001-2014 for 18-69 and >70 year old donor groups and in the older group donor age was reported to be an independent risk factor for graft loss on multivariable analysis (HR 1.0; 95% CI 1.0-1.0;  $p < 0.001$ ), however note although the p value is significant the hazard ratio and confidence interval actually show no difference. Another review of 90 year old donors by Jimenez-Romero with 4 nonagenarian donors celebrated the ongoing successful function of grafts which had reached their 100<sup>th</sup> year of function and in 3 recipients with ongoing normal liver function(26). It has been suggested that although outcomes in general can be worse following liver transplantation with an older graft that there is still evidence of septuagenarian and octogenarian donor LTs with good survival outcomes (25). Survival rates can be >70% even at 5 years (25). These donors were matched with recipients with MELD scores <24 and so carefully selected to reduce host stress on the older liver.

Although these studies show no overall graft or recipient survival in different donor age groups the patient numbers are relatively low and most report a single centre experience.

A meta-analysis assessing 8 studies with 4376 recipients of liver transplantation showed no survival difference in graft or recipient at 1 year but did show improved graft and recipient survival in the older >70 year age group(21). It was also noted that other complications such as biliary, vascular or graft function issues showed no statistical difference between donor age groups(21).

Similarly, Jimenez-Romero looked at >70 vs younger donor age groups and no significantly different trends in graft or patient survival were found at 1, 3 and 5 years, even when considering HCV positive recipient status(48). Multivariable analysis did show increased donor BMI to be of significance in poorer survival and it was noted that this tends to cause increased rates or severity of graft steatosis which has been shown in other studies to have poorer outcomes(48). The same team later

reviewed donors in the octogenarian group vs <65 year old controls. They were very strict about selection criteria with the need for good LFTs, low CIT, no or low vasopressor use, short ICU stay, normal histology on biopsy and good organ appearance with no atherosclerosis. They showed no difference at 1,3 and 5 year survival for graft or recipient(49) but essentially although donors were >80 they had checked every facet and condition and likely had better graft quality than other younger or marginal donors.

Several papers suggest donor age from as young as 40 years old can affect recipient outcome and the widely utilised Donor Risk Index (DRI) gives heavy weighting to donor age(25).

### 1.3.0 Donation after Cardiac Death (DCD)

There is a general reluctance to use DCD liver transplantation to plug the waiting list gaps and subsequently reduce waiting list mortality. This is due to local and national studies suggesting poorer graft and recipient survival in comparison to DBD liver transplantations(50). Despite this DCD still accounts for around 20% of liver transplantation in Europe and 15% worldwide (2015 figures)(51).

Interestingly in the UK, although DCD constitutes and overall larger proportion of liver transplantations in recent years, Perera noted in 2011 that this appeared to be due to replacement of what would otherwise have been a DBD case(52). Review of UNOS showed that an increase in utilisation of DCD livers was matched by a concurrent increase in DBD liver transplantation(52). This discrepancy in the UK was speculated to perhaps represent referral of ICU patients to consider DCD prematurely to any brainstem death that had yet to occur(52). This means that instead of filling waiting list shortages the UK was perhaps replacing one type of liver transplantation with another without shortening the list.

Donation after cardiac death (DCD) can be described as an organ procured for transplantation from a donor who has died following cardiac arrest. In donation after

brainstem death donation the organs procured are retrieved whilst the donor is still ventilated and perfusing those organs. A DCD donor has ceased all cardiac activity and so this adds a variable length of time where the patient is either having reduced cardiac output or no cardiac output prior to retrieval. This results in what is known as a warm ischaemic time while the retrieval occurs until the organ is perfused with cold solution via cannula (aortic/ femoral etc), and then starts the cold ischaemic time. This warm ischaemic time is unique to DCD donor organs and does not occur in DBD. The DCD donors can then be described in varying categories depending on the individual clinical circumstances leading to cardiac arrest.

### 1.3.1 Classification of DCD Type

Maastricht Criteria are used to explain the type of death experienced by a donor after cardiac death to categorise the variations in either controlled or uncontrolled circumstances to give a more accurate indication of risks posed to the organ. The classification was initially described and utilised in 1995 and a revised version was released in 2013(53). These criteria can be summarised as follows:

Maastricht Category	Description	Type of DCD
I	Dead on arrival to hospital after OOH cardiac arrest	Uncontrolled
II	Unsuccessful emergency resuscitation attempt after OOH cardiac arrest	Uncontrolled
III	Brain-dead ICU donor, awaiting cardiac death (after withdrawal)	Controlled
IV	Cardiac arrest in brain-dead ICU donor	Controlled
V (in modified criteria)	Unexpected cardiac arrest in ICU/ in hospital	Uncontrolled

The Maastricht criteria have implications for which donors are eligible for retrieval dependent on legislation in each Country. For example, in Korea until 2018 only Maastricht IV was possible until legislation was passed allowing withdrawal of life-support treatment (WLST) therefore able to utilise controlled/planned DCD livers(53). In Spain prior to 2012 only uncontrolled DCD was used whereas in the same time

period Belgium, the Netherlands and the UK were all using controlled Maastricht III and IV livers in addition to uncontrolled DCD(51). Spain introduced uncontrolled DCD in 2012(54). In France, Savier *et al* noted in 2015 that Maastricht type III was still not utilised(55). Maastricht type I LT was also not used due to the unknown duration of WIT which means the degree of ischaemic damage is not quantifiable(55).

Original reports of DCD outcomes in liver transplantation suggested PNF rates up to 50% and only 16% graft survival and 67% patient survival for uncontrolled (Maastricht I-II) DCD donors(4) and 50% each for controlled DCD donors (Maastricht II-IV)(4).

### 1.3.2 Warm Ischaemic time

When treatment in ICU is withdrawn this includes cessation of drugs and ventilation, except for analgesia and possibly Heparin depending on unit policy(4). The Warm Ischaemic Time (WIT) is usually deemed to begin when the donor BP (blood pressure) falls below 50mmHg systolic pressure or the oxygen saturations are less than 70% and ends when cold perfusate is infiltrated to the aorta(4). There is some variability in other units. Detry *et al* defined donor WIT as the time between extubation/ stopping ventilation and the start of cold perfusion(56). They described 2 phases: the “withdrawal phase” (extubation until cardiac arrest) and the “acirculatory phase” (from cardiac arrest to cold perfusion)(56). Death is certified when there is asystole and there is no respiratory effort and oxygen saturations of 0% and the retrieval team then must wait for a further 5 minutes before beginning retrieval of organs(4). Initially a 10 minutes stand-off time was determined by the original Maastricht consensus meeting in 1995 but later shortened after agreement by the Institute of Medicine(51). Of note when considering different analyses of WIT between units the actual time of death in some US states, for example, can be determined at recognition of ventricular fibrillation or pulseless electrical activity on ECG and so stand-off time starts sooner(57). This means that total WIT can be significantly shorter than in units who observe asystole as the start of the 5 minute

stand-off period(57). Controlled DCD donors are exposed to lower WIT and uncontrolled DCD donors to higher WIT(51).

WIT causes an increased ischaemic injury to the liver and is subsequently associated with poorer outcomes(11). Cellular metabolism becomes anaerobic, creating lactic acidosis which interrupts cell ion pumps. Cell energy is depleted and oedema and then cell death occurs in hepatocytes usually at a WIT of around 30 minutes(52). This causes higher rates of PNF, up to 15% after DCD compared to a quarter of this in DBD(52). Methods have been developed or trialled to attempt to mitigate effects of WIT. These include “rapid procurement” strategies limiting operative time during retrieval to 20-30 minutes(11). There are also donor recipient matching policies and a variety of centres to match extended WIT with suitable recipients. These include choosing recipients with technically less challenging operations such as no re-transplantations (58) or organ allocation within the local region rather than geographically wider sharing to limit cold ischaemic times (46).

There are variations in the literature as to the WIT cut-off that should be used to reduce risk of graft loss. Abt *et al* summarised these and noted that >15 minutes WIT showed increased risk of graft loss in a study by Lee *et al*, with a further deterioration in graft outcomes >30minutes WIT(59, 60). Mathur *et al* suggested a similar increase in risk but not until >35minutes WIT(59, 61). It is evident that WIT generally correlates with poorer graft survival. It is suggested, however, that WIT alone is so variable in its definition across units that it is not reliable(59, 61). This may suggest the reason for lack of consensus in associated outcomes and cut-off times. In the Abt *et al* study they scrutinised more specific haemodynamic variables in a group of 110 Maastricht III DCD liver transplantations and concluded that WIT had no effect on graft survival(59). More specific timings including the area under the curve of mean systolic BP (AUCSBP), the slope of the systolic BP on a regression line from extubation to cross-clamp time, and the slope of systolic BP 10 minutes port-cross-clamp (SBP10) were also reviewed, and also dichomatised SBP10 which increased the strength of association with graft survival. The steeper than median SBP10 had

5-year graft survival of 76% whilst those below the median had graft survival of only 45% ( $p < 0.007$ )(59).

#### 1.3.4 Cold ischaemic time

The cold perfusate strategy used for DCD donors varies depending on country or unit policy adopted and variations can be found in how the recipient is cannulated and the timing of this. For example, in Wisconsin the rules allow insertion of a femoral cannula before cardiac standstill allowing flush of UW fluid immediately, while in other centres the cannulation and flush with preservation fluid of choice happens at a slight delay(51). In DBD donors the cold perfusate is commenced almost simultaneously as the aorta is clamped it is thought that this rapid cooling is one of the most important steps to preserve function as organs instantly convert to a cold inactive state(51). The metabolic rate reduces by around 50% for every 10°C reduction in graft temperature(51). DCD grafts do not have the benefit of this almost instant disabling of metabolism and so other strategies have been used to attempt to reduce ischaemic damage until the state can be reached(51). These include attempts to reduce WIT, use of heparin to prevent thrombosis during WIT which could otherwise further reduce blood flow, attempts to reduce CIT and in more recent years the introduction of normothermic liver perfusion and ECMO(extra-corporeal membrane oxygenation)(51). Of note the use of heparin or other thrombolytic drugs prior to withdrawal is not always allowed ethically as there is no benefit to the donor. In the UK this is the case and no heparin is administered prior to withdrawal or donor death(57). Another strategy described includes the “super-rapid technique” includes a speedy laparotomy then aortic cannulation as soon as time of death is certified and is used by the majority of centres now performing DCD procurement(51).

Warm ischaemia followed by cold ischaemia provides the double hit that contributes to an ischaemic reperfusion injury (IRI) causing increased rates of biliary complications such as ischaemic cholangiopathy and therefore increased risk of graft failure (and subsequently higher incidence of re-transplantation)(62).

### 1.3.5 Matching DCD Graft to Recipient

More stringent analysis of graft quality appears to take place intra-operatively with the suggestion that up to 45% of DCD livers are rejected in situ prior to retrieval(51). Anecdotal reports by the Barcelona Group suggest only around 18% of potential DCD grafts actually made it to transplantation in the recipient(51).

Many early studies of DCD liver transplantations in comparison to DBD suggested higher rates of complications such as PNF, hepatic artery thrombosis, ischaemic cholangiopathy and graft failure and as a result there were higher rates of recipient morbidity and mortality and re-transplantation(2, 51, 59, 63, 64). HAT is thought to be more common in DCD livers due to stasis of blood in the vessels during the WIT phase when cardiac output is in decline(51). DCD livers transplanted have a much higher incidence of ischaemic-type biliary strictures or ischaemic cholangiopathy than DBD (16% vs 3% in a study by Jay *et al*)(51). Theories to explain this include changes to vessel patency and IRI including small vessel thrombosis in situ, CMV (cytomegalovirus) infection, ABO (blood group) incompatibility, changes to bile salt composition and IRI affecting the biliary epithelium(51). In more recent years' studies have started to show outcomes improving in DCD liver transplantations, in particular to the morbidity recipients would otherwise experience whilst awaiting a DBD transplantation(63).

Davila *et al* at King's College London Look at protective factors affecting utilisation of potential DCD donors they found that there were certain factors that could predict cardiac arrest in ICU patients who would become potential DCD donors. These included a donor less than 40 years old, current inotrope infusion and absent gag reflex(4). They also noted that donor age >50 years, elevated BMI (>30), WIT >25 mins, elevated ALT serum level (4x normal or greater) and prolonged ICU stay were all factors that were predictive of a graft that would be unlikely to be approved for use(4). They concluded that these observations could be used to aid in decision making regarding procurement efforts.

Generally, DCD livers are used in patients who have chronic liver disease with or without hepatocellular carcinoma(58). It is unlikely that DCD livers will be allocated to recipients with an acute liver failure, and it is also avoided where there will be operative or technical considerations that will prolong the process and therefore ischaemic times(58). Typically, DCD livers are not used in Hepatitis C positive recipients due to increased risk of rapid recurrence of HCV post-transplantation and exacerbation of already an ischaemia-damaged graft(65). Wells *et al* performed a systematic review of 3 main studies and determined an increased risk of primary non-function in HCV positive recipients who received a DCD graft (RR 5.49; CI 1.53-19.64, p=0.009)(65).

#### 1.3.6 DCD LT does not affect graft or recipient survival

Similar DCD vs DBD outcomes for graft and recipient survival have been reported in a number of studies, including reports from single centres such as King's College London and the Oschner Clinic(57).

A single centre study by Singh *et al* reviewed the experience of liver transplantation between 2012 to 2019 (39 DCDs versus 208 DBDs) and reported similar donor and recipient characteristics and a similar outcome for both graft and recipient survival(63). Although six-month survival was different (recipient 3.8% DCD vs 10.3% DBD, p=0.17; graft 4.8% DCD vs 10.3% DBD, p=0.08) these were not statistically significant(63).

Other single centre studies reported similar results. Scalea *et al* in Birmingham reviewed their outcomes but looked more specifically at lower risk DCD. They showed that in DCD transplantation from younger donors with lower CIT (<6hrs) had similar rates of graft survival to their DBD comparison group(66). The Mayo Clinic in Jacksonville similarly studied single centre outcomes to conclude that DCD and DBD graft survival rates were equivocal at 1 year and 3 years post transplantation(66).

Analysis of large databases have also shown similar outcomes for DCD grafts vs DBD(51). A study of the UNOS database by Mateo *et al* showed similar results comparing graft survival between groups but did specify that this was when pairing low-risk grafts and recipients(51, 67).

A review of the OPTN (Organ Procurement Transplantation Network) database between 1995-2009 analysing survival for both graft and recipients was noted to be significantly better for DBD LTs compared with DCD. Results were reviewed at 1, 3, 5 and 10 years post transplantation and survival rates for graft (86.7%, 78.5%, 72.4%, and 58.1% for DBD vs 83.7%, 74.2%, 67.1%, and 52.0% for DCD)( $p < 0.001$ ), were more notably different than for recipient (89.8%, 82.2%, 76.1%, and 60.9% for DBD vs 89.5%, 81.3%, 74.9%, and 58.2% for DCD)( $p = 0.027$ )(66). Of note in the DCD group donor age was younger and, in the recipient, age was higher than in the DBD group, with a more likely diagnosis of HCC among recipients(66). However, when propensity score matching was performed to allocate a more comparative demographic DBD control group the advantage gained by DBD was negated and graft survival and recipient survival rates were no different to DCD(66).

A propensity matched score analysis at University of California Los Angeles (UCLA) later reviewed DCD liver transplantation from 2004-2011 and reviewed 74 DCD grafts in this cohort(68). Although DCD had higher rates of hyperkalaemia and post-reperfusion syndrome, there were no significant differences in graft or patient survival between DCD and the propensity score matched DBD control group(68). It is very relevant here that DCD donors were noted to have donor age  $< 40$  years, BMI  $< 30$  and hospital stay  $< 5$  days prior to organ procurement(68), so no extended criteria characteristics.

Duan *et al* considered not only DCD but the combination of a DCD graft which also had moderate steatosis (30-60% on pre-transplantation biopsy in this study) to assess whether this extended characteristic meant this sub-category of DCD graft was not viable(64). Previously steatotic livers would only be used in very controlled circumstances i.e. DBD graft with a low CIT. It was also suggested that previous

studies have indicated 13% of moderately steatotic grafts suffer liver failure compared to 3% of non-steatotic grafts(64). Comparing groups of DCD + moderate steatosis with DCD grafts with no steatosis they found that, although rates of initial poor function and certain LFTs were elevated post-transplantation, there are no differences in survival of other factors between steatotic and non-steatotic DCD grafts(64).

A single centre study by Mihaylov reviewed more extended criteria DCD donor transplantations with characteristics such as advanced donor age (>50), elevated donor BMI (>35), moderate steatosis (>30%) and WIT >30 minutes(66). They also showed that with application of certain protocols to maximise success that the extended DCDs could have similar outcomes to optimal DCD grafts(66).

### 1.3.7 DCD causes poorer graft and recipient survival

There are several studies that clearly state poorer DCD outcomes for graft and recipient survival. Foley *et al* retrospectively reviewed DCD vs DBD LT between 1993-2008 and noted significantly poorer graft survival and recipient survival at 1, 5, 10 and 15 years post transplantation(50). Biliary complications and ischaemic cholangiopathy were also more common in the DCD group and it was noted that donor age was higher in this group(50). The same team had already published (in 2005) data from 1993-2002 commenting on graft and recipient survival at 1 and 3 years post transplantation. Outcomes were universally significantly poorer for DCD LTs. Graft survival was 67% at 1 year for DCD and 86% for DBD, then 56% vs 80% at 3 years ( $p=0.0001$ )(69). For recipient survival 1 year and 3 year outcomes were also poorer than DBD (80% and 68% respectively for DCD vs 91% and 84% for DBD,  $p=0.002$ )(69).

A study of the United Network for Organ Sharing (UNOS) database over a similar time period 1996-2003 reviewing, a much larger number, 367 DCD liver transplantations aimed to create a risk index (recipient cumulative relative risk; RCRR) following cox-regression to identify variables associated with poorer

outcomes. These included increased recipient age and medical condition, whether first transplant or re-transplantation and renal function (creatinine and dialysis status)(67). They determined that DCD liver transplantation graft survival rates (71% at year 1, 60% at year 3) were poorer than those in DBD transplantation (80% at year 1, 72% at year 3) and that this was statistically significant ( $p < 0.001$ )(67). They then used this to determine that if they combined the RCRR with appropriately selected DCD liver graft they could improve survival(67). The combination of low RCRR with low-risk DCD organ (low donor WIT and low CIT) they could show graft survival similar to rates in DBD transplantation(67).

A matched paired analysis approach to a cohort of 39 DCD LTs in the European Liver Transplant Registry (ELTR) database used variables deemed significant to predict graft survival outcomes to create a control DBD group(70). 1 and 3 year graft survival was lower in the DCD group (79.5% vs 97.4% at 1 year,  $p = 0.029$ ; 63.6% vs 97.4% at 3 years,  $P = 0.001$ )(70). 3 year recipient survival was also inferior (68.2% vs 100%,  $p < 0.0001$ )(70). De Vera also completed a matched-pairs analysis with similar results of poorer graft survival in DCD recipients at 1, 5 and 10 years (69%, 56%, 44% vs 82%, 73%, 63%,  $p < 0.0001$ )(71). Overall recipient survival was similar in both groups(71).

When considering DCD transplantation in specific recipient groups, those with a diagnosis of Hepatocellular Carcinoma (HCC), Croome *et al* allocated pairs into 4 groups to study depending on DCD/DBD and HCC/non-HCC and found poorer survival rates when testing for interactions between these two variables ( $p = 0.049$ )(62). This study, which looked retrospectively at the Scientific Registry of Transplant Recipients between 1995 – 2011 in Florida, also identified other significant variables affecting survival in this patient group including increased donor age ( $P < 0.001$ ), high MELD score of recipient ( $P < 0.001$ ), and a HCV positive recipient status ( $P < 0.001$ )(62).

When stratifying recipient cause of liver failure (primary liver disease) into low, medium and high risk groups it can be observed that DCD LTs in the low risk group

have the best graft survival at 5 years (86%) and poorest survival in the high risk recipient group (64.5% at 5 years)(58). Notably WIT was not a significant factor in univariable analysis but was included by Khorsandi *et al* in their prediction model as it is generally felt to be an indicator of outcome in DCD(58).

DCD donors are used more in recipients with hepatocellular carcinoma (HCC)(20.2% vs 13%), possibly due to likelihood for these recipients to have a lower MELD with the belief that they will be more robust to aid in a marginal donor transplanted liver(62).

Other studies have shown within DCD cohorts that poorer outcomes can result where there is increased donor weight, increased CIT (61), increased donor age and longer WIT (71). In DCD, liver grafts used for low MELD recipients (MELD <30) the outcome for graft survival has been shown to be poorer than if DBD grafts are used in those recipients (71).

Some studies noted that the Early Allograft Dysfunction (EAD) so often associated with DCD transplantations would be a surrogate variable to assess survival outcomes(2). EAD is defined as one of ongoing cholestasis with elevated bilirubin ( $\geq 10\text{mg/dL}$ ), coagulopathy with INR (international normalised ratio)( $\geq 1.6$ ), or AST/ALT (aspartate aminotransferase/alanine aminotransferase)( $>2000\text{IU/ml}$ ) measured on day 7 post transplantation(2). A study by Lee *et al* described not as such a direct effect of DCD on survival outcomes but indirectly linked DCD with the risk of EAD to then analyse this complication and its effect on survival. Recipient survival was compared between those with EAD and those without and there was a significant decrease in recipient survival where an early graft dysfunction occurred (1yrs survival 97% vs 79%; 3yrs 89% and 61%; 5yrs 79% and 54%;  $p=0.009$ )(2). For graft survival rates were similarly poorer in the EAD group ( $p=0.003$ )(2). EAD seemed on MV analysis to correlate with increasing CIT and a secondary diagnosis of HCC in recipients(2). In this study the authors found no correlation between donor WIT and the risk of developing EAD. Zhou *et al* felt that prevention of EAD was key to preventing graft failure and recipient death(72). Another team that focussed on

EAD rather than DCD specifically found 79% EAD in the DCD cohort and 40% in the DBD graft cohort (overall 52% incidence EAD)(73). Those who developed EAD were more likely to originate from DCD donors (48% vs 13.8%,  $p < 0.0001$ ) and had increased DRI suggesting extended criteria(73). Despite linking EAD with DCD, the study showed no significant difference in either graft survival or recipient survival between EAD and non-EAD groups(73).

## 2.0 Methods

### 2.1 Data collection

An application was submitted to NHSBT (National Health Service Blood and Transfusion) to request details of all liver transplantations carried out in the United Kingdom between 2001-2012. This request was submitted via the UK Liver Advisory Group who reviewed the original study protocol and approved the data request. Data requested was to include all deceased donor liver only transplants performed in adult patients (18 or older at the time of transplant) in the UK between 1 January 2001 and 31 December 2011, extracted from the UK transplant registry. Exclusions included transplants known to have used livers from donors after circulatory death (DCD) that were not Maastricht category 3, transplants not performed at any of the 7 main UK liver transplant centres, multi-organ transplants, split or reduced liver transplants, living donor transplants and heterotopic transplants.

The original dataset obtained in 2012 contained whole liver transplantations meeting the above criteria. Individual units were contacted to provide details of biliary complications in some cases were having difficulty in identifying patients according to NHSBT ID. This was an identifier provided in the original NHSBT dataset to anonymise recipients and donors. To overcome this barrier a further application was submitted to NHSBT to request an updated dataset from UK transplant registry to include date of donation and to update data to include cases until 2015. In the interim Liver Advisory Group had updated the regulations around supply of Liver Transplantation data and at that time a standardised dataset was supplied for most applications for this information. Although the data included recipients up to and including part of 2016, the identifying information was even more limited with no unit information, no specific donor or recipients ID or anything to identify individual transplantations.

Following difficulties in obtaining data for assessment of ischaemic cholangiopathy specifically, the focus of the study became more directed towards graft and recipient survival outcomes and identification of which variables can impact on these.

Ethical considerations were discussed with the Principal Supervisor and the Liver Advisory Group when applying for data to use to study liver transplantation survival outcomes. As this study was observational and database centred with no direct impact on patient care and with all individual datapoints anonymised the decision was that no further formal ethical approval was required.

## 2.2 Data Analysis

Data analysis was completed in R Studio Version 4.1.1. The large excel file provided by NHSBT was uploaded and the central argonaut server held the dataset securely. All patient identifiable features were removed by NHSBT prior to obtaining the database. All formatting and statistical tests were performed using this software by the lead author. The R script used for analyses is included in Appendices A and B. Using the associated liver specification file provided by NHSBT the individual variables in the dataset were examined for type (categorical or continuous) and renamed accordingly to allow the variable and outcomes to be easily understood during analysis. The groups were also checked with various methods to summarise each variable to ensure that their vector and levels were appropriate, and any discrepancies were corrected. Factors including recipient cause of liver failure, donor cause of death and recipient ethnic group had a very large number of redundant variables where there were overlapping, or similar outcomes recorded and at times with low numbers in these groups. To allow more streamlined analysis these were combined to gather outcomes into suitable categories. Across multiple variables there were a variety of codes or labels for “unknown”, such as “not reported”, “missing”, “not known” and where this occurred these were combined to one category “unknown”. Data that was truly missing was left as “NA” and allowed true representation of completely missing data within demographics tables and statistical analysis. More detail regarding missing data handling is included below.

There were a number of categories that included dates and using appropriate packages (lubridate) these were all formatted to the same structure to allow consistent interpretation and calculation of time across appropriate categories (such as survival times and cold ischaemic time).

It is worth noting that when originally requesting the NHSBT dataset the specifications in the request included whole liver transplantations only and from adult patients over 16 years of age. There were, however, a persistent group of both donors and recipients in the paediatric category and this was evident in the demographics tables shown, and these have been incorporated into the analysis.

### 2.3 Missing Data

A large dataset containing 16847 rows or transplantation episodes (after excluding living donor transplantations and recipients <18 years old) was analysed to identify missing data and methods used to determine if missing data were missing at random or in relation to other factors. On first observation of the raw dataset in excel, for example, it was apparent that overall transplantation numbers were very low and variable between 1968 and 1994 and thereafter numbers steadily increased year on year. It was also apparent that many variables, in particular recipient clinical and laboratory data were only collected from the year 2000 onwards and so many rows of data would be excluded from analysis on this basis alone. Given that this had a pattern due to the variables recorded in the dataset at each point in time this data was determined to be Missing Not at Random (MNAR).

The decision was taken subsequently to filter data prior to this date to aim to show more consistent results in both numbers of transplants and also in being able to analyse all columns (variables) reliably. Similarly, although the dataset included transplantations performed in 2016 many of the results and data was missing and so this was also excluded. All statistical analysis was performed for patients between 2000-2015.

Given that there were a very large number of variables included in this dataset and many of these were not going to be included in any part of the analysis, an initial look at individual variables plotting and charting of these was performed to identify the variables which would be required for all analysis – and these were then the focus of methods used to identify missing data.

First `ff_glimpse` was used to provide a summary of all factor variables and determine if these had all been categorised properly as numerical or categorical variables – working with these variables extensively prior to analysis meant that these were already allocated appropriately and reliability had been checked on multiple occasions.

It was considered for the data “Missing Completely at Random” or “Missing at Random” how to deal with these – either to leave missing values as “missing” or “NA” and include in the tests, exclude the missing data, or use imputation methods to fill in missing values with a reasonable value. For most variables examined these were categorical variables missing with no reasonable way to guess an outcome for each patient, for example CMV status or renal support status. Altering these at random is completely altering the potential clinical state of the patient. It was felt that as a result survival analysis would be unreliable and so imputation was not performed for any of these categorical variables.

For continuous variables such as BMI it was felt that this could relatively safely be predicted using imputation methods, however this was not deemed to be a significant variable of interest during the univariable analysis stage of the study and so further benefit would not be gained from further imputation.

## 2.4 Donor Age Variable Analysis

For the purposes of analysis of outcomes across different donor age groups and to allow easy categorisation of young vs old groups., the values chosen reflected

similar category cut offs in other analyses of donor age in the literature. The age groups chosen here were 0-35, 35-50, 50-60 and 60+ years.

In the first instance simple crosstables to assess donor and recipient demographics and observe important trends were performed. Donor and recipient variables and characteristics against individual donor age groups to visualise any significant difference across groups. Simple statistical tests to determine mean, standard deviation and proportions were performed to further categorise the data. Pearson chi-squared test was performed to show any significant differences across age groups.

Simple histograms were used to show the trends in number of liver transplantation over time and linear regression was used to visualise the trend in donor age over time. The proportion of donors in each age group per year were also calculated and shown to visually indicate the variation in proportion of older donor liver use over time. As an adjunct to this, trends were visually inspected using boxplots for each variable across donor age groups.

In order to begin to consider univariable analysis the main outcome measures or dependant variables for this study were graft survival and recipient survival. The hypothesis to test was whether donor age affected these outcomes. Initially individual variables were scrutinised to assess effect on survival to then allow best fit of multivariable analysis model. These were plotted on Kaplan Meier survival curves to look at effect on both graft and patient survival with a logrank test allowing p value to be added. This allowed generation of a collection of variables that had some impact on survival where analysed independently of any covariates. Variables were chosen which showed a visual difference across groups and also an associated significant p value less than 0.05. This selection was then used to consider which would populate the multivariable analysis.

For numeric/continuous variables this was not possible with the data in this format to perform survival analysis, so these were split into categorical variables. This was

performed for MELD score, CIT and BMI in addition to donor and recipient age groups.

In addition to survival curves, the donor, recipient and operative variables were also all assessed in explanatory tables using the finalfit package. This showed the impact of each variable independently on whether graft was functioning or failing, or whether recipient was alive or had died and the p value allowed some determination of statistical significance. The output here was obviously limited by the lack of a time to event component and so was used as an adjunct to the KM survival curves to aid in assessing variables to include in later models.

Lifetables to show survival at 1, 3, 5 and 10 years post-transplantation were created to allow comparison of graft and recipient survival rates at each stage post-transplantation for the different donor age groups.

Finally, consideration was given to the clinically relevant variables encountered frequently in practice and the variables frequently associated with donor age analysis in the literature to further refine the variables chosen to pass forward to multivariable analysis.

## 2.5 DCD Variable Analysis

Univariable analysis of DCD compared to DBD liver transplantation was performed in a similar manner to that for donor age.

Crosstables were created for donor and recipient demographics and observe important trends were performed comparing DCD and DBD LTs. Proportions and mean values were represented and p values again presented.

A histogram to demonstrate proportion of DCD compared to DBD LT over time was created. Boxplots for each variable across donor type (DCD vs DBD) were created to visually represent differences between groups.

The second hypothesis in this study focussed on determining the effect of DCD LT on graft and recipient survival. To assess DCD impact KM survival curves were created to analyse survival outcomes. As already described univariable analysis was used to determine which variables independently had an impact on these survival rates and these were used in comparisons for multivariable analysis alongside DCD.

Lifetables were also created for graft and recipient survival for DCD compared to DBD LT to show survival at 1, 3, 5 and 10 years post-transplantation.

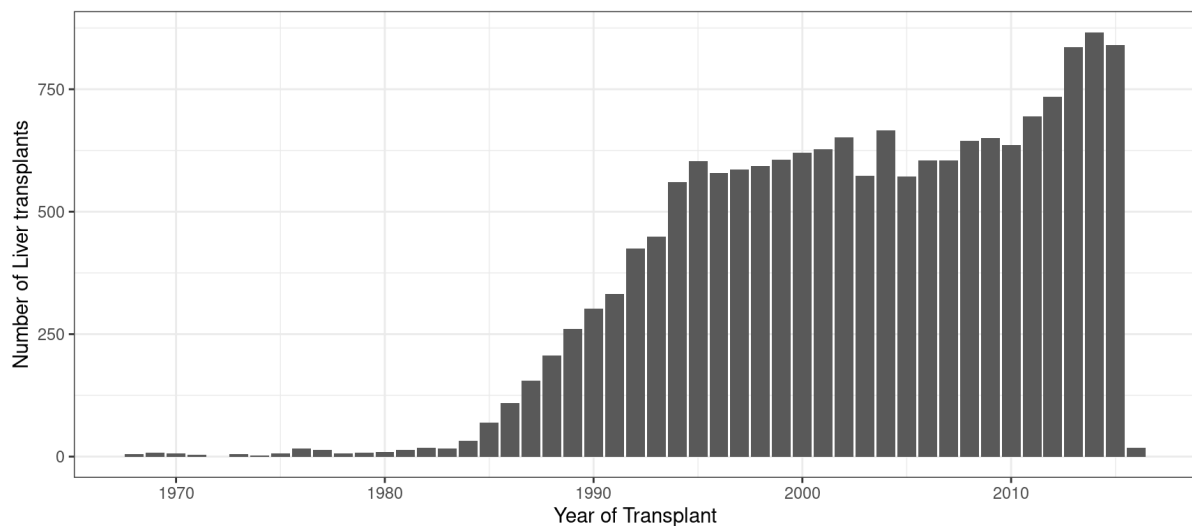
## 2.6 Multivariable Analysis

Multivariable analysis was performed using FinalFit allowing visualisation of univariate and multivariate analysis with tests for significance. This model uses a cox proportional hazards model allowing time to event survival analysis. Variables chosen at univariate analysis were slightly different between graft survival and recipient survival models and are described in the relevant results section. Hazard Ratio plots were created with variables of interest to display any significant differences in outcomes visually as an adjunct to the FinalFit output. 95% confidence intervals and p-values were demonstrated to allow assessment of statistical significance. Model fit statistics generated with the analysis were reported.

### 3.0 Results 1 – Associations between donor Age and Graft and Recipient survival

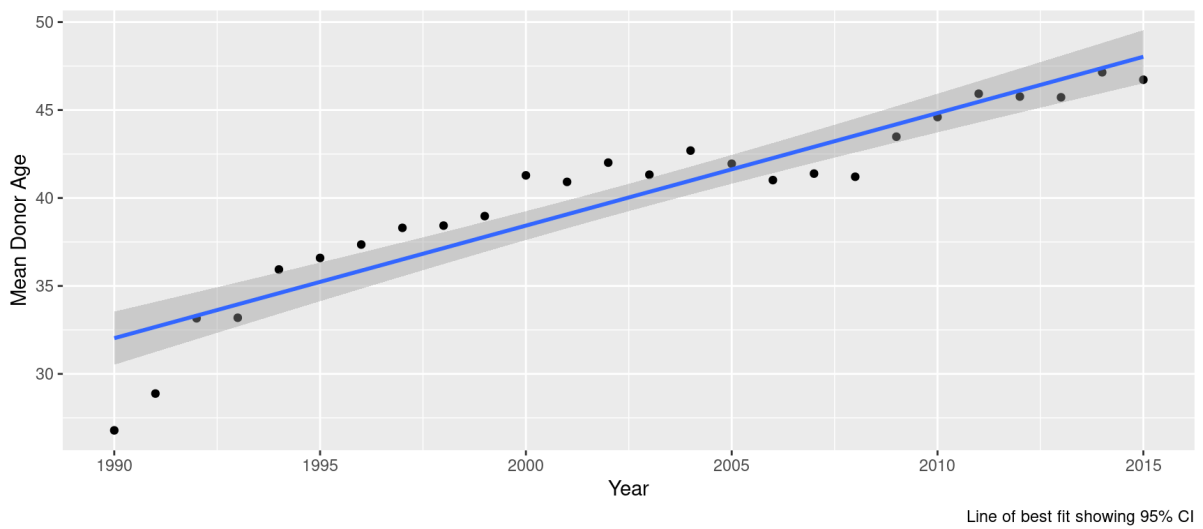
A total of 16847 first-time liver transplantations were analysed in this study. A limitation of this dataset was the absence of a donor or recipient gender variable. This dataset included 1187 donation after cardiac death (DCD) donors and 15656 donation after brainstem death (DBD) donors (donor type was missing for 4 transplantations). All liver transplantations analysed were whole orthotopic liver transplantations.

Figure 1 – Number of Whole Liver Transplantations per Year



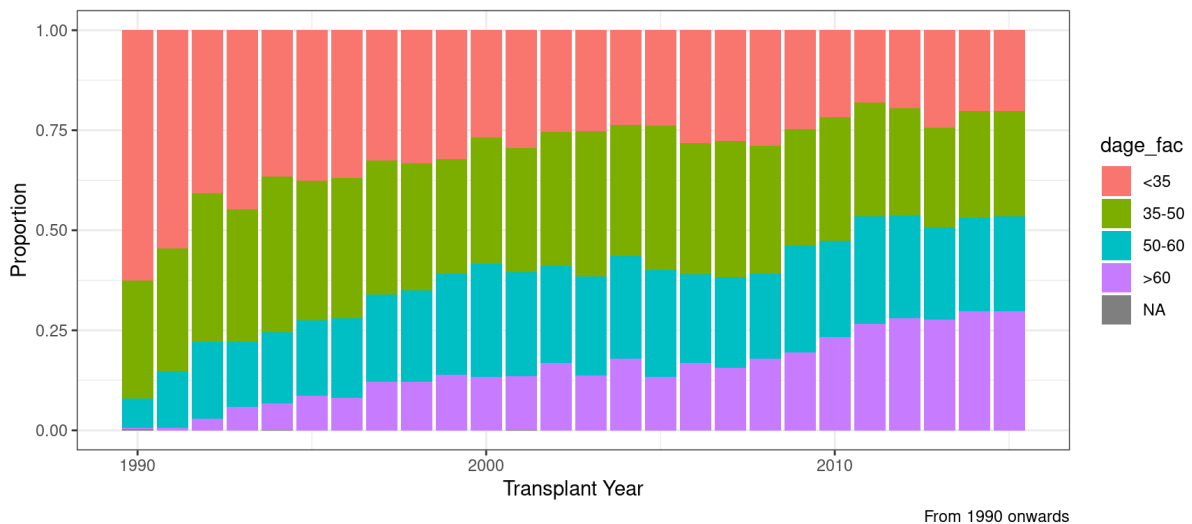
There was a steady increase in the number of first-time liver transplantations in UK between 1980 - 2015 (Figure 1).

Figure 2 – Mean Donor Age over Time



Mean donor age in UK increased per calendar year (Figure 2) shown from 1990 - 2015. When looking at the data split into 4 donor age groups there has been an increase specifically in the number of liver transplants from donors aged 60-86 over time. Other age groups have remained fairly steady (age 35-50 and 50-60) or have shown some decline in number (age 0-35) (Figure 3).

Figure 3 – Donor Age Group Proportion per Year



Older donors in this study were those >60 years old (2718 transplantations or 13.7%). Donor age was not available for 104 (0.5%) transplantations.

### 3.1 Donor demographics:

To review the donor demographics, significant risk factors were reviewed as a proportion of each donor age group. As also shown in (Figure 3) it is clear that there were a much larger proportion of older donors in more recent years with 56.8% of all liver donations from 60-86 year olds between 2004-2008 ( $p < 0.001$ ) (Table 1).

Table 1 - Donor Demographics

Donor Age (Years)		<35	35-50	50-60	>60	p
Era of Transplant	Pre-2004	3242 (62.6)	2763 (52.7)	1646 (44.8)	767 (28.6)	<0.001
	2004-2008	632 (12.2)	829 (15.8)	595 (16.2)	391 (14.6)	
	Post-2008	1309 (25.3)	1651 (31.5)	1435 (39.0)	1524 (56.8)	
Donor Age	Mean (SD)	23.5 (6.4)	42.5 (4.3)	54.3 (2.8)	66.3 (5.1)	<0.001
Donor Type	DBD	4869 (93.9)	4918 (93.8)	3396 (92.4)	2411 (89.9)	<0.001
	DCD	311 (6.0)	325 (6.2)	280 (7.6)	271 (10.1)	
	(Missing)	3 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	
Urgent	No	4473 (86.3)	4562 (87.0)	3164 (86.1)	2354 (87.8)	0.166
	Yes	710 (13.7)	681 (13.0)	512 (13.9)	328 (12.2)	
Donor BMI Category	Underweight <18.5	283 (5.5)	90 (1.7)	53 (1.4)	34 (1.3)	<0.001
	Normal 18.5-25	2421 (46.7)	2080 (39.7)	1370 (37.3)	917 (34.2)	
	Overweight 25-30	887 (17.1)	1556 (29.7)	1264 (34.4)	1082 (40.3)	
	Obese >30	207 (4.0)	612 (11.7)	516 (14.0)	424 (15.8)	
	(Missing)	1385 (26.7)	905 (17.3)	473 (12.9)	225 (8.4)	
Donor Blood Group	O	2591 (50.0)	2632 (50.2)	1810 (49.2)	1343 (50.1)	0.340
	A	1937 (37.4)	2036 (38.8)	1403 (38.2)	1018 (38.0)	
	B	497 (9.6)	438 (8.4)	355 (9.7)	255 (9.5)	
	AB	147 (2.8)	132 (2.5)	107 (2.9)	66 (2.5)	
	(Missing)	11 (0.2)	5 (0.1)	1 (0.0)	0 (0.0)	
Graft Steatosis	No	2065 (39.8)	1884 (35.9)	1273 (34.6)	928 (34.6)	<0.001

Donor Age (Years)		<35	35-50	50-60	>60	p
	Yes	386 (7.4)	1231 (23.5)	1268 (34.5)	1238 (46.2)	
	(Missing)	2732 (52.7)	2128 (40.6)	1135 (30.9)	516 (19.2)	
Donor CMV Status	Negative	2965 (57.2)	2617 (49.9)	1563 (42.5)	919 (34.3)	<0.001
	Positive	1714 (33.1)	2357 (45.0)	1988 (54.1)	1691 (63.0)	
	Unknown	446 (8.6)	219 (4.2)	80 (2.2)	31 (1.2)	
	(Missing)	58 (1.1)	50 (1.0)	45 (1.2)	41 (1.5)	
Cold Ischaemic Time (Hours)	<6h	726 (14.0)	834 (15.9)	657 (17.9)	445 (16.6)	0.016
	6-8h	746 (14.4)	979 (18.7)	739 (20.1)	583 (21.7)	
	8-12h	1434 (27.7)	1701 (32.4)	1313 (35.7)	1039 (38.7)	
	>12h	821 (15.8)	871 (16.6)	651 (17.7)	536 (20.0)	
	(Missing)	1456 (28.1)	858 (16.4)	316 (8.6)	79 (2.9)	

The donor was more likely to be CMV positive as age increased with proportion increasing steadily from 33.1% in the 0-35 age group up to 63.0% in the oldest 60-86 age group ( $p<0.001$ )(Table 1). Similarly, donor BMI steadily increased from the youngest age group where 46.7% had a normal BMI between 18.5-25, to the oldest age group where 40.3% were overweight with a BMI 25-30 ( $p<0.001$ )(Table 1). There were no significant differences in the urgency of transplantation across the age groups.

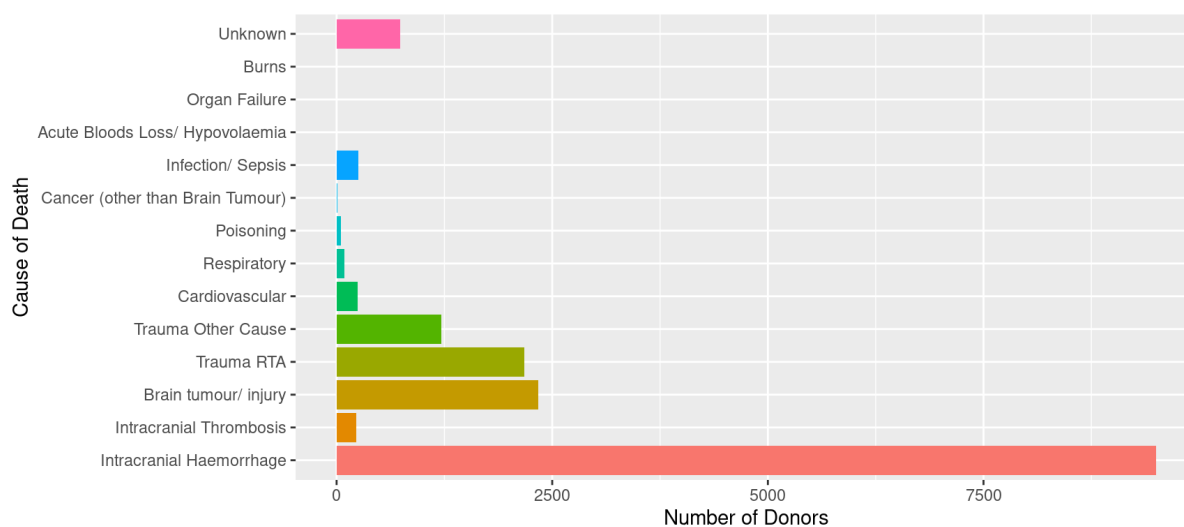
There were a slightly higher proportion of donation after cardiac death donors as donor age increased (6.0% of 0-35 year olds vs 10.1% of 60-86 year olds)( $p<0.001$ )(Table 1). There were no significant differences in Donor blood group between age groups. Another expected effect of age with increasing graft steatosis was also evident with only 7.4% of younger donors but 46.2% of older donors having graft steatosis( $p<0.001$ )(Table 1).

Table 2 – Donor cause of death per age group

Donor Age (Years)		<35	35-50	50-60	>60	p
Donor Cause of Death	Living Donor	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	<0.001
	Intracranial Haemorrhage	1434 (27.7)	3378 (64.4)	2714 (73.8)	1971 (73.5)	
	Intracranial Thrombosis	49 (0.9)	77 (1.5)	58 (1.6)	44 (1.6)	
	Brain tumour/ injury	777 (15.0)	765 (14.6)	436 (11.9)	355 (13.2)	
	Trauma RTA	1718 (33.1)	298 (5.7)	103 (2.8)	56 (2.1)	
	Trauma Other Cause	626 (12.1)	329 (6.3)	159 (4.3)	102 (3.8)	
	Cardiovascular	68 (1.3)	68 (1.3)	61 (1.7)	48 (1.8)	
	Respiratory	52 (1.0)	23 (0.4)	11 (0.3)	6 (0.2)	
	Poisoning	34 (0.7)	16 (0.3)	2 (0.1)	2 (0.1)	
	Cancer (other than Brain Tumour)	1 (0.0)	3 (0.1)	0 (0.0)	3 (0.1)	
	Infection/ Sepsis	137 (2.6)	67 (1.3)	28 (0.8)	24 (0.9)	
	Acute Bloods Loss/ Hypovolaemia	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
	Organ Failure	0 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)	
	Sudden Infant Death Syndrome (SIDS)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
	Burns	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.0)	
	Unknown	286 (5.5)	219 (4.2)	103 (2.8)	70 (2.6)	

There were a number of living donors included in the dataset when obtained from NHSBT and so these were later excluded and the analysis repeated without these. It was evident that the vast majority of donors died following intracranial haemorrhage (Table 2, Figure 4) and that this was more likely to be in donor age groups 50-60 and 60-86 (73.8% and 73.5% of deaths respectively) with only 27.7% of deaths in the 0-35 year age group with this cause of death. Trauma following RTA was the second most common cause and conversely much more common in the 0-35 year group contributing 33.1% of deaths and the most common cause in this group (Table 2). There were only 2.1% of 60-86 year old donors who died of Trauma/RTA (Table 2).

Figure 4 – Donor Cause of Death



There were less than 5.5% in each age group with an unknown cause of death.

### 3.2 Recipient demographics:

Recipient demographics are indicated in (Table 3) showing the spread of characteristics per donor age group before analysis of cause and effect was performed.

Table 3 - Recipient Demographics

Donor Age (Years)		<35	35-50	50-60	>60	p
Recipient Age (Years)	<35	995 (19.2)	756 (14.4)	455 (12.4)	256 (9.5)	<0.001
	35-50	1645 (31.7)	1670 (31.9)	1094 (29.8)	694 (25.9)	
	50-60	1675 (32.3)	1792 (34.2)	1253 (34.1)	936 (34.9)	
	>60	868 (16.7)	1025 (19.5)	874 (23.8)	796 (29.7)	
	(Missing)	2195 (42.3)	1616 (30.8)	917 (24.9)	463 (17.3)	
MELD Score	<10	360 (6.9)	444 (8.5)	348 (9.5)	290 (10.8)	0.101
	10-15	852 (16.4)	994 (19.0)	804 (21.9)	655 (24.4)	
	15-20	824 (15.9)	968 (18.5)	732 (19.9)	627 (23.4)	
	>20	952 (18.4)	1221 (23.3)	875 (23.8)	647 (24.1)	
	(Missing)	2195 (42.3)	1616 (30.8)	917 (24.9)	463 (17.3)	
Recipient Blood Group	O	2152 (41.5)	2271 (43.3)	1589 (43.2)	1206 (45.0)	0.004
	A	2096 (40.4)	2146 (40.9)	1498 (40.8)	1071 (39.9)	
	B	633 (12.2)	576 (11.0)	423 (11.5)	294 (11.0)	
	AB	300 (5.8)	242 (4.6)	163 (4.4)	110 (4.1)	
	(Missing)	2 (0.0)	8 (0.2)	3 (0.1)	1 (0.0)	
Recipient Ethnicity Group	White	3386 (65.3)	3930 (75.0)	2976 (81.0)	2241 (83.6)	<0.001
	Asian or Asian-British	299 (5.8)	335 (6.4)	239 (6.5)	226 (8.4)	
	Black or Black-British	101 (1.9)	105 (2.0)	84 (2.3)	76 (2.8)	

Donor Age (Years)		<35	35-50	50-60	>60	p
	Chinese/ Oriental	29 (0.6)	27 (0.5)	30 (0.8)	19 (0.7)	
	Mixed	4 (0.1)	3 (0.1)	2 (0.1)	1 (0.0)	
	Other/Unknown	1364 (26.3)	843 (16.1)	345 (9.4)	119 (4.4)	
Recipient CMV Status	Negative	1386 (26.7)	1475 (28.1)	1103 (30.0)	836 (31.2)	<0.001
	Positive	2074 (40.0)	2381 (45.4)	1746 (47.5)	1419 (52.9)	
	Unknown	1698 (32.8)	1374 (26.2)	822 (22.4)	427 (15.9)	
	(Missing)	25 (0.5)	13 (0.2)	5 (0.1)	0 (0.0)	
Recipient HCV Status	Negative	1716 (33.1)	1881 (35.9)	1323 (36.0)	754 (28.1)	<0.001
	Positive	372 (7.2)	481 (9.2)	350 (9.5)	214 (8.0)	
	Unknown	3095 (59.7)	2881 (54.9)	2003 (54.5)	1714 (63.9)	
Recipient Ventilation Status	No	3273 (63.1)	3903 (74.4)	3006 (81.8)	2368 (88.3)	0.001
	Yes	457 (8.8)	471 (9.0)	351 (9.5)	239 (8.9)	
	(Missing)	1453 (28.0)	869 (16.6)	319 (8.7)	75 (2.8)	
Recipient Renal Support Status	haemodialysis	258 (5.0)	298 (5.7)	189 (5.1)	132 (4.9)	0.013
	Filtration	298 (5.7)	334 (6.4)	260 (7.1)	185 (6.9)	
	Not Required	3161 (61.0)	3734 (71.2)	2895 (78.8)	2283 (85.1)	
	(Missing)	1466 (28.3)	877 (16.7)	332 (9.0)	82 (3.1)	
Donor vs Recipient Blood Group	Identical	4552 (87.8)	4729 (90.2)	3366 (91.6)	2498 (93.1)	<0.001
	Compatible	589 (11.4)	480 (9.2)	284 (7.7)	179 (6.7)	
	Incompatible	29 (0.6)	21 (0.4)	22 (0.6)	4 (0.1)	
	(Missing)	13 (0.3)	13 (0.2)	4 (0.1)	1 (0.0)	
Recipient Liver Failure Grade	Hyperacute	379 (7.3)	389 (7.4)	315 (8.6)	217 (8.1)	0.001
	Acute	200 (3.9)	187 (3.6)	143 (3.9)	94 (3.5)	
	Subacute	123 (2.4)	128 (2.4)	94 (2.6)	56 (2.1)	
	Not Acute	2999 (57.9)	3630 (69.2)	2772 (75.4)	2207 (82.3)	
	(Missing)	1482 (28.6)	909 (17.3)	352 (9.6)	108 (4.0)	
Recipient Lifestyle Activity Score	0	161 (3.1)	164 (3.1)	137 (3.7)	107 (4.0)	<0.001
	1	745 (14.4)	905 (17.3)	693 (18.9)	667 (24.9)	
	2	1613 (31.1)	1934 (36.9)	1441 (39.2)	1101 (41.1)	
	3	485 (9.4)	580 (11.1)	510 (13.9)	338 (12.6)	
	4	693 (13.4)	764 (14.6)	545 (14.8)	373 (13.9)	
	5	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
	Not Reported	59 (1.1)	56 (1.1)	51 (1.4)	34 (1.3)	
	Unknown	2 (0.0)	3 (0.1)	1 (0.0)	3 (0.1)	
	(Missing)	1424 (27.5)	837 (16.0)	298 (8.1)	59 (2.2)	
Recipient Inpatient Status	No	2546 (49.1)	3034 (57.9)	2358 (64.1)	1901 (70.9)	0.001
	Yes	1186 (22.9)	1345 (25.7)	1002 (27.3)	705 (26.3)	
	(Missing)	1451 (28.0)	864 (16.5)	316 (8.6)	76 (2.8)	
Recipient UKELD	Mean (SD)	55.5 (6.1)	55.6 (6.1)	55.4 (6.0)	54.9 (5.9)	0.001
Recipient Ascites	No	1878 (36.2)	2127 (40.6)	1639 (44.6)	1267 (47.2)	0.093
	Yes	1720 (33.2)	2114 (40.3)	1645 (44.7)	1306 (48.7)	
	(Missing)	1585 (30.6)	1002 (19.1)	392 (10.7)	109 (4.1)	
Recipient Diuretic Therapy Status	No	1954 (37.7)	2118 (40.4)	1651 (44.9)	1260 (47.0)	<0.001
	Yes	1633 (31.5)	2111 (40.3)	1620 (44.1)	1307 (48.7)	
	(Missing)	1596 (30.8)	1014 (19.3)	405 (11.0)	115 (4.3)	
Recipient Encephalopathy Grade	Not Encephalopathic	2518 (48.6)	2913 (55.6)	2216 (60.3)	1659 (61.9)	<0.001
	Grade 1	562 (10.8)	742 (14.2)	571 (15.5)	536 (20.0)	
	Grade 2	224 (4.3)	239 (4.6)	197 (5.4)	179 (6.7)	
	Grade 3	124 (2.4)	142 (2.7)	107 (2.9)	63 (2.3)	
	Grade 4	271 (5.2)	290 (5.5)	228 (6.2)	145 (5.4)	

Donor Age (Years)		<35	35-50	50-60	>60	p
	(Missing)	1484 (28.6)	917 (17.5)	357 (9.7)	100 (3.7)	
Recipient Abdominal Surgery Indicator	No	2774 (53.5)	3336 (63.6)	2598 (70.7)	2069 (77.1)	<0.001
	Yes	943 (18.2)	1022 (19.5)	748 (20.3)	530 (19.8)	
	(Missing)	1466 (28.3)	885 (16.9)	330 (9.0)	83 (3.1)	
Recipient Oesophageal Varices	No Previous Variceal Bleed	1336 (25.8)	1620 (30.9)	1262 (34.3)	981 (36.6)	0.781
	Previous Variceal Bleed	875 (16.9)	1061 (20.2)	803 (21.8)	651 (24.3)	
	Not Present	1357 (26.2)	1539 (29.4)	1198 (32.6)	929 (34.6)	
	(Missing)	1615 (31.2)	1023 (19.5)	413 (11.2)	121 (4.5)	
Recipient Shunt for Varices(if Present)	No Portosystemic Shunt	1274 (24.6)	1534 (29.3)	1186 (32.3)	874 (32.6)	0.433
	Surgical Shunt	23 (0.4)	28 (0.5)	12 (0.3)	8 (0.3)	
	TIPS	133 (2.6)	166 (3.2)	126 (3.4)	90 (3.4)	
	(Missing)	3753 (72.4)	3515 (67.0)	2352 (64.0)	1710 (63.8)	
Recipient Sepsis Confirmed Indicator	No	3397 (65.5)	4014 (76.6)	3105 (84.5)	2461 (91.8)	0.278
	Yes	188 (3.6)	219 (4.2)	165 (4.5)	109 (4.1)	
	(Missing)	1598 (30.8)	1010 (19.3)	406 (11.0)	112 (4.2)	

Looking initially at donor and recipient age it is evident immediately that there are much fewer donors overall aged >60 years and the lowest number of transplantations to recipients in the <35 year age group after the under 18 year olds were removed from the dataset. The highest number of transplantations occurred with a 35-50 year old donor to 50-60 year old recipients. It is also evident that younger donor livers <35yrs are proportionally more likely to be allocated to the youngest recipients (19.2% <35yrs donor age group vs only 9.5% >60 yrs old donor group)( $p<0.001$ )(Table 3). The oldest donor livers were more likely to be paired with the older recipients. 34.9% of the oldest donors were allocated to recipients 50-60 years of age and 29.7% to the oldest recipients >60yrs( $p<0.001$ )(Table 3).

It can be seen that recipients receiving older donor livers were more likely to be of White ethnicity (83.6% White recipients received an older donor liver vs 65.3% receiving a younger donor liver)( $p<0.001$ )(Table 3). Other recipient ethnicity groups were relatively evenly spread across donor age groups. It was noted that a much larger proportion of younger donor livers were allocated to those with an “unknown” or “other” ethnicity recorded (26.3% or 0-35yrs donor livers to this cohort). Recipient blood group was relatively standard split across donor age groups with group O most common (41.4-45.0%) and group AB least common (4.1-5.8%)(Table 3)).

When reviewing the CMV status of a recipient it was noted that the majority of the older donor livers were allocated to CMV positive recipients (52.9% of 60-76 yr donor group)( $p < 0.001$ ) with younger donor livers more likely to be spread between positive, negative and unknown CMV status groups (Table 3). There were no real patterns to the age range of donor livers allocated to recipients who were HCV positive in that the youngest and oldest age groups had slightly more likelihood of transplantation to a recipient HCV status was unknown and the middle aged donor groups proportionally had more allocated to the negative and positive HCV recipients (Table 3). Older donor livers were more likely to be allocated to recipients who were not ventilated prior to transplantation with 88.3% of 60-86 year old donors allocated to non-ventillated recipients but only 63.1% of 0-35 year old donors( $p = 0.001$ )(Table 3). A larger proportion of the oldest donor livers were also more likely to be allocated to the recipients requiring no renal support ( $p = 0.013$ )(Table 3). Identical ABO blood group match between donor and recipient was more likely in the older donor age group (93.1% of 60-86 year old donors vs 87.8% of 0-35 year old donors)( $p < 0.001$ )(Table 3). Compatible or incompatible pairings were more common in the younger donor age group.

Older donor livers were more likely to be transplanted in a recipient who did not have any acute liver failure with 82.3% of older donors allocated to this recipient group and only 57.9% of the youngest donors allocated to this cohort (Table 3). The results here were significant ( $p = 0.001$ ) and the recipients with hyperacute, acute and subacute liver failure had no real pattern with regard to donor age. Proportionally the 60-86year old donor group was more likely to be allocated to a recipient with a lower lifestyle score 1-2 (Table 3). The other donor age groups  $< 60$  years old had a similar pattern of spread with more allocoated to those with better lifestyle scores but with more of a spread to the recipients with a poorer lifestyle score/ pre-transplant functional status. A much larger proportion of older donor livers were allocated to recipients who were not inpatients prior to transplantation (70.9% vs 49.1% 0-35 year olds)( $p = 0.001$ )(Table 3).

Recipient UKELD scores were fairly similar across donor age groups. Recipients had a mean UKELD score of 55.5 +/-6.1SD in <35 year olds vs 54.9 +/-5.9SD in the >60 yr old donor group(p=0.001)(Table 3). Recipient MELD score was stratified into 4 groups to allow survival analysis and it can be noted that there was a fairly consistent pattern of recipient MELD score across all age groups. Recipients with a MELD score <10 proportionally were the smallest group across donor age categories and other MELD score groups were all fairly similar. Of note the recipients with missing MELD scores seemed proportionally to be allocated much more commonly in the <35 year old donor group, contributing 42.3% of this lower donor age group(Table 3). It is worth noting that for the whole dataset there were 6556 missing values for MELD in the entire cohort (from 1968-2016) and 6878 missing for UKELD.

Interestingly the youngest donor age groups were more likely to be allocated to recipients where there was no ascites present and a similar pattern was noted with regards to recipient diuretic status. A larger proportion of older donor livers >60 were allocated to recipients who were not encephalopathic (61.9% of 60-86yrs vs 48.6% 0-35yrs) or had only grade 1 encephalopathy (20.0% 60-86yrs vs 10.8% 0-35yrs)(p<0.001)(Table 3). Again with regards to missing data the younger donor age group had a higher proportion of missing data here (28.6% of 0-35yr group missing vs 3.7% of 60-86yrs donor group)(Table 3). This was also true of recipient varices status with the youngest donor group much more likely to be allocated to a recipient where this data was missing (31.2% <35ys old donors missing data for this variable vs only 3.1% >60yr old donors)(Table 3).

With regards to the recipient having had previous abdominal surgery, the younger donors were more likely to be allocated to a recipient where the abdominal surgery indicator was missing (28.3% of youngest donor group vs 3.1% of oldest donor group)(p<0.001)(Table 3). The older donors were more likely to be paired with a virgin abdomen (77.1% 60-86yrs donor group vs 53.5% of 0-35 group)(p<0.001)(Table 3). There were no significant differences in the donor age group allocation regarding the recipient's sepsis status prior to transplantation or whether they had any prior shunt procedures for varices if they were present.

Table 4 - Recipient Cause of Failure per Donor Age Group

Donor Age (Years)		<35	35-50	50-60	>60	p
Recipient Primary Liver Disease	Unknown	158 (3.0)	171 (3.3)	115 (3.1)	82 (3.1)	<0.001
	Autoimmune	976 (18.8)	1038 (19.8)	762 (20.7)	505 (18.8)	
	Infective	591 (11.4)	784 (15.0)	600 (16.3)	437 (16.3)	
	Genetic	127 (2.5)	153 (2.9)	130 (3.5)	99 (3.7)	
	Vascular	151 (2.9)	167 (3.2)	102 (2.8)	88 (3.3)	
	Benign Causes Liver Disease	840 (16.2)	1148 (21.9)	915 (24.9)	866 (32.3)	
	Congenital	22 (0.4)	19 (0.4)	16 (0.4)	5 (0.2)	
	Paediatric/ Neonatal Causes	4 (0.1)	1 (0.0)	2 (0.1)	0 (0.0)	
	Acute Hepatic Failure	459 (8.9)	471 (9.0)	368 (10.0)	235 (8.8)	
	Fulminant Hepatic Failure	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
	Malignancy	233 (4.5)	265 (5.1)	226 (6.1)	215 (8.0)	
	Metabolic	44 (0.8)	24 (0.5)	24 (0.7)	17 (0.6)	
	Rejection	154 (3.0)	165 (3.1)	118 (3.2)	74 (2.8)	
	(Missing)	1424 (27.5)	837 (16.0)	298 (8.1)	59 (2.2)	

Older donors much more likely to be transplanted to recipients with a benign cause of their liver failure – accounting for 32.3% of >60 year old donor group (Table 4). Only 16.2% of <35 year old donors were paired with a recipient with a benign cause of their liver disease (Table 4). Again, a much larger proportion of the youngest donors <35 years were allocated to recipients where the cause of their liver failure was missing (27.5%) compared with only 2.2% of >60 year old donors to this group (Table 4).

Table 5 - Recipient Cause of Liver Failure per Recipient Age Group

Recipient Age (Years)		<35	35-50	50-60	>60	p
Recipient Primary Liver Disease	Unknown	142 (5.7)	156 (3.0)	134 (2.4)	94 (2.6)	<0.001
	Autoimmune	409 (16.5)	959 (18.7)	1005 (17.7)	908 (25.5)	
	Infective	68 (2.7)	826 (16.1)	1052 (18.6)	466 (13.1)	
	Genetic	77 (3.1)	142 (2.8)	174 (3.1)	116 (3.3)	
	Vascular	109 (4.4)	177 (3.4)	151 (2.7)	71 (2.0)	

Recipient Age (Years)	<35	35-50	50-60	>60	p
Benign Causes Liver Disease	124 (5.0)	1003 (19.5)	1554 (27.4)	1088 (30.5)	
Congenital	47 (1.9)	6 (0.1)	5 (0.1)	4 (0.1)	
Paediatric/ Neonatal Causes	6 (0.2)	0 (0.0)	1 (0.0)	0 (0.0)	
Acute Hepatic Failure	663 (26.7)	507 (9.9)	256 (4.5)	107 (3.0)	
Fulminant Hepatic Failure	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	
Malignancy	65 (2.6)	194 (3.8)	353 (6.2)	328 (9.2)	
Metabolic	51 (2.1)	24 (0.5)	17 (0.3)	17 (0.5)	
Rejection	150 (6.0)	125 (2.4)	159 (2.8)	77 (2.2)	
(Missing)	569 (22.9)	1018 (19.8)	805 (14.2)	288 (8.1)	

Of note the most common cause of liver failure requiring transplantation in the older recipients >60 years old (30.5%) are benign causes (Table 5). Benign causes of liver disease for the purpose of this analysis included cryptogenic cirrhosis, secondary biliary cirrhosis, alcoholic liver disease, non-alcoholic fatty liver disease, benign liver tumour and trauma. Congenital causes of primary liver disease are more common proportionally in the <35 year old recipients accounting for 1.9% (Table 5). Congenital causes here account for only 0.1% of the >60 year old recipients (Table 5).

In addition to these younger recipients <35 years are also more likely to have rejection as a cause for liver failure (6.0% of this group), acute hepatic failure (26.7%) and much more likely to have cause of failure missing from the data (22.9% under 35 years have cause missing) compared with the older cohort of recipients (Table 5). Older recipients >60 years are more likely to have autoimmune causes of liver disease (25.5%) or malignancy (9.2%) as a cause for their liver failure in comparison proportionally to the younger groups (Table 5). Middle aged recipient groups 35-60 years are more likely to have infective causes of liver failure (Table 5).

### 3.3 Univariate analysis – Graft Survival

As mentioned in the methods section the variables of interest regarding graft survival were all visualised and plotted individually on KM curves and this highlighted variables of interest to then rationalise for univariate analysis (Table 6).

Table 6 - Graft Survival Variables

Graft Survival		Functioning	Failed	p
Era of Transplant	Pre-2004	2145 (75.6)	692 (24.4)	<0.001
	2004-2008	2201 (77.3)	647 (22.7)	
	Post-2008	5664 (87.0)	847 (13.0)	
Donor Age	Mean (SD)	43.3 (17.0)	44.4 (16.7)	0.009
Donor Age (Years)	<35	3058 (83.9)	587 (16.1)	0.007
	35-50	2987 (81.6)	673 (18.4)	
	50-60	2183 (81.0)	513 (19.0)	
	>60	1778 (81.2)	411 (18.8)	
	(Missing)	4 (66.7)	2 (33.3)	
Donor Type	DBD	8751 (81.7)	1957 (18.3)	0.377
	DCD	955 (82.8)	198 (17.2)	
	(Missing)	304 (90.7)	31 (9.3)	
Donor Cause of Death	Living Donor	300 (91.2)	29 (8.8)	<0.001
	Intracranial Haemorrhage	5619 (81.1)	1313 (18.9)	
	Intracranial Thrombosis	164 (84.1)	31 (15.9)	
	Brain tumour/ injury	1626 (85.4)	278 (14.6)	
	Trauma RTA	932 (81.9)	206 (18.1)	
	Trauma Other Cause	530 (80.8)	126 (19.2)	
	Cardiovascular	104 (81.9)	23 (18.1)	
	Respiratory	28 (75.7)	9 (24.3)	
	Poisoning	36 (81.8)	8 (18.2)	
	Cancer (other than Brain Tumour)	3 (75.0)	1 (25.0)	
	Infection/ Sepsis	221 (83.4)	44 (16.6)	
	Acute Bloods Loss/ Hypovolaemia	0 (NaN)	0 (NaN)	
	Organ Failure	1 (100.0)	0 (0.0)	
	Sudden Infant Death Syndrome (SIDS)	0 (NaN)	0 (NaN)	
	Burns	1 (100.0)	0 (0.0)	
	Unknown	445 (79.0)	118 (21.0)	
Graft Steatosis	No	5972 (82.2)	1295 (17.8)	0.518
	Yes	3460 (81.7)	776 (18.3)	
	(Missing)	578 (83.4)	115 (16.6)	
Donor CMV Status	Negative	5060 (82.7)	1060 (17.3)	0.021
	Positive	4406 (80.8)	1048 (19.2)	
	Unknown	92 (78.6)	25 (21.4)	
	(Missing)	452 (89.5)	53 (10.5)	
Recipient CMV Status	Negative	3537 (83.1)	717 (16.9)	<0.001
	Positive	4679 (80.7)	1122 (19.3)	
	Unknown	1705 (83.9)	327 (16.1)	
	(Missing)	89 (81.7)	20 (18.3)	

Graft Survival		Functioning	Failed	p
Recipient HCV Status	Negative	3294 (76.9)	987 (23.1)	<0.001
	Positive	694 (71.1)	282 (28.9)	
	Unknown	6022 (86.8)	917 (13.2)	
Recipient Ventilation Status	No	8831 (82.3)	1897 (17.7)	0.048
	Yes	1060 (80.1)	264 (19.9)	
	(Missing)	119 (82.6)	25 (17.4)	
Recipient Renal Support Status	haemodialysis	503 (79.7)	128 (20.3)	0.120
	Filtration	791 (80.6)	190 (19.4)	
	Not Required	8584 (82.3)	1842 (17.7)	
	(Missing)	132 (83.5)	26 (16.5)	
Donor vs Recipient Blood Group	Identical	9132 (82.1)	1989 (17.9)	0.102
	Compatible	821 (81.0)	193 (19.0)	
	Incompatible	48 (92.3)	4 (7.7)	
	(Missing)	9 (100.0)	0 (0.0)	
Recipient Liver Failure Grade	Hyperacute	966 (81.9)	213 (18.1)	0.937
	Acute	396 (82.0)	87 (18.0)	
	Subacute	248 (80.8)	59 (19.2)	
	Not Acute	8154 (82.2)	1770 (17.8)	
	(Missing)	246 (81.2)	57 (18.8)	
Recipient Inpatient Status	No	6958 (82.8)	1444 (17.2)	0.002
	Yes	2934 (80.4)	716 (19.6)	
	(Missing)	118 (81.9)	26 (18.1)	
Recipient Ascites	No	5250 (81.5)	1194 (18.5)	0.068
	Yes	4621 (82.8)	962 (17.2)	
	(Missing)	139 (82.2)	30 (17.8)	
Recipient Diuretic Therapy Status	No	5282 (81.6)	1193 (18.4)	0.130
	Yes	4556 (82.7)	956 (17.3)	
	(Missing)	172 (82.3)	37 (17.7)	
Recipient Encephalopathy Grade	Not Encephalopathic	6694 (81.6)	1513 (18.4)	0.015
	Grade 1	1633 (84.7)	296 (15.3)	
	Grade 2	543 (82.5)	115 (17.5)	
	Grade 3	247 (79.2)	65 (20.8)	
	Grade 4	669 (81.3)	154 (18.7)	
	(Missing)	224 (83.9)	43 (16.1)	
Recipient Abdominal Surgery Indicator	No	7591 (83.3)	1524 (16.7)	<0.001
	Yes	2268 (78.2)	632 (21.8)	
	(Missing)	151 (83.4)	30 (16.6)	
Recipient Sepsis Confirmed Indicator	No	9440 (82.4)	2011 (17.6)	<0.001
	Yes	411 (74.7)	139 (25.3)	
	(Missing)	159 (81.5)	36 (18.5)	
Preservation FLuid	Not Known	0 (NaN)	0 (NaN)	<0.001
	Other	359 (84.9)	64 (15.1)	
	University of Wisconsin (ViaSpan)	2347 (90.2)	256 (9.8)	
	U.W. (Commercial)	7116 (79.7)	1815 (20.3)	
	Unknown	94 (75.8)	30 (24.2)	
	Not Perfused	0 (NaN)	0 (NaN)	
	(Missing)	94 (81.7)	21 (18.3)	
Biliary Anastomosis	No Stent	6786 (82.9)	1395 (17.1)	0.006
	T-Tube	493 (81.4)	113 (18.6)	
	Roux	2439 (80.2)	601 (19.8)	

Graft Survival		Functioning	Failed	p
	Stent	39 (76.5)	12 (23.5)	
	(Missing)	253 (79.6)	65 (20.4)	
Anti-Fibrinolytic Therapy	No	6712 (83.9)	1288 (16.1)	<0.001
	Yes	2846 (78.1)	800 (21.9)	
	(Missing)	452 (82.2)	98 (17.8)	
Recipient Primary Liver Disease	Unknown	481 (83.7)	94 (16.3)	<0.001
	Autoimmune	1888 (80.7)	451 (19.3)	
	Infective	1420 (79.3)	370 (20.7)	
	Genetic	463 (87.0)	69 (13.0)	
	Vascular	331 (75.9)	105 (24.1)	
	Benign Causes Liver Disease	2528 (84.5)	465 (15.5)	
	Congenital	480 (88.7)	61 (11.3)	
	Paediatric/ Neonatal Causes	58 (86.6)	9 (13.4)	
	Acute Hepatic Failure	1086 (82.7)	227 (17.3)	
	Fulminant Hepatic Failure	0 (NaN)	0 (NaN)	
	Malignancy	734 (81.8)	163 (18.2)	
	Metabolic	128 (84.8)	23 (15.2)	
	Rejection	319 (71.4)	128 (28.6)	
	(Missing)	94 (81.7)	21 (18.3)	
Donor Organ Appearance	Healthy	6810 (81.8)	1514 (18.2)	<0.001
	Suboptimal	1526 (77.5)	444 (22.5)	
	(Missing)	1674 (88.0)	228 (12.0)	
Recipient UKELD	Mean (SD)	54.8 (6.0)	55.1 (6.1)	0.033
MELD Score	<10	1169 (81.8)	260 (18.2)	0.601
	10-15	2292 (81.8)	509 (18.2)	
	15-20	2243 (83.1)	457 (16.9)	
	>20	2530 (82.5)	535 (17.5)	
	(Missing)	1776 (80.7)	425 (19.3)	
Cold Ischaemic Time (Hours)	<6h	2207 (85.0)	390 (15.0)	<0.001
	6-8h	2418 (82.5)	512 (17.5)	
	8-12h	3688 (80.1)	914 (19.9)	
	>12h	1559 (82.2)	338 (17.8)	
	(Missing)	138 (81.2)	32 (18.8)	

Variables which were determined significant ( $p < 0.05$ ) in the univariable analysis were considered further to determine whether they would be included in multivariable analysis as co-variables with donor age.

When reviewing era of transplantation the more recent years' liver transplants have better graft survival outcome with 87% of grafts still functioning compared to 75.6% of grafts performed <2004 ( $p < 0.001$ ) (Table 6). There was a slightly higher rate of graft failure in the older donor age groups 50-60 years, >50 years and >60 years (18.5%, 19.0% and 18.8% respectively) compared with the lowest rate of graft failure in the youngest donor age group <35 yrs (17.4%) although this binary analysis was

not statistically significant ( $p=0.478$ )(Table 6). When reviewing donor cause of death the living donor transplantations have the best graft survival and the poorest survival rates are associated with donors who died of respiratory deaths (28.1% grafts failed) and cancers (33.3% failed)( $p=0.049$ )(Table 6). Donor CMV status (19.6% vs 17.3%,  $p=0.009$ ), recipient CMV status (19.5% vs 17.6%,  $p=0.011$ ), and recipient HCV status (29.2% vs 23.5%,  $p<0.001$ ) all appeared to have poorer graft survival where viral status was positive (Table 6). Similarly recipient ventilation status (20.5% vs 18.2% non-ventilated,  $p=0.065$ ), recipient inpatient status (20.0% vs 17.8% non-inpatients,  $p=0.008$ ), and recipient abdominal surgery status (24.0% vs 17.0% no previous surgery,  $p<0.001$ ), and recipient sepsis status (25.4% vs 18.1% no-sepsis,  $p<0.001$ ) were also all associated with increased incidence of graft loss where they were present (Table 6).

The recipient primary cause of liver disease with the highest rate of graft failure was congenital (31.2%), second most common was rejection (28.6%), and third was vascular causes (23.8% graft loss)( $p<0.001$ )(Table 6).

Where the donor organ appearance was classed as suboptimal by the operating surgeon there was a higher risk of graft loss (22.7% of suboptimal group failed vs 18.5% of healthy group)( $p<0.001$ )(Table 6). Recipient mean UKELD was slightly higher in the group where graft loss had occurred (55.2 $\pm$ 6.0SD) than in the group where graft survived (55.0 $\pm$ 5.8) but not statistically significant ( $p=0.125$ )(Table 6). Recipient MELD score did not appear to significantly alter the likelihood of graft survival or failure ( $p=0.712$ )(Table 6).

Cold ischaemic time showed an almost linear relationship with risk of graft loss with the least morbidity in the lowest CIT of 0-6 hours (15.3% graft loss) compared to the highest loss in CIT 8-12 hours (20.5% graft loss) and CIT >720 minutes (18.7% graft loss)( $p<0.001$ )(Table 6).

Based on my review of the literature on donor age and the common variables noted to have effect on graft and recipient survival I rationalised the studied variables

further. Regardless of their significant p value I chose to remove donor cause of death, recipient grade of encephalopathy, preservation fluid(p<0.001), type of biliary anastomosis (p=0.006) and antifibrinolytic therapy status(p<0.001), from the multivariate analysis. Recipient grade of encephalopathy did have a significant pvalue (p=0.015) but this was not associated with any meaningful pattern of graft failure as grade/ severity of encephalopathy increased or decreased.

I also chose to add recipient MELD score (p=0.712), graft steatosis (p=0.767) and donor type (p=0.410) as although not significant in the above univariate analysis these are variables noted to be of importance in the literature. Although not as significant as other variables I retained the recipient cause of liver failure as this assists in indication of patients who may have clinically relevant diagnoses such as HCC.

### 3.4 Univariate analysis – Recipient Survival

As with graft survival the univariate analysis below contains variables deemed to be of significance upon visual inspection of KM curves for each individual variable of interest.

Table 7 - Recipient Survival Variables

Patient Survival		Alive	Died	p
Era of Transplant	Pre-2004	1322 (59.4)	903 (40.6)	<0.001
	2004-2008	1531 (69.8)	663 (30.2)	
	Post-2008	4398 (86.7)	672 (13.3)	
Donor Age	Mean (SD)	46.3 (15.8)	46.4 (15.3)	0.692
Donor Age (Years)	<35	1741 (77.6)	502 (22.4)	0.104
	35-50	2192 (76.0)	692 (24.0)	
	50-60	1777 (74.9)	595 (25.1)	
	>60	1540 (77.4)	449 (22.6)	
	(Missing)	1 (100.0)	0 (0.0)	
Donor Type	DBD	6314 (75.3)	2073 (24.7)	<0.001
	DCD	935 (85.1)	164 (14.9)	
	(Missing)	2 (66.7)	1 (33.3)	
Donor Cause of Death	Living Donor	0 (NaN)	0 (NaN)	<0.001
	Intracranial Haemorrhage	4328 (75.2)	1425 (24.8)	
	Intracranial Thrombosis	144 (85.7)	24 (14.3)	
	Brain tumour/ injury	1244 (82.1)	271 (17.9)	
	Trauma RTA	553 (72.7)	208 (27.3)	

Patient Survival		Alive	Died	p
	Trauma Other Cause	396 (77.5)	115 (22.5)	
	Cardiovascular	88 (79.3)	23 (20.7)	
	Respiratory	21 (67.7)	10 (32.3)	
	Poisoning	26 (81.2)	6 (18.8)	
	Cancer (other than Brain Tumour)	2 (100.0)	0 (0.0)	
	Infection/ Sepsis	125 (80.1)	31 (19.9)	
	Acute Bloods Loss/ Hypovolaemia	0 (NaN)	0 (NaN)	
	Organ Failure	1 (100.0)	0 (0.0)	
	Sudden Infant Death Syndrome (SIDS)	0 (NaN)	0 (NaN)	
	Burns	1 (100.0)	0 (0.0)	
	Unknown	322 (72.0)	125 (28.0)	
Donor BMI Category	Underweight <18.5	199 (79.0)	53 (21.0)	0.205
	Normal 18.5-25	3191 (75.9)	1011 (24.1)	
	Overweight 25-30	2641 (76.5)	812 (23.5)	
	Obese >30	1094 (78.5)	300 (21.5)	
	(Missing)	126 (67.0)	62 (33.0)	
Graft Steatosis	No	4143 (76.9)	1248 (23.1)	0.865
	Yes	2883 (76.7)	877 (23.3)	
	(Missing)	225 (66.6)	113 (33.4)	
Donor CMV Status	Negative	3701 (77.6)	1070 (22.4)	0.002
	Positive	3347 (75.0)	1118 (25.0)	
	Unknown	64 (68.1)	30 (31.9)	
	(Missing)	139 (87.4)	20 (12.6)	
Recipient CMV Status	Negative	2536 (78.3)	701 (21.7)	0.002
	Positive	3633 (76.1)	1144 (23.9)	
	Unknown	1067 (73.9)	377 (26.1)	
	(Missing)	15 (48.4)	16 (51.6)	
Recipient HCV Status	Negative	2151 (66.2)	1096 (33.8)	<0.001
	Positive	521 (61.0)	333 (39.0)	
	Unknown	4579 (85.0)	809 (15.0)	
Recipient Ventilation Status	No	6619 (76.8)	1997 (23.2)	0.014
	Yes	598 (72.9)	222 (27.1)	
	(Missing)	34 (64.2)	19 (35.8)	
Recipient Ethnicity Group	White	6253 (76.3)	1938 (23.7)	0.361
	Asian or Asian-British	584 (76.8)	176 (23.2)	
	Black or Black-British	187 (74.5)	64 (25.5)	
	Chinese/ Oriental	65 (77.4)	19 (22.6)	
	Mixed	5 (50.0)	5 (50.0)	
	Other	154 (81.5)	35 (18.5)	
	Not Reported	1 (100.0)	0 (0.0)	
	Unknown	2 (66.7)	1 (33.3)	
Recipient Renal Support Status	haemodialysis	351 (73.9)	124 (26.1)	0.002
	Filtration	455 (71.3)	183 (28.7)	
	Not Required	6402 (77.0)	1911 (23.0)	
	(Missing)	43 (68.3)	20 (31.7)	
Donor vs Recipient Blood Group	Identical	6774 (76.6)	2071 (23.4)	0.284
	Compatible	466 (73.9)	165 (26.1)	
	Incompatible	8 (80.0)	2 (20.0)	
	(Missing)	3 (100.0)	0 (0.0)	
Recipient Inpatient Status	No	5465 (77.2)	1611 (22.8)	0.004

Patient Survival		Alive	Died	p
	Yes	1753 (74.3)	607 (25.7)	
	(Missing)	33 (62.3)	20 (37.7)	
Recipient Ascites	No	3582 (76.7)	1087 (23.3)	0.645
	Yes	3624 (76.3)	1126 (23.7)	
	(Missing)	45 (64.3)	25 (35.7)	
Recipient UKELD	Mean (SD)	54.9 (5.8)	54.7 (5.9)	0.394
MELD Score	<10	840 (73.8)	298 (26.2)	0.001
	10-15	1833 (75.4)	597 (24.6)	
	15-20	1771 (78.6)	481 (21.4)	
	>20	1791 (78.5)	490 (21.5)	
	(Missing)	1016 (73.2)	372 (26.8)	
Recipient Encephalopathy Grade	Not Encephalopathic	4733 (76.0)	1495 (24.0)	0.001
	Grade 1	1386 (79.9)	348 (20.1)	
	Grade 2	439 (76.9)	132 (23.1)	
	Grade 3	184 (72.7)	69 (27.3)	
	Grade 4	417 (72.3)	160 (27.7)	
	(Missing)	92 (73.0)	34 (27.0)	
Recipient Shunt for Varices(if Present)	No Portosystemic Shunt	2281 (72.6)	859 (27.4)	0.935
	Surgical Shunt	22 (73.3)	8 (26.7)	
	TIPS	264 (73.5)	95 (26.5)	
	(Missing)	4684 (78.6)	1276 (21.4)	
Recipient Sepsis Confirmed Indicator	No	6966 (76.8)	2110 (23.2)	<0.001
	Yes	220 (68.1)	103 (31.9)	
	(Missing)	65 (72.2)	25 (27.8)	
Preservation FLuid	Not Known	0 (NaN)	0 (NaN)	<0.001
	Other	278 (80.8)	66 (19.2)	
	University of Wisconsin (ViaSpan)	1821 (91.9)	160 (8.1)	
	U.W. (Commercial)	5066 (72.0)	1968 (28.0)	
	Unknown	69 (71.9)	27 (28.1)	
	Not Perfused	0 (NaN)	0 (NaN)	
	(Missing)	17 (50.0)	17 (50.0)	
Anti-Fibrinolytic Therapy	No	4990 (80.5)	1211 (19.5)	<0.001
	Yes	2020 (68.1)	946 (31.9)	
	(Missing)	241 (74.8)	81 (25.2)	
Recipient Primary Liver Disease	Unknown	250 (75.1)	83 (24.9)	<0.001
	Autoimmune	1750 (79.8)	442 (20.2)	
	Infective	1258 (73.3)	459 (26.7)	
	Genetic	327 (80.1)	81 (19.9)	
	Vascular	55 (79.7)	14 (20.3)	
	Benign Causes Liver Disease	2218 (76.6)	679 (23.4)	
	Congenital	34 (77.3)	10 (22.7)	
	Paediatric/ Neonatal Causes	5 (100.0)	0 (0.0)	
	Acute Hepatic Failure	826 (76.6)	253 (23.4)	
	Fulminant Hepatic Failure	0 (NaN)	0 (NaN)	
	Malignancy	465 (72.1)	180 (27.9)	
	Metabolic	44 (68.8)	20 (31.2)	
	Rejection	2 (100.0)	0 (0.0)	
	(Missing)	17 (50.0)	17 (50.0)	
Donor Organ Appearance	Healthy	4907 (75.7)	1579 (24.3)	0.140
	Suboptimal	1350 (73.9)	476 (26.1)	

Patient Survival		Alive	Died	p
	(Missing)	994 (84.5)	183 (15.5)	
Cold Ischaemic Time (Hours)	<6h	1584 (81.1)	368 (18.9)	<0.001
	6-8h	1903 (79.9)	479 (20.1)	
	8-12h	2703 (72.8)	1008 (27.2)	
	>12h	1016 (73.7)	362 (26.3)	
	(Missing)	45 (68.2)	21 (31.8)	

As with graft survival era of transplantation was also significant in affecting recipient survival with later era liver transplantations having better recipient survival; only 13.3% of recipients transplanted >2008 died compared with 40.6% of those transplanted <2004 ( $p<0.001$ )(Table 7). The youngest donor age group is associated with the best recipient survival (only 22.4% died) but the other groups did not show a linear association and this was not significant ( $p=0.104$ )(Table 7). DCD donor LTs had actually proportionally better recipient survival than DBD donor LTs (only 14.9% died vs 24.7% of DBD)( $p<0.001$ )(Table 7). Recipients who have died are most likely to be associated with donor cause of death in the respiratory cause category (32.3% recipients died) followed by traumatic RTA (27.3%) and then intracranial haemorrhage (24.8% recipients died)( $p<0.001$ )(Table 7).

Donor CMV status (25.0% positive vs 22.4% negative,  $p=0.002$ ), recipient CMV status (23.9% positive vs 21.7% negative,  $p=0.002$ ) and recipient HCV status (39.0% positive vs 33.8% negative,  $p<0.001$ ) are all associated negatively with recipient mortality with proportions who died shown (Table 7).

Recipients who were ventilated pre-LT are less likely to survive (27.1% died vs 23.2% not ventilated,  $p=0.014$ )(Table 7). Similarly recipients receiving renal support prior to transplantation had poorer outcomes with 26.1% of those on haemodialysis having died, filtration 28.7% died whilst only 23.0% of those requiring no support have since died ( $p=0.002$ )(Table 7). Recipients who were inpatient prior to LT were also more likely to die (25.7% vs 22.8% not-inpatients,  $p=0.004$ )(Table 7).

Recipient MELD showed an increased risk of recipient death in those with a lower MELD score <10 (26.2%) and 10-15 (24.6%) compared to higher MELD recipients

>20 (21.5%)( $p=0.001$ )(Table 7). Those with Grades 3-4 encephalopathy had poorer survival (27.3-27.7% died) whilst those with no encephalopathy or Grades 1 or 2 encephalopathy had slightly better outcomes (24.0%, 20.1% and 23.1% died respectively)( $p=0.001$ )(Table 7). Recipient sepsis status was associated negatively with recipient survival (31.9% with sepsis died vs 23.2% no sepsis,  $p<0.001$ )(Table 7).

Again as with graft survival, use of antifibrinolytic therapy had a negative effect on recipient survival (31.9% died vs 19.5% who had no anti-fibrinolytic therapy( $p<0.001$ )(Table 7).

The recipient liver diseases causing failure which were most likely associated with recipient death were metabolic causes (31.2% died), malignancy (27.9% died) and infective causes (26.7% died)( $p<0.001$ )(Table 7).

With regards to donor organ appearance as with graft survival a suboptimal organ appearance did not correlate on univariable analysis with higher proportion of recipients dead (26.1% vs 24.2%,  $p=0.140$ )(Table 7).

Cold ischaemic time similarly to graft survival can be seen to have a negative effect on recipient survival. As CIT increases recipient survival deteriorates (<6 hrs 18.9% died vs 8-12hrs 27.2% died and >12hrs 26.3% died,  $p<0.001$ )(Table 7).

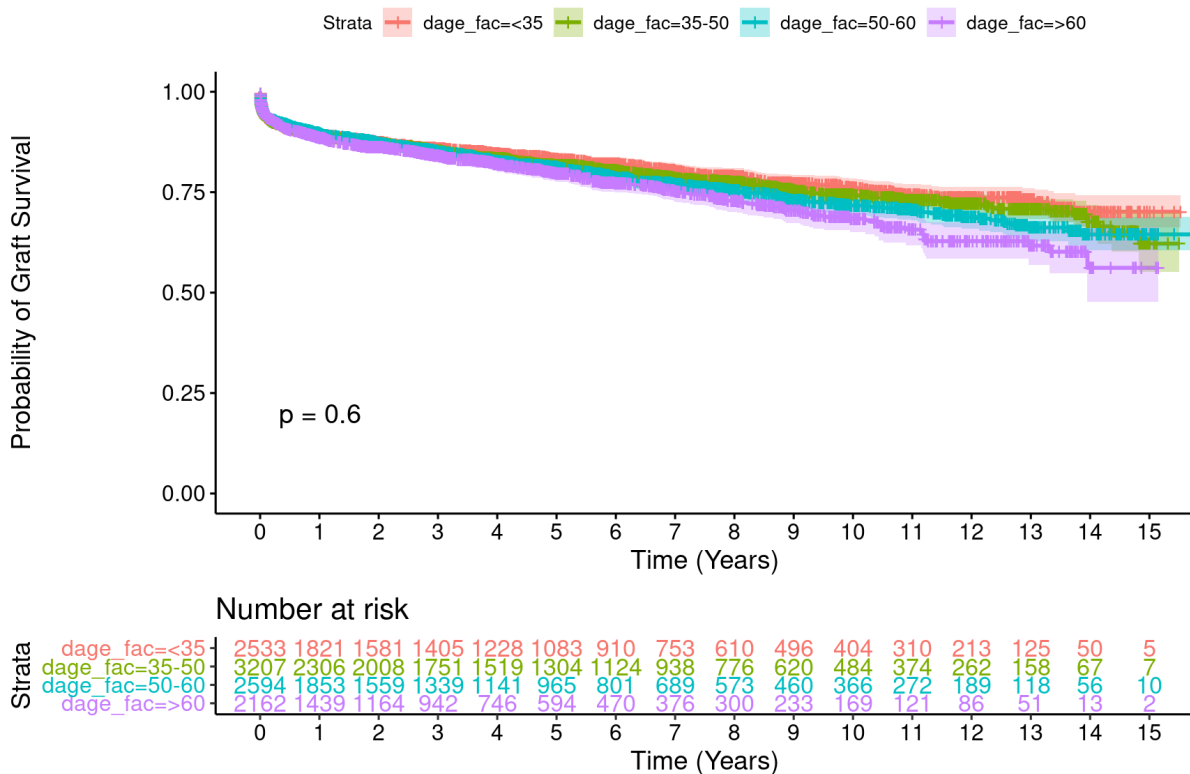
For multivariable analysis of recipient survival I again regardless of significant p value chose to remove variables that were not deemed clinically as relevant based on the literature when assessing the impact of donor age on survival. The variables removed included era of transplantation, donor and recipient CMV status, recipient grade of encephalopathy, preservation fluid ( $p<0.001$ ), anti-fibrinolytic therapy, and recipient primary liver disease.

The variables which were not statistically significant but I added on the basis of historical and clinical merit include UKELD ( $p=0.394$ ) and graft steatosis ( $p=0.865$ ).

### 3.5 Graft survival per Donor Age

To assess the effect of donor age on survival the continuous donor age variable was converted to a factor allowing 4 distinct groups to be analysed and compared using Kaplan-meier survival analysis. As shown in figure 5 survival in all groups can be seen to deteriorate over time.

Figure 5 – Graft survival per Donor Age



Overall probability of graft survival can be seen to deteriorate as donor age group increases (Figure 5). The oldest donor age group 60-86 years consistently post transplantation has poorer rates of graft survival and the 0-35 year old donor livers have the best survival (Figure 5). This result is not statistically significant (p=0.6) on KM analysis but logrank test shows significance with p=0.008.

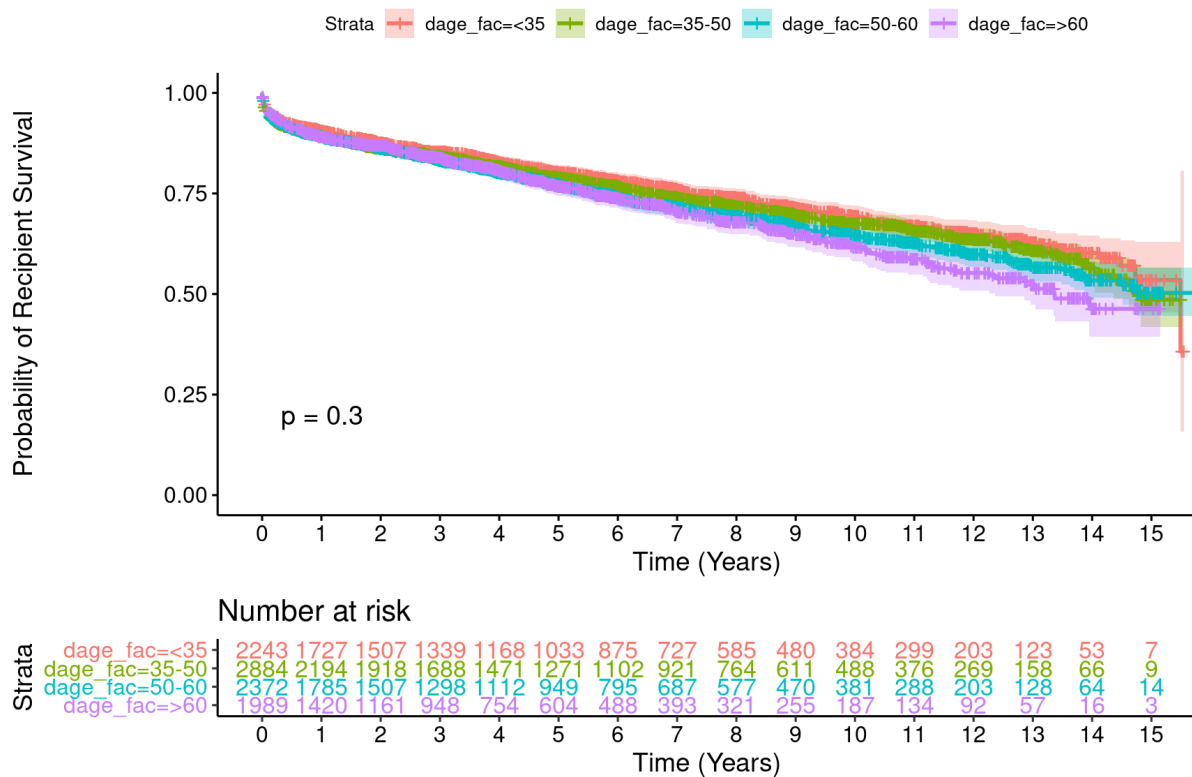
The 1, 3, 5 year and 10 year survival rates for graft survival are best for <35 year old donor grafts and poorest for >60 year old donor grafts. Rates of graft survival are 89.4%, 85.9%, 83.3% and 76.1% respectively for <35 year old donors. In

comparison rates of graft survival in the >60 year old donors are 88.5%, 84.1%, 79.6% and 68.4% respectively. The other donor age groups 35-50 and 50-60 years as expected from the KM curve show trends of gradually reducing survival as age increases and time progresses.

### 3.6 Recipient Survival per Donor Age

When analysing the KM-survival curve for recipient survival with respect to donor age group as the dependant variable (Figure 6) it is also evident that increasing donor age results in poorer recipient survival at all stages post-transplantation. The poorest probability of survival is evident in the 60-86 year old donor group and the best survival results are evident in the <35 year old donors (Figure 6). Test for trend ( $p=0.3$ ) showed low significance but the logrank test showed that this result is statistically significant ( $p=0.006$ ).

Figure 6 – Recipient Survival per Donor Age Group

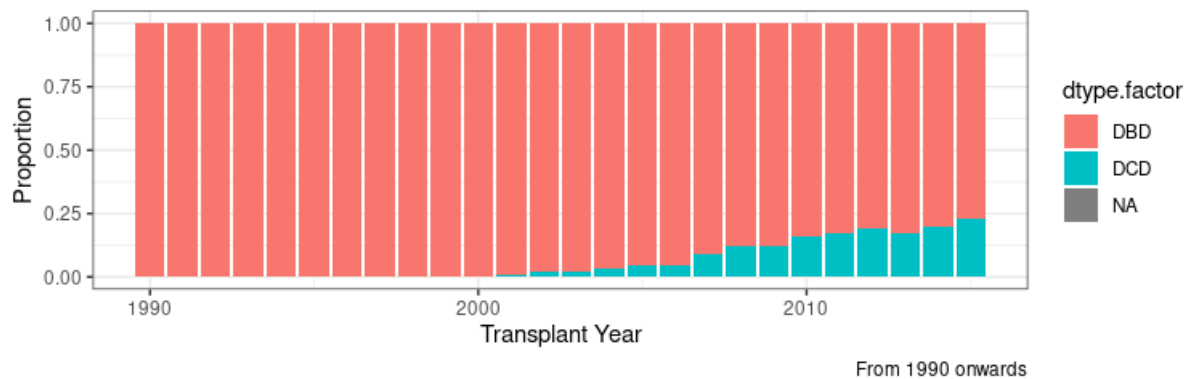


The 1, 3, 5 and 10 year recipient survival rates for <35 year old donor group are 90.6%, 85.3%, 80.2% and 69.4% respectively. In contrast at the opposite age spectrum with much poorer survival rates the >60 year old donor group has rates of 89.1%(year 1), 83.8% (year 3), 76.6% (year 5) and 61.6% (year 10).

## 4.0 Data 2 – Donation After Cardiac Death (DCD)

It is evident that since around 2001 DCD liver transplantation has become increasingly common as a proportion of all liver transplantations (Figure 7).

Figure 7 – Transplant type proportion per year



### 4.1 Donor demographics per Donor Type

Table 10 shows that 86.4% of DCD livers were transplanted >2008 and only 2.5% <2004 ( $p < 0.001$ ). Mean donor age was older in the DCD population ( $45.7 \pm 16.5$ SD vs  $42.8 \pm 16.0$ SD,  $p < 0.001$ ) (Table 10). However, as a proportion of the DCD group there were more in the <35 years (26.2%) and 35-50 years donor group (27.4%) than in the older groups 50-60 years and >60 years (23.6% and 22.8%,  $p < 0.001$ ) (Table 10). Only 1.1% of DCD livers were transplanted urgently vs 14.2% of DBD livers ( $p < 0.001$ ) (Table 10).

Table 10 – Donor Demographics DBD vs DCD

Donor Type		DBD	DCD	p
Era of Transplant	Pre-2004	8450 (54.0)	30 (2.5)	<0.001
	2004-2008	2315 (14.8)	132 (11.1)	
	Post-2008	4891 (31.2)	1025 (86.4)	
Donor Age	Mean (SD)	42.8 (16.0)	45.7 (16.5)	<0.001
Donor Age (Years)	<35	4869 (31.1)	311 (26.2)	<0.001
	35-50	4918 (31.4)	325 (27.4)	
	50-60	3396 (21.7)	280 (23.6)	
	>60	2411 (15.4)	271 (22.8)	

Donor Type		DBD	DCD	p
	(Missing)	62 (0.4)	0 (0.0)	
Urgent	No	13438 (85.8)	1174 (98.9)	<0.001
	Yes	2218 (14.2)	13 (1.1)	
Donor BMI	Mean (SD)	25.3 (4.8)	25.3 (4.6)	0.748
Donor Blood Group	O	7817 (49.9)	561 (47.3)	0.002
	A	5913 (37.8)	485 (40.9)	
	B	1422 (9.1)	125 (10.5)	
	AB	436 (2.8)	16 (1.3)	
	(Missing)	68 (0.4)	0 (0.0)	
Graft Steatosis	No	5433 (34.7)	715 (60.2)	0.001
	Yes	3727 (23.8)	396 (33.4)	
	(Missing)	6496 (41.5)	76 (6.4)	
Donor CMV Status	Negative	7440 (47.5)	624 (52.6)	<0.001
	Positive	7221 (46.1)	528 (44.5)	
	Indeterminate	5 (0.0)	2 (0.2)	
	Repeat Negative	0 (0.0)	0 (0.0)	
	Confirmed Positive	0 (0.0)	0 (0.0)	
	Test Result Awaited	41 (0.3)	12 (1.0)	
	Not Tested	21 (0.1)	0 (0.0)	
	Not Reported	289 (1.8)	3 (0.3)	
	Unknown	463 (3.0)	1 (0.1)	
	Non-specific Reactivity	0 (0.0)	0 (0.0)	
	(Missing)	176 (1.1)	17 (1.4)	
Cold Ischaemic Time (Hours)	<6h	2136 (13.6)	524 (44.1)	<0.001
	6-8h	2627 (16.8)	419 (35.3)	
	8-12h	5351 (34.2)	136 (11.5)	
	>12h	2781 (17.8)	98 (8.3)	
	(Missing)	2761 (17.6)	10 (0.8)	

Donor BMI was very similar across donor type and blood group was distributed normally as per the population with Group O most common and AB least common. Graft steatosis looked to be more common as a proportion of DCD donor livers with 32.3% affected compared with only 21.3% of the DBD group (p=0.001)(Table 10) although also there were more DCD with no graft steatosis and to compensate a large proportion of DBD donors had data missing for graft steatosis (41.5% vs only 6.4% of DCD donor livers). Donor CMV status was similar between DCD and DBD groups (44.5% and 44.6.1% positive)(Table 10).

Table 11 – Donor Cause of Death DBD vs DCD

Donor Type		DBD	DCD	p
Donor Cause of Death	Living Donor	0 (0.0)	0 (0.0)	<0.001
	Intracranial Haemorrhage	8976 (57.3)	522 (44.0)	
	Intracranial Thrombosis	203 (1.3)	25 (2.1)	
	Brain tumour/ injury	1975 (12.6)	359 (30.2)	
	Trauma RTA	2060 (13.2)	117 (9.9)	
	Trauma Other Cause	1158 (7.4)	60 (5.1)	
	Cardiovascular	222 (1.4)	23 (1.9)	
	Respiratory	69 (0.4)	23 (1.9)	
	Poisoning	51 (0.3)	3 (0.3)	
	Cancer (other than Brain Tumour)	7 (0.0)	0 (0.0)	
	Infection/ Sepsis	247 (1.6)	9 (0.8)	
	Acute Bloods Loss/ Hypovolaemia	1 (0.0)	0 (0.0)	
	Organ Failure	0 (0.0)	1 (0.1)	
	Sudden Infant Death Syndrome (SIDS)	0 (0.0)	0 (0.0)	
	Burns	0 (0.0)	1 (0.1)	
	Unknown	687 (4.4)	44 (3.7)	

DCD donors as a group had a higher proportion of donors who had died of Brain tumour/ brain injury compared to the DCD group (30.2% vs 12.6%)(Table 11). Although the largest proportion of DCD donors had died of intracranial haemorrhage (44.0%) this was the most common cause of death across all donors and made up a larger proportion of the DBD group (57.3%)(Table 11). Trauma following RTA accounted for 9.9% of DCD donors and 13.2% of DBD donors (Table 11).

#### 4.1 Recipient demographics per Donor Type

Recipient characteristics were reviewed depending on DCD or DBD donor type(Table 12). Both DBD and DCD had proportionally more transplantations to recipients in the 50-60 year age group. DCD donors were more often transplanted to older recipients >60 years (31.7% vs 20.4% of the DBD group) and less likely in

younger recipients <35 years (5.2% vs 15.4% of the DBD group)(p<0.001)(Table 12).

Table 12 – Recipient Demographics DBD vs DCD

Donor Type		DBD	DCD	p
Recipient Age (Years)	<35	2418 (15.4)	62 (5.2)	<0.001
	35-50	4859 (31.0)	276 (23.3)	
	50-60	5192 (33.2)	473 (39.8)	
	>60	3187 (20.4)	376 (31.7)	
Recipient Blood Group	O	6699 (42.8)	538 (45.3)	0.007
	A	6363 (40.6)	477 (40.2)	
	B	1794 (11.5)	138 (11.6)	
	AB	785 (5.0)	34 (2.9)	
	(Missing)	15 (0.1)	0 (0.0)	
Recipient Ethnicity Group	White	11551 (73.8)	984 (82.9)	<0.001
	Asian or Asian-British	983 (6.3)	117 (9.9)	
	Black or Black-British	329 (2.1)	37 (3.1)	
	Chinese/ Oriental	89 (0.6)	16 (1.3)	
	Mixed	9 (0.1)	1 (0.1)	
	Other/Unknown	2695 (17.2)	32 (2.7)	
Recipient CMV Status	Negative	4383 (28.0)	418 (35.2)	<0.001
	Positive	6922 (44.2)	699 (58.9)	
	Unknown	4308 (27.5)	70 (5.9)	
	(Missing)	43 (0.3)	0 (0.0)	
Recipient HCV Status	Negative	5570 (35.6)	107 (9.0)	<0.001
	Positive	1358 (8.7)	59 (5.0)	
	Unknown	8728 (55.7)	1021 (86.0)	
Recipient Ventilation Status	No	11388 (72.7)	1159 (97.6)	<0.001
	Yes	1500 (9.6)	18 (1.5)	
	(Missing)	2768 (17.7)	10 (0.8)	
Recipient Renal Support Status	haemodialysis	827 (5.3)	50 (4.2)	<0.001
	Filtration	1053 (6.7)	24 (2.0)	
	Not Required	10966 (70.0)	1104 (93.0)	
	(Missing)	2810 (17.9)	9 (0.8)	
Donor vs Recipient Blood Group	Identical	14000 (89.4)	1149 (96.8)	<0.001
	Compatible	1497 (9.6)	38 (3.2)	
	Incompatible	77 (0.5)	0 (0.0)	
	(Missing)	82 (0.5)	0 (0.0)	
Recipient Liver Failure Grade	Hyperacute	1285 (8.2)	15 (1.3)	<0.001
	Acute	620 (4.0)	4 (0.3)	
	Subacute	391 (2.5)	10 (0.8)	
	Not Acute	10479 (66.9)	1126 (94.9)	
	(Missing)	2881 (18.4)	32 (2.7)	
Recipient Lifestyle Activity Score	0	519 (3.3)	50 (4.2)	<0.001
	1	2524 (16.1)	485 (40.9)	
	2	5590 (35.7)	497 (41.9)	
	3	1823 (11.6)	90 (7.6)	
	4	2336 (14.9)	39 (3.3)	
	5	1 (0.0)	0 (0.0)	

Donor Type		DBD	DCD	p
	Not Reported	177 (1.1)	24 (2.0)	
	Unknown	8 (0.1)	1 (0.1)	
	(Missing)	2678 (17.1)	1 (0.1)	
Recipient Inpatient Status	No	8794 (56.2)	1042 (87.8)	<0.001
	Yes	4102 (26.2)	136 (11.5)	
	(Missing)	2760 (17.6)	9 (0.8)	
Recipient UKELD	Mean (SD)	55.6 (6.1)	53.8 (5.2)	<0.001
MELD Score	<10	1253 (8.0)	188 (15.8)	<0.001
	10-15	2940 (18.8)	364 (30.7)	
	15-20	2832 (18.1)	318 (26.8)	
	>20	3419 (21.8)	276 (23.3)	
	(Missing)	5212 (33.3)	41 (3.5)	
Recipient Ascites	No	6327 (40.4)	582 (49.0)	0.547
	Yes	6192 (39.6)	592 (49.9)	
	(Missing)	3137 (20.0)	13 (1.1)	
Recipient Diuretic Therapy Status	No	6439 (41.1)	543 (45.7)	<0.001
	Yes	6036 (38.6)	633 (53.3)	
	(Missing)	3181 (20.3)	11 (0.9)	
Recipient Encephalopathy Grade	Not Encephalopathic	8475 (54.1)	828 (69.8)	<0.001
	Grade 1	2150 (13.7)	261 (22.0)	
	Grade 2	777 (5.0)	62 (5.2)	
	Grade 3	430 (2.7)	6 (0.5)	
	Grade 4	922 (5.9)	12 (1.0)	
	(Missing)	2902 (18.5)	18 (1.5)	
Recipient Abdominal Surgery Indicator	No	9696 (61.9)	1080 (91.0)	<0.001
	Yes	3145 (20.1)	96 (8.1)	
	(Missing)	2815 (18.0)	11 (0.9)	
Recipient Oesophageal Varices	No Previous Variceal Bleed	4735 (30.2)	464 (39.1)	0.027
	Previous Variceal Bleed	3074 (19.6)	315 (26.5)	
	Not Present	4631 (29.6)	390 (32.9)	
	(Missing)	3216 (20.5)	18 (1.5)	
Recipient Shunt for Varices(if Present)	No Portosystemic Shunt	4505 (28.8)	363 (30.6)	0.026
	Surgical Shunt	70 (0.4)	1 (0.1)	
	TIPS	465 (3.0)	50 (4.2)	
	(Missing)	10616 (67.8)	773 (65.1)	
Recipient Sepsis Confirmed Indicator	No	11828 (75.5)	1146 (96.5)	<0.001
	Yes	653 (4.2)	28 (2.4)	
	(Missing)	3175 (20.3)	13 (1.1)	

Blood group was again distributed as would be expected in the population.

Recipients' ethnicity for both DBD and DCD groups was most commonly white (73.8% and 82.9% of LTs) with Asian or Asian-British second most prevalent (6.3% and 9.9%)(Table 12). DCD livers were much more likely to be used in a CMV positive recipient (58.9% DCD donors vs 44.2% DBD donors,  $p<0.001$ )(Table 12).

Conversely, they were less likely to be transplanted to HCV positive recipients (5.0% DCD LTs vs 8.7% DBD LTs,  $p < 0.001$ )(Table 12).

DCD livers were much more likely to be transplanted in recipients not ventilated (97.6% vs 72.7% DBD) and on no renal support (93.0% vs 70.0% DBD)( $p < 0.001$ )(Table 12). Identical ABO match was also much more likely in DCD LT (96.8% vs 89.4% DBD) and an increased proportion of DBD livers were in the compatible or incompatible groups (Table 12). Similarly, recipients with levels of acute liver failure (hyperacute 8.2% of DBD, acute 4.0% DBD, subacute 2.5% DBD) were more likely to have a DBD liver (Table 12). The majority of DCD livers were used for non-acute liver failure (94.9%)( $p < 0.001$ )(Table 12). Recipient lifestyle scores 1-2 were more common in the DCD group (Grade 1 40.9%, Grade 2 41.9%) whilst a higher proportion of DBD livers were from Grade 3 or 4 (11.6% and 14.9%)(Table 12). Proportionally fewer DCD transplantations occurred in recipients who were inpatients compared to DBD (11.5% vs 26.2%,  $p < 0.001$ )(Table 12).

Recipient MELD scores when comparing DBD and DCD groups showed that at all levels MELD scores were more likely associated with DCD transplantation, whilst missing data was more likely associated with DBD (33.3% MELD score missing vs only 3.5% DCD MELD scores missing) ( $p < 0.001$ )(Table 12).

DCD livers were more likely to be transplanted to recipients on diuretic therapy (53.3% vs 38.6% of DBD group,  $p < 0.001$ )(Table 12). When considering encephalopathy status, the DCD group had higher proportions in the non-encephalopathy groups and Grades 1 and 2 compared proportionally to the DBD group. The DBD group had a higher proportion transplanted to recipients with Grade 3 and 4 encephalopathy.

Recipients who had previous abdominal surgery were less likely to receive a DCD liver with only 8.1% of DCD liver transplanted to this group compared to 20.1% of the DBD group ( $P < 0.001$ )(Table 12).

Most of the DCD group were transplanted to recipients who did not have any confirmed sepsis prior to transplantation (96.5% vs 75.5% DBD LTs,  $p < 0.001$ ) (Table 12).

Missing data for variables including recipient ventilation status, renal support, grade of liver failure, recipient lifestyle scores, recipient inpatient status, diuretic therapy, encephalopathy, previous abdominal surgery, sepsis or oesophageal varices indicators were all markedly more likely in DBD transplantations. Around 20% of all DBDs had missing data for these variables compared with around 1-2% for DCD (Table 12).

Table 13 – Recipient Cause of Liver Failure DBD vs DCD

Donor Type		DBD	DCD	p
Recipient Primary Liver Disease	Unknown	494 (3.2)	32 (2.7)	<0.001
	Autoimmune	3032 (19.4)	248 (20.9)	
	Infective	2129 (13.6)	282 (23.8)	
	Genetic	473 (3.0)	36 (3.0)	
	Vascular	498 (3.2)	10 (0.8)	
	Benign Causes Liver Disease	3340 (21.3)	429 (36.1)	
	Congenital	58 (0.4)	4 (0.3)	
	Paediatric/ Neonatal Causes	7 (0.0)	0 (0.0)	
	Acute Hepatic Failure	1523 (9.7)	10 (0.8)	
	Fulminant Hepatic Failure	0 (0.0)	0 (0.0)	
	Malignancy	815 (5.2)	124 (10.4)	
	Metabolic	104 (0.7)	5 (0.4)	
	Rejection	505 (3.2)	6 (0.5)	
	(Missing)	2678 (17.1)	1 (0.1)	

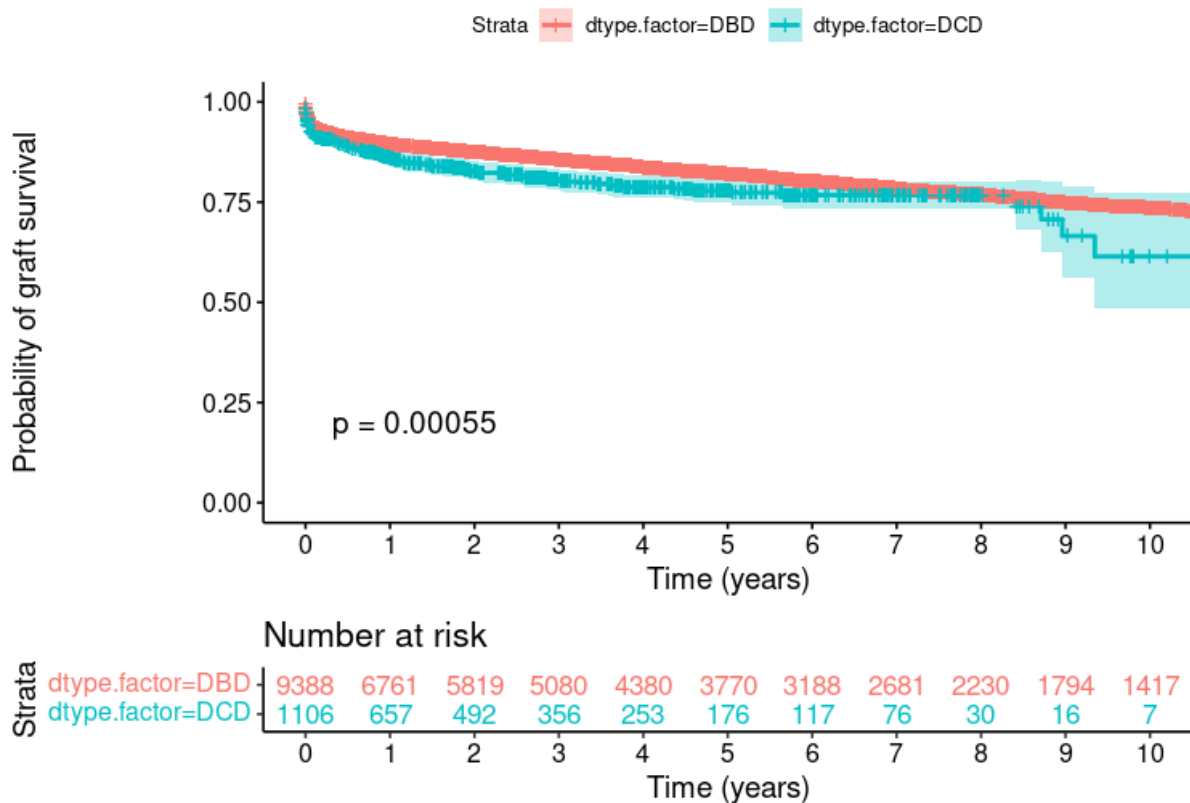
The highest proportion of DCD livers were transplanted to recipients who had benign causes of liver failure (36.1%) (Table 13). DBD livers were more likely to be used in recipients compared to DCD livers who had acute hepatic failure (9.7% vs 0.8%) and

DCD livers were more likely to be used in recipients with malignancy (10.4% vs 5.2%)(Table 13).

#### 4.2 Graft survival DCD vs DBD

Graft survival on KM analysis shows consistently poorer graft survival probability in DCD liver transplantations when compared to the DBD donor transplants (Figure 8). Test for trend and logrank tests show that this is indeed statistically significant ( $p < 0.001$ ).

Figure 8 – Kaplan Meier Graft Survival Curve: DBD vs DCD



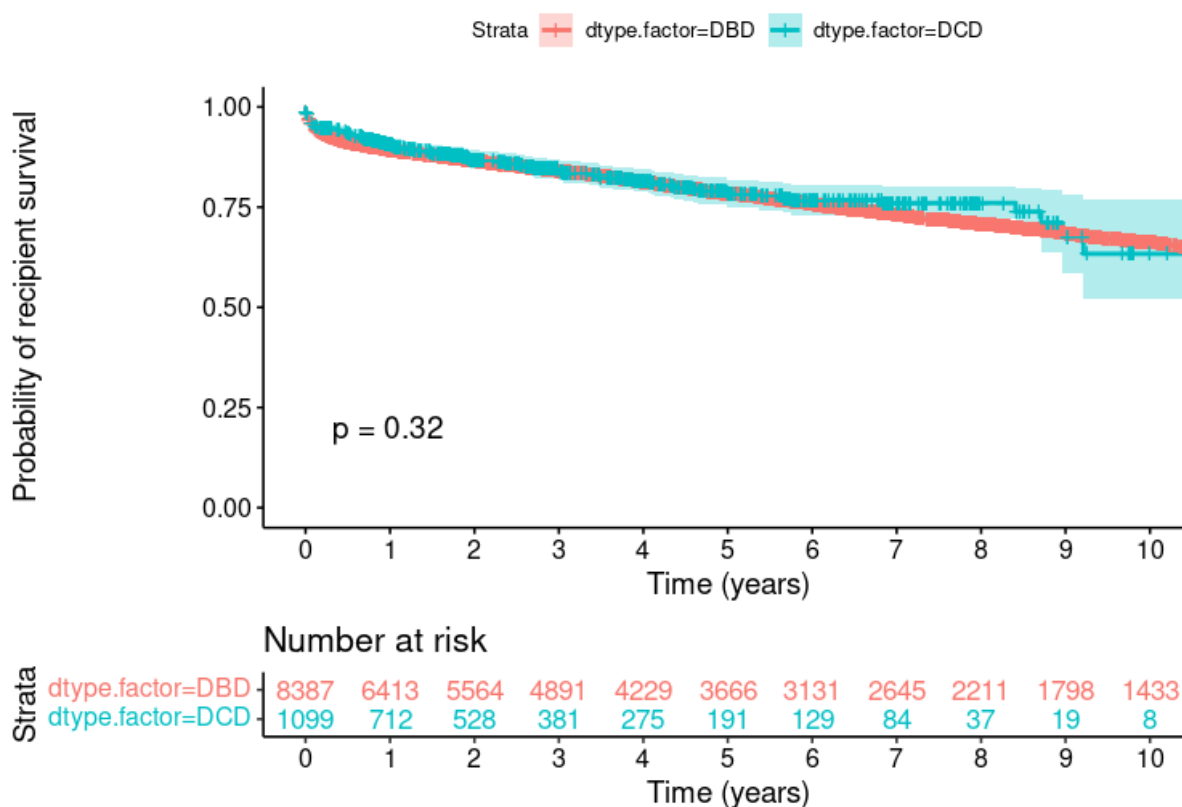
The 1, 3, 5 and 10 year graft survival rates for DBD were 89.6%, 85.7%%, 82.1% and 73.6% respectively.

The 1, 3, 5 and 10 year survival rates for DCD were 86.2%%, 80.6%, 77.8% and 61.4% respectively.

### 4.3 Recipient Survival DCD vs DBD

Recipient survival on KM survival analysis shows DCD recipients also with a higher probability of survival than DBD transplantations (Figure 9). This obviously looks at Donor type as an individual variable with no other co-variates taken into account. Logrank test shows that this result is not statistically significant ( $p=0.3$ ).

Figure 9 – Kaplan Meier Recipient Survival Curve: DBD vs DCD



The 1, 3 and 5 year recipient survival rates for DBD liver transplantation were 89.3%, 84.1% and 78.4% respectively.

The 1, 3 and 5 year recipient survival rates for DCD transplantation were 90.6%, 84.3% and 78.3% respectively.

## 5.0 Data 3 – Multivariable Analysis

The variables of study, donor age and donor type, were shown to affect graft survival rates with significance demonstrated with Logrank test (increased donor age  $p=0.008$  and DCD LT  $p=0.006$ ). Increased donor age negatively affected graft survival rates ( $p<0.001$ ). However, these were based on univariate analysis with no allowance made for confounding variables. To incorporate important variables into assessment of both older donor age impact and DCD impact the appropriate variables were chosen from univariate analysis (significant statistically), excluded on basis of not in the literature, or added on basis of weight in literature in previous studies.

As a result, the list of variables analysed in graft survival multivariable analysis were – donor age group, donor type (DCD vs DBD), graft steatosis, recipient Hepatitis C Virus status, recipient ventilation status, recipient inpatient status, recipient sepsis status, organ appearance at time of operation, recipient previous abdominal surgery status, meld score group and cold ischaemic time.

Analysis of recipient survival incorporated similar variables but with the exclusion of recipient abdominal surgery status and the addition of recipient renal support status.

### 5.1 Multivariable Analysis – Graft Survival

Donor age on cox proportional hazards model for graft survival showed a significant increase in the probability of graft failure between the youngest and oldest donor age group. Those in the oldest 60-86 year donor age group showed 29% increase in the risk of failure compared to the <35 year donor age group (HR 1.29, CI 1.09-1.53,  $p=0.004$ )(Table 8).

For DCD donors there was also a persistent poorer graft survival compared to DBD donors when adjusting for co-variates (HR 1.69, CI 1.40-2.04,  $p<0.001$ ).

Table 8 – Cox Proportional Hazards Model Graft Survival

Graft survival			HR (univariable)	HR (multivariable)
5	Donor Age (Years)	<35	2596 (24.0)	●
7		35-50	3291 (30.4)	1.07 (0.95-1.22, p=0.252)
8		50-60	2665 (24.6)	1.14 (1.00-1.29, p=0.051)
6		>60	2267 (21.0)	1.26 (1.10-1.44, p=0.001)
9	Donor Type	DBD	9635 (89.1)	●
10		DCD	1182 (10.9)	1.30 (1.12-1.51, p=0.001)
28	Graft Steatosis	No	6150 (59.9)	●
29		Yes	4123 (40.1)	1.08 (0.98-1.19, p=0.104)
19	Recipient HCV Status	Negative	3771 (34.9)	●
20		Positive	966 (8.9)	1.42 (1.24-1.63, p<0.001)
21		Unknown	6083 (56.2)	0.89 (0.81-0.99, p=0.027)
26	Recipient Ventilation Status	No	9615 (89.8)	●
27		Yes	1098 (10.2)	1.23 (1.07-1.42, p=0.003)
22	Recipient Inpatient Status	No	7633 (71.2)	●
23		Yes	3080 (28.8)	1.17 (1.07-1.29, p=0.001)
24	Recipient Sepsis Confirmed Indicator	No	10172 (95.3)	●
25		Yes	498 (4.7)	1.51 (1.25-1.81, p<0.001)
15	Donor Organ Appearance	Healthy	7447 (79.1)	●
16		Suboptimal	1965 (20.9)	1.36 (1.22-1.52, p<0.001)
17	Recipient Abdominal Surgery Indicator	No	8460 (79.2)	●
18		Yes	2216 (20.8)	1.47 (1.33-1.63, p<0.001)
11	MELD Score	<10	1227 (13.7)	●
13		10-15	2618 (29.2)	0.97 (0.83-1.14, p=0.712)
14		15-20	2410 (26.8)	0.93 (0.79-1.09, p=0.359)
12		>20	2721 (30.3)	1.03 (0.88-1.21, p=0.726)
1	Cold Ischaemic Time (Hours)	<6h	2292 (21.4)	●
3		6-8h	2685 (25.1)	1.09 (0.95-1.26, p=0.208)
4		8-12h	4140 (38.7)	1.11 (0.98-1.26, p=0.094)
2		>12h	1580 (14.8)	1.07 (0.91-1.25, p=0.417)

Other variables which showed significant impact on graft survival included Hepatitis C positive status of the recipient (HR 1.47, CI 1.27-1.71, p<0.001). For recipients where the HCV status was unknown this reduced risk of graft failure by ~10% although not statistically significant (HR 0.88, CI 0.79-1.03, p=0.121).

Grafts transplanted where a recipient was an inpatient at the time of LT had poorer survival (HR 1.17, CI 1.01-1.36, p=0.032). Recipients who had previous abdominal surgery also correlated with poorer graft survival (HR 1.39, CI 1.23-1.58, p<0.001). Donor organ appearance as determined by the operating surgeon was detrimental to graft survival where the graft was labelled “suboptimal” (HR 1.32, CI 1.16-1.51, p<0.001) when compared to a “healthy” appearing graft.

As MELD increased these appeared to cause an increased hazard of graft failure, with MELD >20 showing HR 1.07 or 7% increased risk of graft failure compared to

MELD <10. None of these results, however, were statistically significant on cox regression analysis.

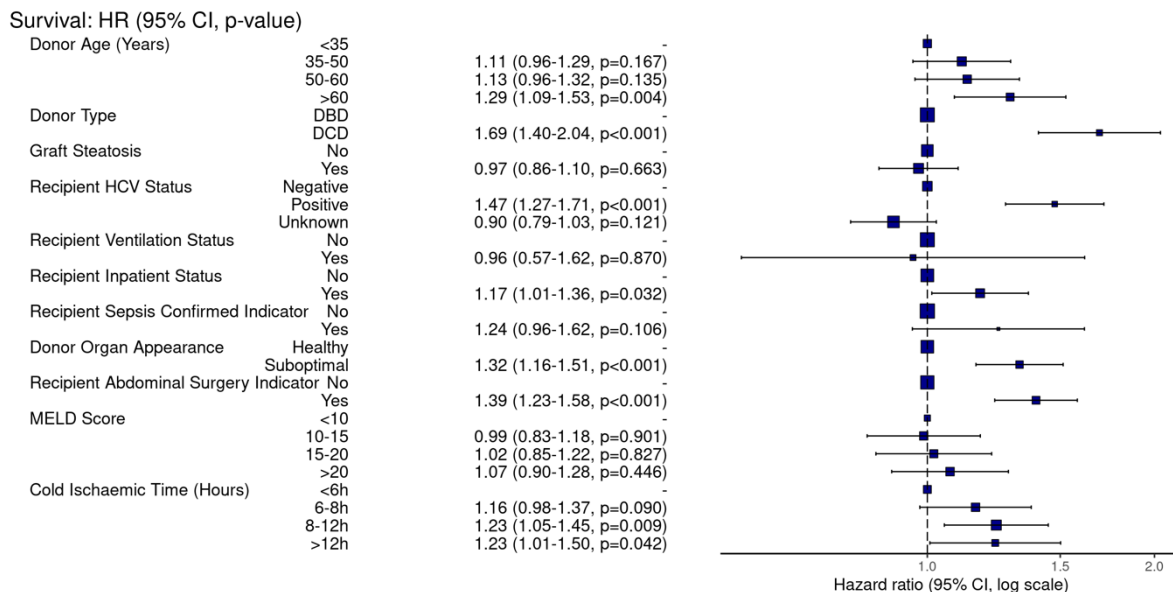
Cold ischaemic time impacted negatively on graft survival and this became statistically significant where CIT was longer than 8 hours. When compared to the <6hrs CIT group the 8-12hour CIT group (HR 1.23, CI 1.05-1.45, p=0.009) and the >12hrs CIT group (HR 1.23, CI 1.01-1.50, p=0.042) both showed statistically significant increase in the odds of graft failure.

It is worth noting that there were 7295 transplantations passed to the model with 1383 events. Unfortunately there were 3525 observations excluded due to missing data.

Table 8 shows the final fit multivariable analysis using cox proportional hazards for the chosen variables and the corresponding hazard ratio plot (Figure 10) helps to visualise this.

The concordance for this cox-regression model for multivariate analysis was 0.597 suggesting that the model was to some degree able to draw reasonable conclusions about event data. (able to predict 59.7% of survival events). The likelihood ratio test (137 on 18df), Wald Test (146.1 on 18df) and Score (Logrank) test (147.1 on 18df) are all similar as would be expected with this larger model. These test all have a significance level of  $p < 0.0001$  and so this suggests that the model is statistically significant.

Figure 10 – Graft Survival HR Plot



## 5.2 Multivariable analysis – Recipient Survival

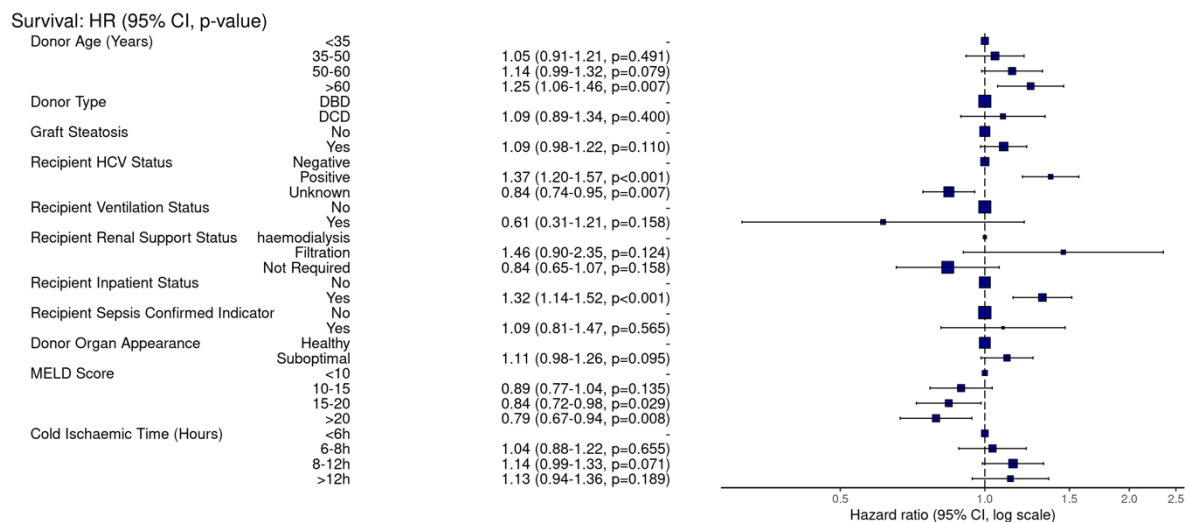
As already described in the univariable analysis chapter, the variables passed into the recipient survival multivariable analysis were – donor age group, donor type (DCD vs DBD), graft steatosis, recipient Hepatitis C Virus status, recipient ventilation status, recipient renal support status, recipient inpatient status, recipient sepsis status, donor organ appearance at the time of transplantation, meld score group and cold ischaemic time.

Table 9 – Cox Proportional Hazards Model Recipient Survival

Recipient survival			HR (univariable)	HR (multivariable)
5	Donor Age (Years)	<35	2596 (24.0)	●
7		35-50	3291 (30.4)	1.09 (0.97-1.22, p=0.146)
8		50-60	2665 (24.6)	1.18 (1.05-1.33, p=0.006)
6		>60	2267 (21.0)	1.23 (1.08-1.40, p=0.002)
9	Donor Type	DBD	9635 (89.1)	●
10		DCD	1182 (10.9)	0.92 (0.79-1.08, p=0.324)
29	Graft Steatosis	No	6150 (59.9)	●
30		Yes	4123 (40.1)	1.10 (1.01-1.20, p=0.024)
17	Recipient HCV Status	Negative	3771 (34.9)	●
18		Positive	966 (8.9)	1.38 (1.22-1.56, p<0.001)
19		Unknown	6083 (56.2)	0.84 (0.76-0.93, p<0.001)

Recipient survival			HR (univariable)	HR (multivariable)
27	Recipient Ventilation Status	No	9615 (89.8)	●
28		Yes	1098 (10.2)	1.19 (1.03-1.36, p=0.015)
23	Recipient Renal Support Status	haemodialysis	574 (5.4)	●
22		Filtration	866 (8.1)	1.21 (0.96-1.52, p=0.105)
24		Not Required	9257 (86.5)	0.84 (0.70-1.01, p=0.069)
20	Recipient Inpatient Status	No	7633 (71.2)	●
21		Yes	3080 (28.8)	1.14 (1.04-1.25, p=0.007)
25	Recipient Sepsis Confirmed Indicator	No	10172 (95.3)	●
26		Yes	498 (4.7)	1.40 (1.15-1.70, p=0.001)
15	Donor Organ Appearance	Healthy	7447 (79.1)	●
16		Suboptimal	1965 (20.9)	1.20 (1.08-1.33, p=0.001)
11	MELD Score	<10	1227 (13.7)	●
13		10-15	2618 (29.2)	0.88 (0.77-1.02, p=0.083)
14		15-20	2410 (26.8)	0.80 (0.69-0.92, p=0.002)
12		>20	2721 (30.3)	0.85 (0.74-0.99, p=0.033)
1	Cold Ischaemic Time (Hours)	<6h	2292 (21.4)	●
3		6-8h	2685 (25.1)	1.01 (0.88-1.16, p=0.902)
4		8-12h	4140 (38.7)	1.13 (1.00-1.27, p=0.052)
2		>12h	1580 (14.8)	1.15 (0.99-1.33, p=0.067)

Figure 11 – Recipient Survival HR Plot



Increasingly donor age remains significant in affecting recipient survival on multivariable analysis. Transplantations from the >60 year donor age group are most likely to be associated with recipient death (HR 1.25, CI 1.06-1.46, p=0.007)(Table 9,

Figure 11). Transplantations from the 35-50 donor group (HR 1.05, CI 0.91-1.21,  $p=0.491$ ) and the 50-60 year old donor group (HR 1.14, CI 0.99-1.32,  $p=0.079$ ) show the trend for increased risk to survival correlating with increasing donor age (Table 9, Figure 11) but these are not statistically significant.

For recipient survival DCD does not show any statistical significance of impact (HR 1.09, CI 0.89-1.34,  $p=0.40$ ) when compared to DBD and other co-variables accounted for (Table 9, Figure 11). On univariate analysis DCD transplantation also showed no statistically significant difference.

As for graft survival, positive recipient HCV status also significantly increases risk of recipient death (HR 1.37, CI 1.20-1.57,  $p<0.0001$ ). Again, it is interesting to note that if HCV status is unknown this has a slightly greater likelihood of recipient survival (HR 0.84, CI 0.74-0.95,  $p=0.0007$ ). Recipient inpatient status significantly negatively impacted on recipient survival (HR 1.32, CI 1.14-1.52,  $p<0.0001$ ) (Table 9, Figure 11). Organ appearance determined by the operating surgeon did not have statistical significance in predicting poorer recipient survival where the organ was deemed to be "suboptimal" (HR 1.11, CI 0.98-1.26,  $p=0.095$ ), when allowing for confounders in multivariable analysis despite significance independently.

As MELD score increases rates of recipient survival looked better on multivariate analysis. MELD 15-20 (HR 0.84, CI 0.72-0.98,  $p=0.029$ ) and MELD >20 (HR 0.79, CI 0.67-0.94,  $p=0.008$ ) both showed statistical significance in lower rates of associated recipient death (Table 9, Figure 11). Cold ischaemic time did not significantly affect recipient survival when considering other confounding factors.

In the multivariate cox-regression model to assess recipient survival there were many missing observations which were deleted from the analysis (10031 observations excluded, 6816 transplantations with 1627 recipient survival events).

Model fit for the cox-proportional hazards was very similar to that for graft survival. Concordance was 0.566 suggesting a 56.6% likelihood of predicting survival events.

The likelihood ratio test (95.5 on 19df), Wald Test (100.5 on 19df) and Score (Logrank) test (101.4 on 19df) are again similar and were all statistically significant ( $p < 0.0001$ ).

## 6.0 Discussions

The quantitative methods in this study aimed to determine the relationships between graft or recipient survival and the variables affecting these. The main variables of interest were Donor Age and Donation after Cardiac Death. This study also allowed incorporation of other variables into multivariable analysis to determine any that had important correlations impacting graft and recipient survival.

### 6.1 Donor age – significant demographics

On average a donor age of >60 years was considered extended criteria in the literature (10, 20) and so this was the chosen cut off in this analysis. On review of donor age it was noted that donors in the oldest groups were transplanted to older recipients and younger donors to younger recipients (Table 3). There was still however a proportion of >60 yrs old donors transplanted to youngest <35yrs recipient age group (9.5%)(Table 3). This demonstrates nicely the role for marginal livers in particular of advanced age in attempting to fill waiting list gaps.

Trends in donor liver allocation were observed and older donor livers (>60 years) were more likely to be allocated to recipients who were not ventilated prior to transplantation, who were less likely to have acute liver failure, no renal support, not inpatients at time of LT, ABO identical and with lower lifestyle scores (Table 3). Similarly older donor livers were more likely to be transplanted to recipients who did not have ascites, were not encephalopathic and who were not on any diuretic therapy prior to transplantation (Table 3). This is all suggestive that although older donor livers were still utilised, that they were allocated to hosts with 'better conditions'. It has been suggested that careful donor and recipient matching should take place (12, 25, 26, 31, 32, 49) to avoid matching a potentially extended criteria donor liver graft to a recipient with hostile conditions which may over-stress the graft. Younger donor livers were also transplanted more often where a recipient had previous abdominal surgery. This suggests a consideration to pair a liver that could withstand longer ischaemic periods during a more technically challenging and thus

prolonged transplantation. Khorsandi *et al* noted that DCD grafts were avoided in such situations where technical issues contributing to longer operations may exacerbate the effects of ischaemic times and therefore IRI(58).

As donor age increased there was an increasing likelihood of being CMV positive (63.0% of >60yrs donors vs 33.1% of <35 years old)(Table 1) and this appeared independently on univariable analysis to have a negative impact on graft and recipient survival (Table 6, Table 7) . It would therefore be difficult to separate whether increased donor age, positive CMV status or both were responsible for these outcomes when these variables are correlated. Also, in a similar theme, graft steatosis increased with donor age although this did not independently appear to affect graft or recipient survival. Older donor livers were also more likely to be DCD grafts (Table 1).

The most common cause of death in donors was intracranial haemorrhage across age groups but more so in older donors (Table 2). As expected from the literature younger donors were much more likely to die of “Trauma/RTA” (33.1% of donors <35 years; only 2.1% of >60yrs)(Table 2). The increased number of intracranial haemorrhage deaths paired with an increase in older donor grafts and DCD grafts (discussed later) all correlate with the observation that donors are no longer “ideal”(3, 5-7).

There were some differences in recipient cause of failure and allocated donor liver age. Older donor livers were more likely to be transplanted to a recipient who had a benign cause of liver failure (32.3% of >60yr old donors)(Table 4). Across other donor age groups these liver grafts were allocated fairly evenly in other causes of recipient liver failure.

## 6.2 Donor age – effect on graft and recipient survival

On univariate analysis of donor age there was no significant difference in the rate of graft failure in the oldest groups >50years (19.0%) and >60 years (18.6%) compared to the younger groups <35 years (17.4%)(p=0.478)(Table 6). Kaplan Meier survival

curves showed a linear deterioration in graft survival with increasing donor age (Figure 7) with poorest survival in the >60 year donor group. Test for trend ( $p=0.6$ ) suggests that this was not significant, but a Logrank test did show significance ( $p=0.008$ ). There was also poorer recipient survival increasing as donor age increased in this study of UK liver transplantations. This is evident on KM curves and in poorer 1, 3 and 5 year survival rates as donor age increases and a Logrank test suggested significance as an independent variable ( $p=0.006$ ). The poorest survival rates at all stages post transplantation were in the >60 year old donor group (Figure 8).

Similar results were found in single centre studies (14) and larger studies of transplantation databases including UNOS (33), Eurotransplant (31) and SRTR (39). The chosen donor age cut-off varied but most followed a similar design in assessing univariate effect of donor age on graft and recipient survival and then a multivariable analysis including a variety of other important variables. A 3-centre study in the United States also showed poorer graft survival in donors >50 years of age both on univariate and multivariate analysis (22). NHSBT data analysed was able to show significance for outcome differences above a donor age of 60 years. Pratschke highlighted this well in that although graft (and recipient) survival generally became poorer with increasing donor age that no particular “cut-off” could predict the threshold at which this was clinically most significant(31). In the graft survival KM curves plotted (Figure 7) it can be seen that decline in survival is gradual with no sudden step-change in keeping with this.

A conscious decision was made not to alter donor age groups or the age at which donor age was considered an “older” donor. This was to ensure that there was no artificial manipulation of data purely to look for significant results. In the literature there are studies that concluded donor ages as low as 45(34) or 46(30) or even 25-30 years(36) were considered an “older” donor and logically this does not seem in keeping with what would traditionally be described as “older”. The hypothesis for donor age as a variable was that age >60 would impact on graft and recipient

survival and this was evident on univariable analysis in this study, although statistical significance was not strong.

There is no one consensus in the literature other than a general indication that increasing donor age may cause poorer outcomes including graft and recipient survival. Careful recipient selection can aid in optimising these outcomes when using an older donor liver.

### 6.3 DCD – Significant demographics

DCD transplantation can already be shown to be more frequently utilised in recent years (52). Proportionally DCD accounts for an increasing number of LTs each year (Figure 7) accounting for ~20% of LTs in Europe (51). The majority of DCD LTs occurred >2008 (Figure 7). Frequently DCD donor age is younger (66) and associated recipient age is higher(66). Only 1.1% of DCD livers were transplanted urgently compared to 14.2% of DBD livers ( $p<0.001$ ).

Presence of graft steatosis or CMV infection were similar in DBD and DCD grafts. Generally DCD grafts with steatosis present on pre-transplantation biopsy are rejected(64) which may account for this subsequent effect on similar outcomes.

DCD donor livers were more often transplanted to older recipients 50-60 years (39.8% DCD) or >60 years (31.7% vs 20.4% of the DBD group) and less likely in younger recipients 18-35 years old (5.2% vs 15.4% of the DBD group)( $p<0.001$ )(Table 12). This fits with earlier speculation that DCD are potentially seen as extended livers with poorer long-term survival and may be felt not suitable for younger recipients with longer life ahead.

Conversely, DCD livers were less likely to be transplanted to HCV positive recipients. There are suggestions that in combination DCD and HCV are associated with poor outcomes (65) and so this may account for the trends in decision making in this dataset. DCD donor grafts were more likely to be transplanted where the

recipient has HCC with 10.4% to recipients with malignancy compared to 5.2% of DBD grafts (Table 13). This correlates with the literature and in general DCD livers are transplanted where the recipient has chronic liver disease or HCC (58, 62, 63, 66).

There was an evident similarity to the older donor cohort, with DCD donor organs more likely to be transplanted to recipients with healthier or less acute pre-transplantation state. DCD livers were more likely to be transplanted to recipients who were not ventilated, on no renal support, identical ABO match with donor, no acute liver failure, lifestyle scores of 1-2, and not inpatients at the time of LT. Again, this is likely to suggest that DCD are deemed of less quality or less able to withstand further stress/insult in the host body. A common theory is that the DCD graft has already tolerated varying degrees of ischaemic injury and so the recipient pairing is often chosen to avoid further insult where the graft may not recover (11, 58). Previous abdominal surgery provides such an extended technical challenge and so DCD were transplanted more often in virgin abdomens likely to avoid further prolonging ischaemic times(58).

Mathur *et al* described traumatic injury as the most common donor cause of death in DCD donors (61). Foley (2005) noted more anoxic encephalopathy as COD in DCD vs DBD (27.8% vs 14%,  $P < 0.01$ )(69). In this dataset intracranial haemorrhage was the most common cause of death followed by brain injury or tumour.

Many of the studies suggesting equivocal outcomes in DCD transplantation vs DBD suggested that this should be in the context of pairing DCD with a low risk recipient (51, 67, 68) or with lower risk and not extended criteria DCD grafts(66). In a study at UCLA in particular grafts were only transplanted if they had a donor age  $< 40$  years and very favourable criteria such as low BMI and short hospital stay pre-retrieval (68). Mateo *et al* studied groups of DCD donors who were in the younger age category and who had low CIT in order to match the DBD control group survival outcomes(67) in order to develop a risk score (RCRR; recipient cumulative relative risk). Although previous DCD survival outcomes were poorer than DBD when

unselected, choosing low RCRR in addition to a low risk DCD (low WIT and low CIT) they were able to demonstrate good outcomes(67). Conversely, De Vera noted that WIT >20min, CIT >8h and donor age >60years were all associated with poorer DCD outcomes(71).

#### 6.4 DCD – effect on graft and recipient survival

Graft survival continues to be affected by DCD status of the donor as shown in the KM survival curve (Figure 8) and univariate analysis (Table 6). The poorest outcomes are in the DCD group when compared to DBD and logrank test for trend shows statistical significance ( $p<0.001$ ). A number of studies also found DCD grafts to be substandard when compared to DBD in graft survival (50, 67, 69-71).

On multivariable analysis when considering other covariates DCD still resulted in poorer graft survival (Table 8). DBD graft survival at 1, 3 and 5 years was 89.6%, 85.7% and 82.1% respectively and DCD graft survival was 86.2%, 80.6% and 77.8% in comparison.

Pine *et al* found that recipient survival is also affected negatively by DCD transplantation(70) but conflicting studies such as the single centre analysis by de Vera show no difference when compared to DBD(71). The findings in this study of NHSBT data show that there is no statistically significant difference in recipient survival between DCD vs DBD LTs. On univariable analysis a higher proportion of DBD donor recipients had died compared with DCD (24.7% vs 14.9%,  $p<0.001$ ). KM survival curve analysis seemed to correlate with this finding but logrank test ( $p=0.3$ ) showed no statistical difference (Figure 9). When other covariates are taken into account, in the multivariable analysis, this effect continues and there is no statistically significant difference in recipient survival between DCD and DBD transplantations (HR 1.09, CI 0.89-1.34,  $p=0.400$ ).

In general, when considering DCD transplantation, although studies are at times conflicting, it is apparent that the criteria used to determine suitable DCD and subsequent recipient selection are variable in other units.

## 6.5 Univariable analysis showing factors significant in graft and recipient survival

When determining the models for multivariable analyses, it was felt important that clinically significant variables frequently cited in the literature were included.

Univariate analysis was then used to determine which covariates would form part of the multivariable analysis in addition to the variables of interest, donor age and donor type (DCD vs DBD). There were a number of variables that showed statistically significant results affecting both graft and recipient survival.

Very large multivariable analyses with too many covariates should be avoided as they are unselective and can be misinterpreted clinically and show significant results that do not translate into the real world. The outputs of these models show less significance or quality of "fit" and so the techniques here aimed to choose the best variables to answer our clinical questions. On review of the literature many of these were not common factors forming part of other analyses and so the decision was taken to remove any significant but not commonly discussed variables. A number of these such as recipient ascites, encephalopathy, renal support, preservation fluid, and antifibrinolytic therapy are all important in decision making regarding matching of organs but did not occur frequently when looking at donor age or DCD papers. Donor and recipient CMV or HCV status all showed poorer graft survival where the recipient was positive. HCV was the variable included in the analysis as the more commonly discussed variable in the literature(11, 28, 33, 35). As already discussed, CMV in both the donor and recipient increased with age so it was felt that it would be difficult to separate these out as cause/effect for the purpose of survival analysis.

Donor cause of death was removed from multivariable analysis as although significance was high with  $p < 0.001$  at univariable analysis there was no reliable method to interpret the variation. There were a high number of categories and

although observations were made in the results sections there were no clear patterns that could be explained clinically or with any certainty. There will also be many unknown variables regarding donor cause of death and recipient cause of liver failure due to the large number of causes listed but the overlapping pathophysiology for many of them. Similarly anti-fibrinolytic therapy status was removed as there was no further information available as to whether this was given to donor or recipient, at what stage in the process, dosage or frequency details or any clinical indications for this. As a result, only assumptions could be made about why this was given whether to counteract effects of poor vasculature or to prevent thrombosis during long WIT or other difficulties.

Variables that were added despite statistically insignificant results were MELD scores, presence of graft steatosis and the type of donor (DCD did not show significantly relevant negative impact on recipient survival in this study). This ensured that important variables in the literature already studied by many groups could be accounted for in this analysis.

Although increasing MELD score has been shown to correlate with poorer survival outcomes (19) univariable analysis of MELD in this dataset showed alternative results. There was no difference to graft survival across MELD score groups (<10, 10-15, 15-20 and >20). Recipient MELD showed an increased risk of recipient death in those with a lower MELD score <10 (26.2%) and 10-15 (24.6%) compared to higher MELD recipients >20 (21.5%)( $p=0.001$ )(Table 7). This seems counterintuitive given a lower MELD score should suggest a recipient in better clinical condition or less at risk of waiting list mortality (19).

When considering era of transplantation on univariable analysis it can be noted that LTs taking place in more recent years >2008 survival was significantly better despite the donor age or DCD status. This could be multifactorial in that more recent years should correlate with better techniques and policies to maximise survival. There will also be an element of time impacting on how long an organ has been followed up; LTs in more recent years will not have had enough time yet to fail or have the

recipient die. Also, earlier years pre-2000 were filtered out due to lots of missing data. Conversely these early years would have longer follow-up times and potentially more complete survival data and may have falsely inflated effects of variables compared to later years with missing variables.

Recipient sepsis status was shown to negatively affect graft and recipient survival perhaps suggesting that sicker recipients pre-operatively had poorer outcomes and were more likely to die regardless of liver transplantation.

Cold ischaemic times were shown to cause poorer graft and recipient survival and were included therefore in the multivariable analysis as an important factor in previous studies showing similar results (17).

## 6.6 Multivariable analysis

A Cox Proportional Hazards analysis was performed for multivariable analysis to allow “time to event” analysis of graft and recipient survival outcomes rather than a binary analysis with logistic regression. The model used allowed comparison between univariable and multivariable analyses of these variables.

### 6.6.1 Graft Survival

When assessing graft survival and adjusting for confounding variables the factors that impacted negatively on graft survival were increasing donor age, DCD transplantation, HCV positive recipient status, donor organ “suboptimal” appearance (determined by the operating surgeon), MELD score >20 and increasing CIT. Older donors have the poorest graft survival outcomes with a 29% risk of graft failure compared with younger (<35 year old) donors (HR 1.29, CI 1.09-1.53,  $p=0.004$ )(Table 8). From the youngest to the oldest donor age groups survival becomes poorer in an almost linear fashion deteriorating with each increase in age group. Increasing donor age has been shown in many centres to be a significant factor affecting graft survival (17, 22, 23, 31, 33, 38-41).

DCD compared to DBD also had a negative impact on graft survival with a 69% increased likelihood of graft failure on MV analysis (HR 1.69, CI 1.40-2.04,  $p < 0.001$ )(Table 8, Figure 10), correlating with reports widely in the literature (50, 67, 69-71).

Both variables of interest, increased donor age and DCD LT, show a persistent negative effect on graft survival after adjustment for other significant variables, confirming the initial hypothesis in this study.

HCV positive recipients have been shown to be more likely to experience graft failure, in particular in combination with increased donor age (28, 33) due to rapid increase in the development of fibrosis (28). This is supported here at MV analysis with a 47% increase in graft failure when the recipient has HCV (HR 1.47, CI 1.27-1.71,  $p < 0.001$ )(Table 8, Figure 10). Interestingly, where HCV status is unknown there is a protective effect with 11% less risk of graft failure than in the HCV negative recipient group. It could be speculated that better quality grafts have less concern regarding recipient status and so an “unknown” state of a seemingly negative factor would not be so worrying for a “good” graft. This may explain the better survival outcomes for several similar characteristics where status is “unknown”. Graft survival was also poorer where the recipient had been an inpatient prior to LT (HR 1.17, CI 1.01-1.36,  $P = 0.032$ )(Table 8, Figure 10) or where the recipient had previous abdominal surgery pre-LT (HR 1.39, CI 1.23-1.58,  $p < 0.001$ )(Table 8, Figure 10). This coincides with the idea that a poorer host environment in the recipient can negatively impact on graft survival by increasing the stress the organ is subjected to physiologically. Poorer graft survival occurred where the graft was determined to be “suboptimal” by the operating surgeon (HR 1.32, CI 1.16-1.51,  $p < 0.001$ )(Table 8, Figure 10). Given the experience and expertise of the transplant surgeon it would logically fit that a poorer quality graft would be detected in this way. It also then follows that a visually poorer graft would have poorer functional results. A study by Hoofnagle *et al* found similar results with poorer graft and recipient survival where a poorer quality of graft was used (22).

MELD score is considered a predictive tool for waiting list mortality and increasing MELD score has also been found to negatively affect graft survival (19). In this study an increasing MELD did not impact negatively on graft survival until >20 (HR 1.03) and even with this slight increase in mortality this was not statistically significant ( $p=0.718$ )(Table 8). It is also worth considering the missingness of data here where these study results do not correlate with the wider literature it may be that poor availability of MELD data has skewed results.

Finally, increasing cold ischaemic time was found to correlate with poorer graft survival in an almost linear manner. CIT 6-8 hours showed a 16% increased risk of graft loss ( $p=0.090$ ), CIT 8-12 hours a 23% increased risk of graft loss ( $p=0.009$ ) and CIT >12 hours a 23% increased risk of graft loss ( $p=0.042$ ) all compared to the lowest CIT group <6 hours (Table 8). In the literature CIT is limited where possible by geographical and logistical considerations (46), by operative techniques such as rapid procurement strategies (51) or avoiding re-transplantations (58) and graft-recipient matching strategies such as avoiding a recipient with previous abdominal surgery which may increase CIT all to aim to improve graft survival.

Specific to HCV recipient status a large proportion of DBD transplantations were to recipients with unknown status and cox regression showed that this group had better survival. It could be speculated that DBD as a better quality liver graft was allocated to recipients with less need for attention to how unwell they were given that a better graft can cope with poorer host conditions.

### 6.6.2 Recipient Survival

When assessing recipient survival, as already noted, the variables on MV analysis were similar to graft survival with the exclusion of organ appearance and inclusion of the renal support status of the recipient.

The variables of interest in this study, donor age and DCD LT, were analysed by cox proportional hazards model to determine their impact on recipient survival correcting

for significant confounders. Donor age on univariable analysis showed poorer recipient survival with increasing donor age group and this effect was maintained in multivariable analysis. The oldest donor group (>60 years) correlated with the poorest recipient survival with 25% increased risk of mortality in comparison to the <35 year old donor group (HR 1.25, CI 1.06-1.46,  $p=0.007$ )(Table 9, Figure 11). These results would support the hypothesis that increased donor age impacts negatively on recipient survival as is already documented in the literature (17, 36, 38, 41).

DCD LT when compared to DBD was the second variable of interest with the hypothesis that DCD LTs would result in poorer recipient survival (50, 69, 70). In this study, however, on univariable analysis DCD promoted a “protective” effect in comparison to DBD which was not statistically significant. After adjusting for confounding variables on cox proportional hazards model DCD did not significantly affect recipient survival (HR 1.09, CI 0.89-1.34,  $p=0.4$ ). de Vera and Singh found similar survival outcomes for DCD recipients(63, 66, 71).

Other variables of note in multivariable analysis that correlated with poorer recipient survival included HCV positive recipients (HR 1.37, CI 1.20-1.57,  $p<0.001$ ) and recipient inpatient status pre-LT (HR 1.32, CI 1.14-1.52,  $p<0.001$ )(Table 9, Figure 11). MELD score and CIT which are frequently variables of interest when assessing both graft and recipient survival outcomes were both insignificant in this study on multivariable analysis of recipient survival. Higher MELD scores correlated with slightly improved recipient survival with those in the MELD >20 group having around 21% improved recipient survival compared to MELD <10 (HR 0.79, CI 0.67-0.94,  $p=0.008$ )(Table 9, Figure 11). During analysis of the data there was no obvious explanation for this result, although it could be the multifactorial interactions between a higher MELD recipient and perhaps better quality grafts transplanted. Missing data may also be a contributing factor to explain this unexpected result.

When the initial analysis of the data was performed there were living donor transplantations and recipients under 18 years of age included which were not initially apparent due to coding and grouping of variables. Thereafter the entire

analysis was performed again after excluding these transplantations. The notable changes were in the significance of survival differences where age was concerned. This is not surprising given a large number of younger recipients were excluded and the entire cohort were therefore older.

## 6.7 Limitations of dataset

This study had a number of limitations initially in the change in study design after ischaemic cholangiopathy data could not be obtained from individual centres in the UK. The change in study focus and design means that the dataset is now more historical. The NHSBT dataset studied provided all liver transplantations up to and including 2016. This means that survival data for more recent transplantations will not be complete as less follow up time recorded and also new advances in techniques and technologies such as machine perfusion cannot be studied here.

Variables in particular for recipient demographics and biochemistry and operative details were not widely recorded until >2000, including MELD and UKELD scores. In this study this was factored into univariable, KM survival and multivariable analyses to ensure that data processed has as little missing as possible. The proportion of DCD donations was variable and given the unpredictable nature of some of the data prior to this point the decision was taken to filter and analyse LTs between 2000-2015 in an attempt to limit some of the effects of this missing information.

In addition to filtering data for analysis based on transplantation year, there was also data missing randomly across sometimes a number of variables within this large cohort. This meant that many observations were still missing from the data after removing earlier transplantations. To rectify this in an ideal system each transplantation episodes' data could be manually searched with patient records at individual units but this would be incredibly time consuming and the balance of benefit would need to be weighed.

The dataset was relatively comprehensive but one major drawback was the lack of a warm ischaemic time (WIT) variable. In DCD transplantation the literature almost always refers to WIT given that the main hypothesis for ischaemic damage and subsequent graft complications and failures all relates to WIT present in DCD but not DBD liver grafts. Subsequently this was a major drawback of this analysis in that WIT was not considered and so could not be compared between DCD transplantations and the effects on survival outcomes. DCD could still be analysed compared to DBD but just not further categorised into high risk/ high WIT or low risk/ low WIT.

Finally another interesting idea about the survival data available came from a study by Foley *et al*, who were one of the only teams encountered in the literature who described the most common cause of graft failure as “death with a functioning graft” and second most common was “death with a poorly functioning graft” i.e. not the graft had not actually failed(69). This raises interesting questions about the handling of almost all other studies cited missing data as very few address how data is censored and therefore very difficult to be certain that in most cases grafts actually survived or failed.

Limitations within the data here are possible as it is not certain as to how the graft and recipient survival events are recorded in this NHSBT dataset. Given that these outcomes have been collected in similar way over years and multiple centres there is no way to determine a more accurate account again without extensive manual searches.

## 6.8 Missing data

As already mentioned much of the data missing was time dependent. Most of the recipient demographic and biochemistry variables were not recorded until after the year 2000 and numbers of DCD transplantations were very variable prior to this date. Analysis was performed between 2000-2015 but again limited follow up time so it may be that repeating with 2000-2010 would be more reliable.

In deciding to filter out the years prior to the main chunk of missing data this seemed to be the most reliable way to still gain meaningful analysis without excessively editing or manipulating with the individual variables. In a large and complex population such as this, other possible methods to minimise any missing data were considered.

Imputation methods (MICE) in R were considered to boost completeness of data, but in the context of many of these variables such as recipient sepsis, HCV status, graft steatosis, renal support, ventilation etc – simply taking imputation methods to make a “best guess” result in each individual transplantation episode seemed like it would make massive changes to the clinical status of the episode. To then consider multiple variables within a single episode handled in this manner it was felt that this would potentially drastically alter the clinical picture and would negate any conclusions drawn from survival outcome data. The only reasonable variables to use MICE would be some of the continuous variables. Donor age was mostly complete and as the dependent variable it was felt appropriate not to “guess” the missing values. Recipient age also had very little missing data and BMI was not a main focus of this analysis, but imputation may have been most appropriate in this variable.

Mathur *et al* actively discussed limitations of missing data. Where CIT was missing it was speculated that this can be a surrogate marker of very long times, perhaps suggesting a poor quality graft, delayed placement of the graft and overall suggestive of poor patient care(61). It could be considered in this study and in others in the literature that missing data across variables can be missing for a large number of reasons that may include bias in recording or interpreting data and this must be considered when analysing these variables and outcomes.

In the NHSBT data studied, the recipient renal support variable was noted to be an abundantly missing or poorly recorded variable. Removing the variable completely from the cox proportional hazards regression, however, did not make any difference in the model to the number of observations deleted. This would suggest that the missing data to impact the model was the outcome or survival variable.

## 6.9 Suggestions for Further Work

In planning or considering further work to develop this study in future the most obvious and a relatively simple way to make the conclusions more relevant would be a more up to date NHSBT dataset. This would allow comparisons to be made for older donor age and DCD transplantations in the current climate with technical and procedural advances and would be more relevant to current practice. DCD transplantation has evolved in the use of machine reperfusion techniques and so new levels of analysis incorporating methods that eliminate WIT would be useful in assessing ways to utilise DCD grafts today.

Identification of a suitable WIT variable to add to this study analyses would be beneficial in further stratifying DCD transplantations. WIT is a variable of interest in the literature and although conclusions can still be drawn regarding DCD outcomes it would add further depth to the validity of such conclusions. It would be of interest to determine whether longer WIT correlated with poorer graft function and survival withing the DCD cohort.

Further work on combinations of donor age or DCD with other significant variables i.e. recipient HCV, HCC, MELD and CIT as noted in the literature to identify any patterns in this dataset would be useful to allow greater understanding of donor-recipient matching decisions in the UK. Similarly, creating variables and sub-sets of data to test popular scoring systems would help to determine these are useful to predict outcomes in the UK cohort.

Propensity score matching (PSM) as a statistical method was considered but not performed. This would allow matching of the study group i.e. DCD with a more matched or similar DBD control group in terms of other donor and recipient characteristics. This would allow limitation in the variation in study groups to more sharply focus on one dependent variable. The problem with this could be that in reality the population is not “controlled”. There is no way in real time to control for

every factor despite different scoring systems and different allocation methods around the world. Univariable analysis when performed takes one dependant variable and assesses the effect on the outcome variable. In PSM in this study in particular it was not clear what else the controlling of other variables would add to the conclusions – in this study each variable was assessed “in spite” of the others.

With many missing variables, sometimes multiple for each transplantation, ways to improve recording of data at a local and national level will always be invaluable. The development of this may be out-with the scope of this study or future work but it is important to consider that recording of data has impacted on the quality of analysis that can be performed across multiple units in the UK. There is continued international scrutiny over donor and recipient matching decisions, and it is therefore important for each unit to record and critically review their outcomes to find the best ways to utilise EDC donors. This includes use of older donors and DCD grafts to continue to improve waiting times and reduce waiting list morbidity and mortality.

## 7.0 Conclusions

The proportion of recipients receiving grafts from older donors is increasing over time due to waiting list demands and a shortage of suitable non-marginal organ donors. It is clear in the literature with regards to both donor age and DCD that there is no universally agreed or standard approach to utilisation of EDC grafts. There is also extensive variation in the methods of analysis and results found across many single centre, multi-centre and large database studies.

In this study increasing donor age, when correcting for confounding variables, was found to negatively impact on both graft survival and recipient survival. DCD grafts impacted on graft survival negatively but had no statistically significant impact on recipient survival. It is evident in the literature and in multivariable analysis here that other variables can also have an impact. In this study graft survival was negatively affected by increasing donor age, DCD transplantation, positive recipient HCV status, recipient inpatient prior to transplantation, suboptimal graft appearance, previous recipient abdominal surgery and increased CIT >8h. Recipient survival was negatively impacted by increasing donor age, positive HCV status of the recipient, recipient as an inpatient prior to transplantation and CIT >8h. DCD did not significantly impact on recipient survival outcomes.

As discussed already the limitations of this study mean that fundamentally there are still many questions regarding variable relationships affecting graft and recipient survival. Ongoing reflective practice on a local, national and international level to continue to develop an understanding of these interactions will hopefully aid in continued improvement in liver transplantation outcomes.

## 8.0 References

1. Dasari BVM, Schlegel A, Mergental H, Perera MTPR. The use of old donors in liver transplantation. *Best Pract Res Clin Gastroenterol.* 2017;31(2):211-7.
2. Lee DD, Singh A, Burns JM, Perry DK, Nguyen JH, Taner CB. Early allograft dysfunction in liver transplantation with donation after cardiac death donors results in inferior survival. *Liver Transpl.* 2014;20(12):1447-53.
3. Merion RM, Goodrich NP, Feng S. How can we define expanded criteria for liver donors? *J Hepatol.* 2006;45(4):484-8.
4. Davila D, Ciria R, Jassem W, Briceño J, Littlejohn W, Vilca-Meléndez H, et al. Prediction models of donor arrest and graft utilization in liver transplantation from maastricht-3 donors after circulatory death. *Am J Transplant.* 2012;12(12):3414-24.
5. Rocha. Can the use of marginal liver donors change recipient survival rate? *Transplantation proceedings.* 2004;36(4):914-5.
6. Busuttil. The Utility of Marginal Donors in Liver Transplantation. *Liver Transplantation.* 2003;9(7):651-63.
7. Gruttadauria. Acceptance of Marginal Liver Donors Increases the Volume of Liver Transplant: Early Results of a Single-Center Experience. *Transplantations Proceedings.*37(6):2567-8.
8. Attia M, Silva MA, Mirza DF. The marginal liver donor--an update. *Transpl Int.* 2008;21(8):713-24.
9. Tekin K, Imber CJ, Atli M, Gunson BK, Bramhall SR, Mayer D, et al. A simple scoring system to evaluate the effects of cold ischemia on marginal liver donors. *Transplantation.* 2004;77(3):411-6.
10. Schlegel A, Scalera I, Perera MTPR, Kalisvaart M, Mergental H, Mirza DF, et al. Impact of donor age in donation after circulatory death liver transplantation: Is the cutoff "60" still of relevance? *Liver Transpl.* 2018;24(3):352-62.
11. Feng S, Lai JC. Expanded criteria donors. *Clin Liver Dis.* 2014;18(3):633-49.
12. Chela H, Yousef MH, Albarrak AA, Romana BS, Hudhud DN, Tahan V. Elderly donor graft for liver transplantation: Never too late. *World J Transplant.* 2017;7(6):324-8.
13. Jiménez-Romero C, Caso Maestro O, Cambra Molero F, Justo Alonso I, Alegre Torrado C, Manrique Municio A, et al. Using old liver grafts for liver transplantation: Where are the limits? *World Journal of Gastroenterology : WJG.* 2014;20(31):10691-702.
14. Pagano D, Barbàra M, Seidita A, Cintorino D, di Francesco F, Petridis I, et al. Impact of Extended-Criteria Donor Liver Grafts on Benchmark Metrics of Clinical Outcome After Liver Transplantation: A Single Center Experience. *Transplant Proc.* 2020;52(5):1588-92.
15. Sarkut. Early graft dysfunction and mortality rate in marginal donor liver transplantation. 2014.
16. Feng. Characteristics Associated with Liver Graft Failure: The Concept of a Donor Risk Index. 2006.
17. Lozanovski VJ, Khajeh E, Fonouni H, Pfeiffenberger J, von Haken R, Brenner T, et al. The impact of major extended donor criteria on graft failure and patient mortality after liver transplantation. *Langenbecks Arch Surg.* 2018;403(6):719-31.
18. Marino IR. Are we ready to match donor and recipient in liver transplantation? *Liver Transpl.* 2006;12(11):1574-6.
19. Dutkowski P, Oberkofler CE, Slankamenac K, Puhan MA, Schadde E, Müllhaupt B, et al. Are there better guidelines for allocation in liver transplantation? A novel score targeting justice and utility in the model for end-stage liver disease era. *Ann Surg.* 2011;254(5):745-53; discussion 53.
20. Chapman WC, Vachharajani N, Collins KM, Garonzik-Wang J, Park Y, Wellen JR, et al. Donor Age-Based Analysis of Liver Transplantation Outcomes: Short- and Long-Term Outcomes Are Similar Regardless of Donor Age. *J Am Coll Surg.* 2015;221(1):59-69.

21. Dasari BV, Mergental H, Isaac JR, Muiesan P, Mirza DF, Perera T. Systematic review and meta-analysis of liver transplantation using grafts from deceased donors aged over 70 years. *Clin Transplant*. 2017;31(12).
22. Hoofnagle JH, Lombardero M, Zetterman RK, Lake J, Porayko M, Everhart J, et al. Donor age and outcome of liver transplantation. *Hepatology*. 1996;24(1):89-96.
23. Houben P, Döhler B, Weiß KH, Mieth M, Mehrabi A, Süsal C. Differential Influence of Donor Age Depending on the Indication for Liver Transplantation-A Collaborative Transplant Study Report. *Transplantation*. 2020;104(4):779-87.
24. Dickson KM, Martins PN. Implications of liver donor age on ischemia reperfusion injury and clinical outcomes. *Transplant Rev (Orlando)*. 2020;34(3):100549.
25. Durand F, Levitsky J, Cauchy F, Gilgenkrantz H, Soubrane O, Francoz C. Age and liver transplantation. *J Hepatol*. 2019;70(4):745-58.
26. Jiménez-Romero LC, Caso Maestro O, Cambra Molero F, Manrique Municio A, Calvo Pulido J, Marcacuzco Quinto A, et al. Octogenarian Liver Grafts Reaching Centennial Age After Transplantation. *Transplantation*. 2017;101(7):e218-e9.
27. Rodríguez González F, Jiménez Romero C, Rodríguez Romano D, Loinaz Seguro C, Marqués Medina E, Pérez Saborido B, et al. Orthotopic liver transplantation with 100 hepatic allografts from donors over 60 years old. *Transplant Proc*. 2002;34(1):233-4.
28. Lué A, Solanas E, Baptista P, Lorente S, Araiz JJ, Garcia-Gil A, et al. How important is donor age in liver transplantation? *World J Gastroenterol*. 2016;22(21):4966-76.
29. Kostakis ID, Iype S, Nasralla D, Davidson BR, Imber C, Sharma D, et al. Combining Donor and Recipient Age With Preoperative MELD and UKELD Scores for Predicting Survival After Liver Transplantation. *Exp Clin Transplant*. 2021;19(6):570-9.
30. Grąt M, Wronka KM, Patkowski W, Stypułkowski J, Grąt K, Krasnodębski M, et al. Effects of Donor Age and Cold Ischemia on Liver Transplantation Outcomes According to the Severity of Recipient Status. *Dig Dis Sci*. 2016;61(2):626-35.
31. Pratschke S, Bender A, Boesch F, Andrassy J, van Rosmalen M, Samuel U, et al. Association between donor age and risk of graft failure after liver transplantation: an analysis of the Eurotransplant database. *Transpl Int*. 2019;32(3):270-9.
32. Dudek K, Kornasiewicz O, Remiszewski P, Zieniewicz K, Wróblewski T, Krawczyk M. Results of liver transplantation from old donors. *Transplant Proc*. 2014;46(8):2762-5.
33. Thuluvath PJ, Guidinger MK, Fung JJ, Johnson LB, Rayhill SC, Pelletier SJ. Liver transplantation in the United States, 1999-2008. *Am J Transplant*. 2010;10(4 Pt 2):1003-19.
34. Marino IR, Doyle HR, Aldrighetti L, Doria C, McMichael J, Gayowski T, et al. Effect of donor age and sex on the outcome of liver transplantation. *Hepatology*. 1995;22(6):1754-62.
35. Dar FS, Khan NY, Ali R, Khokhar HK, Zia HH, Bhatti ABH, et al. Recipient Outcomes with Younger Donors Undergoing Living Donor Liver Transplantation. *Cureus*. 2019;11(3):e4174.
36. Fernández-Merino FJ, Nuño-Garza J, López-Hervas P, López-Buenadicha A, Quijano-Collazo Y, Vicente-López E. Donor age as a risk factor for patient survival in the liver transplant. *Transplant Proc*. 2003;35(5):1795-7.
37. Pagano D, Grosso G, Vizzini G, Spada M, Cintonio D, Malaguarnera M, et al. Recipient-donor age matching in liver transplantation: a single-center experience. *Transplant Proc*. 2013;45(7):2700-6.
38. Marino IR, Doyle HR, Doria C, Aldrighetti L, Gayowski T, Scotti-Foglieni C, et al. Outcome of liver transplantation using donors 60 to 79 years of age. *Transplant Proc*. 1995;27(1):1184-5.
39. Paterno F, Wima K, Hoehn RS, Cuffy MC, Diwan TS, Woodle SE, et al. Use of Elderly Allografts in Liver Transplantation. *Transplantation*. 2016;100(1):153-8.
40. Rustgi SD, Marino G, Halpern MT, Umana WO, Tolleris C, Rustgi VK. Impact of donor age on graft survival among liver transplant recipients: analysis of the United Network for Organ Sharing database. *Transplant Proc*. 2002;34(8):3295-7.

41. Montenovo MI, Hansen RN, Dick AAS, Reyes J. Donor Age Still Matters in Liver Transplant: Results From the United Network for Organ Sharing-Scientific Registry of Transplant Recipients Database. *Exp Clin Transplant*. 2017;15(5):536-41.
42. Cuervas-Mons V, de la Rosa G, Pardo F, San Juan F, Valdivieso A, Hepático erdREdT. [Activity and results of liver transplantation in Spain during 1984-2012. Analysis of the Spanish Liver Transplant Registry]. *Med Clin (Barc)*. 2015;144(8):337-47.
43. Rabelo AV, Bastante MD, Raya AM, Méndez CS, Ramirez AR, Suarez YF. Liver Transplantation Results by Donor Age. *Transplant Proc*. 2016;48(9):2994-6.
44. Chedid MF, Rosen CB, Nyberg SL, Heimbach JK. Excellent long-term patient and graft survival are possible with appropriate use of livers from deceased septuagenarian and octogenarian donors. *HPB (Oxford)*. 2014;16(9):852-8.
45. Faber W, Seehofer D, Puhl G, Guckelberger O, Bertram C, Neuhaus P, et al. Donor age does not influence 12-month outcome after orthotopic liver transplantation. *Transplant Proc*. 2011;43(10):3789-95.
46. Sela N, Croome KP, Chandok N, Marotta P, Wall W, Hernandez-Alejandro R. Changing donor characteristics in liver transplantation over the last 10 years in Canada. *Liver Transpl*. 2013;19(11):1236-44.
47. Rabelo AV, Alvarez MJ, Méndez CS, Villegas MT, MGraneroa K, Becerra A, et al. Liver Transplantation Outcomes Using Grafts From Donors Older Than the Age of 80 Years. *Transplant Proc*. 2015;47(9):2645-6.
48. Jiménez-Romero C, Clemares-Lama M, Manrique-Municio A, García-Sesma A, Calvo-Pulido J, Moreno-González E. Long-term results using old liver grafts for transplantation: sexagenarian versus liver donors older than 70 years. *World J Surg*. 2013;37(9):2211-21.
49. Jiménez-Romero C, Cambra F, Caso O, Manrique A, Calvo J, Marcauzco A, et al. Octogenarian liver grafts: Is their use for transplant currently justified? *World J Gastroenterol*. 2017;23(17):3099-110.
50. Foley DP, Fernandez LA, Levenson G, Anderson M, Mezrich J, Sollinger HW, et al. Biliary complications after liver transplantation from donation after cardiac death donors: an analysis of risk factors and long-term outcomes from a single center. *Ann Surg*. 2011;253(4):817-25.
51. Monbaliu D, Pirenne J, Talbot D. Liver transplantation using Donation after Cardiac Death donors. *J Hepatol*. 2012;56(2):474-85.
52. Perera MT, Bramhall SR. Current status and recent advances of liver transplantation from donation after cardiac death. *World J Gastrointest Surg*. 2011;3(11):167-76.
53. Park H, Jung ES, Oh JS, Lee YM, Lee JM. Organ donation after controlled circulatory death (Maastricht classification III) following the withdrawal of life-sustaining treatment in Korea: a suggested guideline. *Korean J Transplant*. 2021;35(2):71-6.
54. Hessheimer AJ, Gastaca M, Miñambres E, Colmenero J, Fondevila C. Donation after circulatory death liver transplantation: consensus statements from the Spanish Liver Transplantation Society. 8 ed. *Transplant International*2020. p. 902-16.
55. Savier E, Dondero F, Vibert E, Eyraud D, Brisson H, Riou B, et al. First experience of liver transplantation with type 2 donation after cardiac death in France. *Liver Transpl*. 2015;21(5):631-43.
56. Detry O, Donckier V, Lucidi V, Ysebaert D, Chapelle T, Lerut J, et al. Liver transplantation from donation after cardiac death donors: initial Belgian experience 2003-2007. *Transpl Int*. 2010;23(6):611-8.
57. Giorgakis E, Khorsandi SE, Jassem W, Heaton N. Minimization of Ischemic Cholangiopathy in Donation After Cardiac Death Liver Transplantation: Is It Thrombolytic Therapy or Warm Ischemic Time Stringency and Donor Bile Duct Flush? *Am J Transplant*. 2018;18(1):274-5.
58. Khorsandi SE, Giorgakis E, Vilca-Melendez H, O'Grady J, Heneghan M, Aluvihare V, et al. Developing a donation after cardiac death risk index for adult and pediatric liver transplantation. *World J Transplant*. 2017;7(3):203-12.

59. Abt PL, Praestgaard J, West S, Hasz R. Donor hemodynamic profile presages graft survival in donation after cardiac death liver transplantation. *Liver Transpl.* 2014;20(2):165-72.
60. Lee KW, Simpkins CE, Montgomery RA, Locke JE, Segev DL, Maley WR. Factors affecting graft survival after liver transplantation from donation after cardiac death donors. *Transplantation.* 2006;82(12):1683-8.
61. Mathur AK, Heimbach J, Steffick DE, Sonnenday CJ, Goodrich NP, Merion RM. Donation after cardiac death liver transplantation: predictors of outcome. *Am J Transplant.* 2010;10(11):2512-9.
62. Croome KP, Wall W, Chandok N, Beck G, Marotta P, Hernandez-Alejandro R. Inferior survival in liver transplant recipients with hepatocellular carcinoma receiving donation after cardiac death liver allografts. *Liver Transpl.* 2013;19(11):1214-23.
63. Singh N, Helfrich K, Mumtaz K, Washburn K, Logan A, Black S, et al. Donation After Circulatory Death Yields Survival Rates Similar to Donation After Brain Death Liver Transplant, Which Effectively Expands the Donor Pool. *Exp Clin Transplant.* 2021;19(8):771-8.
64. Duan X, Yan L, Shen Y, Zhang M, Bai X, Liang T. Outcomes of liver transplantation using moderately steatotic liver from donation after cardiac death (DCD). *Ann Transl Med.* 2020;8(18):1188.
65. Wells M, Croome KM, Janik T, Hernandez-Alejandro RM, Chandok NM. Comparing outcomes of donation after cardiac death versus donation after brain death in liver transplant recipients with hepatitis C: a systematic review and meta-analysis. *Can J Gastroenterol Hepatol.* 2014;28(2):103-8.
66. Haque O, Yuan Q, Uygun K, Markmann JF. Evolving utilization of donation after circulatory death livers in liver transplantation: The day of DCD has come. *Clin Transplant.* 2021;35(3):e14211.
67. Mateo R, Cho Y, Singh G, Stapfer M, Donovan J, Kahn J, et al. Risk factors for graft survival after liver transplantation from donation after cardiac death donors: an analysis of OPTN/UNOS data. *Am J Transplant.* 2006;6(4):791-6.
68. Pan X, Apinyachon W, Xia W, Hong JC, Busuttill RW, Steadman RH, et al. Perioperative complications in liver transplantation using donation after cardiac death grafts: a propensity-matched study. *Liver Transpl.* 2014;20(7):823-30.
69. Foley DP, Fernandez LA, Levenson G, Chin LT, Krieger N, Cooper JT, et al. Donation after cardiac death: the University of Wisconsin experience with liver transplantation. *Ann Surg.* 2005;242(5):724-31.
70. Pine JK, Aldouri A, Young AL, Davies MH, Attia M, Toogood GJ, et al. Liver transplantation following donation after cardiac death: an analysis using matched pairs. *Liver Transpl.* 2009;15(9):1072-82.
71. de Vera ME, Lopez-Solis R, Dvorchik I, Campos S, Morris W, Demetris AJ, et al. Liver transplantation using donation after cardiac death donors: long-term follow-up from a single center. *Am J Transplant.* 2009;9(4):773-81.
72. Zhou J, Wei Q, Zheng S, Xu X. Early allograft dysfunction after liver transplantation with donation after cardiac death donors. *Hepatobiliary Surg Nutr.* 2019;8(5):566-8.
73. Ohara S, Macdonough E, Egbert L, Brooks A, Lizaola-Mayo B, Mathur AK, et al. Decreasing Significance of Early Allograft Dysfunction with Rising Use of Nonconventional Donors. *Medicina (Kaunas).* 2022;58(6).

## Appendix A

```
#####  
#DONOR AGE Tables & FIGURES#  
# MScR #  
#####  
  
# DATASET IS UKTRANS  
=====
```

```
=  
names(uktrans)  
  
#NEW DATASET >=2000 <2016  
=====
```

```
#Called - uktrans_recent  
  
uktrans %>%  
  filter(tx_yr >=2000, tx_yr<2016) -> uktrans_recent  
  
uktrans_recent$tx_yr %>%  
  summary()  
  
uktrans_recent %>%  
  filter(! dcod.factor == "Living Donor") %>%  
  filter(! rage <= 17) -> uktrans_recent  
  
#Data with NA recoded as unknown uktrans_na.rm - RUN BELOW IN MISSING  
VALUES  
names(uktrans_na.rm)  
  
# PACKAGES TO  
LOAD=====
```

```
=====
```

```
install.packages("finalfit")  
install.packages("dplyr")  
  
#remove.packages("rlang")  
#install.packages("rlang")  
#install.packages("lifecycle")  
#install.packages("cli")  
  
#?rlang  
#?lifecycle  
  
library(finalfit)  
library(dplyr)  
library(readr)  
library(tidyverse)  
library(broom)  
library(Hmisc)
```

```

library(survival)
library(ggplot2)
library(survminer)

library(devtools)
install_github("ggobi/ggally")

#install.packages("gridExtra") - tried when looking to resolve PDF
issue
#library("gridExtra")

#install.packages("devtools")
#devtools::install_github("ewenharrison/summarizer")
library(summarizer)

?rlang

library(rlang)
sessionInfo()

#REMOVE OLD PLOTS/ VARIABLES ETC
=====

rm(plot0)
rm(p1)
rm(plot3)
rm(plot4)
rm(plotA)
rm(plotB)
rm(s)
rm(t)
rm(t1)
rm(t1.1)
rm(t2)
rm(t2.1)
rm(t3)
rm(t4)
rm(t5)
rm(t6)

# SET UP DATA AND LABELS
=====

?readr::cols()

spec(uktrans)

ff_glimpse(uktrans)

#Making new factors with labels:

uktrans %>%
  mutate(

```

```

urgent.factor = factor(urgent, levels = c(0, 1),
                      labels = c("No", "Yes")) %>%
  ff_label("Urgent"),
dtype.factor = factor(dtype, levels = c(1, 2),
                      labels = c("DBD", "DCD")) %>%
  ff_label("Donor Type"),
dbg.factor = factor(dbg, levels = c(1, 2, 3, 4),
                   labels = c("O", "A", "B", "AB")) %>%
  ff_label("Donor Blood Group"),
tcens.factor = factor(tcens, levels = c(0, 1),
                     labels = c("Functioning", "Graft Failure or
Death")) %>%
  ff_label("Transplant Survival"),
gcens.factor = factor(gcens, levels = c(0, 1),
                     labels = c("Functioning", "Failed")) %>%
  ff_label("Graft Survival"),
pcens.factor = factor(pcens, levels = c(0, 1),
                     labels = c("Alive", "Died")) %>%
  ff_label("Patient Survival"),
steatosis.factor = factor(steatosis, levels = c(1, 2),
                          labels = c("No", "Yes")) %>%
  ff_label("Graft Steatosis"),
re_txd.factor = factor(re_txd, levels = c(0, 1),
                      labels = c("No", "Yes")) %>%
  ff_label("Re-transplanted"),
tx_type.factor = factor(tx_type, levels = c(40, 80, 83, 84, 110,
115, 120, 140, 160, 190),
                      labels = c("Liver only",
"Intestinal failure liver-only",
"Intestinal Failure Liver, Small
bowel & Pancreas",
"Intestinal Failure
Multivisceral",
"Liver & Kidney",
"Liver, Kidney & Pancreas",
"Liver, Heart & Lung",
"Liver & Pancreas",
"Liver & Heart",
"Liver & Lung")) %>%
  ff_label("Type of Transplant"),
multi_tx.factor = factor(multi_tx, levels = c(0, 1),
                        labels = c("Liver Only Transplant",
"Multiple Organ Transplant")) %>%
  ff_label("Multi-organ Transplant Indicator"),
sm_bowel.factor = factor(sm_bowel, levels = c(0, 1),
                        labels = c("No Small Bowel", "Combined
Liver and Small Bowel")) %>%
  ff_label("Small Bowel with Liver Indicator"),
tx_method.factor = factor(tx_method, levels = c(1, 2, 8, 9),
                         labels = c("Orthotopic", "Heterotopic",
"Missing", "Unknown")) %>%
  ff_label("Transplant Method"),
organ.factor = factor(organ, levels = c(40, 41, 42, 46, 47),
                     labels = c("Whole liver", "Left lobe", "Right
lobe",
"Left Lateral Segment", "Liver
Segment IV")) %>%
  ff_label("Lobe/segment of Liver Transplanted"),

```

```

liver.factor = factor(liver, levels = c(0, 1, 2),
                      labels = c("Whole", "Reduced", "Split")) %>%
  ff_label("Completeness of Liver Transplanted"),
dcod.factor = factor(dcod, levels = c(0, 10, 11, 12, 13, 19, 20,
21, 22, 23,
                                24, 29, 30, 31, 39, 40, 41,
42, 43, 44,
                                45, 49, 50, 51, 52, 53, 54,
59, 60, 70,
                                71, 72, 73, 74, 75, 76, 77,
78, 80, 81,
                                82, 85, 88, 90, 98, 99),
                      labels = c("Living Donor",
                                "Intracranial Haemorrhage",
                                "Intracranial Thrombosis",
                                "Brain Tumour",
                                "Hypoxic Brain Damage",
                                "Intracranial - Type Unspecified
(CVA)",
                                "Trauma RTA - Car",
                                "Trauma RTA - Motorbike",
                                "Trauma RTA - Pushbike",
                                "Trauma RTA - Pedestrian",
                                "Trauma RTA - Other",
                                "Trauma RTA - Unknown Type",
                                "Other Trauma - Known or Suspected
Suicide",
                                "Other Trauma - Accident",
                                "Other Trauma - Unknown Cause",
                                "Cardiac Arrest",
                                "Myocardial Infarction",
                                "Aneurysm (including Aortic)",
                                "Ischaemic Heart Disease",
                                "Congestive Cardiac Failure",
                                "Pulmonary Embolism",
                                "Cardiovascular - Type
Unclassified",
                                "Chronic Pulmonary Disease",
                                "Pneumonia",
                                "Asthma",
                                "Respiratory Failure",
                                "Carbon Monoxide Poisoning",
                                "Respiratory - Type Unclassified
(inc Smoke Inhalation)",
                                "Cancer (other than Brain Tumour)",
                                "Meningitis",
                                "Septicaemia",
                                "Infections - Type Unclassified",
                                "Acute Bloods Loss/ Hypovolaemia",
                                "Liver failure (not Self
Poisoning)",
                                "Renal Failure",
                                "Multi-organ Failure",
                                "Sudden Infant Death Syndrome
(SIDS)",
                                "Burns",
                                "Alcohol Poisoning",
                                "Paracetamol Overdose",

```

```

"Other Drug Overdose",
"Self Poisoning - Type
Unclassified",

"Not Reported",
"Other",
"Other, please specify",
"Unknown")) %>%
  ff_label("Donor Cause of Death"),
  dcmv.factor = factor(dcmv, levels = c(1, 2, 3, 4, 5, 6, 7, 8, 9,
10),
    labels = c("Negative",
      "Positive",
      "Indeterminate",
      "Repeat Negative",
      "Confirmed Positive",
      "Test Result Awaited",
      "Not Tested",
      "Not Reported",
      "Unknown",
      "Non-specific Reactivity")) %>%
  ff_label("Donor CMV Status"),
  rage_grp.factor = factor(rage_grp, levels = c(0, 1, 9),
    labels = c("Paediatric (<16)",
      "Adult (>17)",
      "Unknown")) %>%
  ff_label("Recipient Paediatric. Adult Indicator"),
  rbg.factor = factor(rbg, levels = c(1, 2, 3, 4),
    labels = c("O", "A", "B", "AB")) %>%
  ff_label("Recipient Blood Group"),
  rethnic.factor = factor(rethnic, levels = c(1, 2, 3, 4, 6, 7, 8,
9),
    labels = c("White",
      "Asian or Asian-British",
      "Black or Black-British",
      "Chinese/ Oriental",
      "Mixed",
      "Other",
      "Not Reported",
      "Unknown")) %>%
  ff_label("Recipient Ethnicity Group"),
  rcmv.factor = factor(rcmv, levels = c(1, 2, 3, 4, 5, 6, 7, 8, 9,
10),
    labels = c("Negative",
      "Positive",
      "Indeterminate",
      "Repeat Negative",
      "Confirmed Positive",
      "Test Result Awaited",
      "Not Tested",
      "Not Reported",
      "Unknown",
      "Non-specific Reactivity")) %>%
  ff_label("Recipient CMV Status"),
  rhcv.factor = factor(rhcv, levels = c(1, 2, 3, 4, 5, 6, 7, 8, 9,
10),
    labels = c("Negative",
      "Positive",
      "Indeterminate",

```

```

"Repeat Negative",
"Confirmed Positive",
"Test Result Awaited",
"Not Tested",
"Not Reported",
"Unknown",
"Non-specific Reactivity")) %>%
  ff_label("Recipient HCV Status"),
  rcod.factor = factor(rcod, levels = c(0, 500, 511, 512, 513, 514,
515, 516, 517,
518, 519, 520, 521, 522, 523,
524, 525, 526,
527, 528, 529, 530, 531, 532,
533, 534, 535,
536, 537, 538, 539, 541, 542,
543, 544, 545,
546, 547, 548, 549, 551, 552,
553, 554, 561,
562, 563, 564, 566, 567, 568,
569, 570, 571,
572, 573, 574, 575, 576, 577,
578, 579, 581,
582, 590, 595, 598, 599,
888),
  labels = c("None",
"Uncertain/ Not Determined",
"Myocardial Ischaemia/ Infarction",
"Hyperkalaemia",
"Haemorrhagic Pericarditis",
"Other Causes of Cardiac Failure",
"Sudden Unexplained Cardiac Death",
"Hypertensive Cardiac Failure",
"Hypokalaemia",
"Fluid Overload",
"Elevated PVR/ Pulmonary
Hypertension",
"Aurway Dehiscence",
"Pulmonary Embolus",
"Cerebro-Vascular Accident",
"Gastro-intestinal Haemorrhage",
"Haemorrhage from Graft Site",
"Haemorrhage from Vascular Access
or Dialysis Circuit",
"Haemorrhage from Ruptured Vascular
Aneurysm",
"Haemorrhage from Surgery",
"Other Haemorrhage",
"Mesenteric Infarction",
"Pulmonary Infection (Protozoal)",
"Pulmonary Infection (Bacterial)",
"Pulmonary Infection (Viral)",
"Pulmonary Infection (Fungal)",
"Infections Elsewhere (except Viral
Hepatitis)",
"Septicaemia",
"Tuberculosis (Lung)",
"Tuberculosis (Elsewhere)",
"Generalised Viral Infection",

```

```

"Peritonitis",
"Liver Failure - due to Hepatitis B
Virus",
"Liver Failure - Other Viral
Hepatitis",
"Liver Failure - Drug Toxicity",
"Cirrhosis - Non Viral",
"Cystic Liver Disease",
"Liver Failure - Cause Unknown",
"Renal Failure",
"Recurrent Primary Disease -
Benign",
"Recurrent Primary Disease -
Malignant",
"Patient Refused Further
Treatment",
"Suicide",
"Therapy Ceased for Any Other
Reason",
"ESRF Treatment Withdrawn for
Medical Reasons",
"Uraemia Caused by Graft Failure",
"Pancreatitis",
"Bone Marrow Depression",
"Cachexia",
"Lymphoid Malignant Disease
(Induced by Immunosuppressive Therapy)",
"Lymphoid Malignant Disease (Not
Induced by Immunosuppressive Therapy)",
"Malignant Disease -
Lymphoproliferative Disorders",
"Dementia",
"Sclerosing (or Adhesive)
Peritoneal Disease",
"Perforation of Peptic Ulcer",
"Perforation of Colon",
"Non-Lymphoid Malignant Disease
(Induced by Immunosuppressive Therapy)",
"Non-Lymphoid Malignant Disease
(Not Induced by Immunosuppressive Therapy)",
"Early Graft Dysfunction",
"Cardiac Tamponade",
"ARDS",
"Respiratory Failure",
"Multi-System Failure",
"Accident Related to Treatment",
"Accident Unrelated to Treatment",
"Donor Organ Failure",
"Other Identified Cause of Death",
"Other Identified Cause of Death",
"Unknown",
"COD Not Requested")) %>%
  ff_label("Recipient Cause of Death"),
  rcod2.factor = factor(rcod2, levels = c(0, 500, 511, 512, 513, 514,
515, 516, 517,
518, 519, 520, 521, 522, 523,
524, 525, 526,

```

```

533, 534, 535,
543, 544, 545,
553, 554, 561,
569, 570, 571,
578, 579, 581,
888),
527, 528, 529, 530, 531, 532,
536, 537, 538, 539, 541, 542,
546, 547, 548, 549, 551, 552,
562, 563, 564, 566, 567, 568,
572, 573, 574, 575, 576, 577,
582, 590, 595, 598, 599,
labels = c("None",
"Uncertain/ Not Determined",
"Myocardial Ischaemia/ Infarction",
"Hyperkalaemia",
"Haemorrhagic Pericarditis",
"Other Causes of Cardiac Failure",
"Sudden Unexplained Cardiac Death",
"Hypertensive Cardiac Failure",
"Hypokalaemia",
"Fluid Overload",
"Elevated PVR/ Pulmonary
Hypertension",
"Aurway Dehiscence",
"Pulmonary Embolus",
"Cerebro-Vascular Accident",
"Gastro-intestinal Haemorrhage",
"Haemorrhage from Graft Site",
"Haemorrhage from Vascular Access
or Dialysis Circuit",
"Haemorrhage from Ruptured Vascular
Aneurysm",
"Haemorrhage from Surgery",
"Other Haemorrhage",
"Mesenteric Infarction",
"Pulmonary Infection (Protozoal)",
"Pulmonary Infection (Bacterial)",
"Pulmonary Infection (Viral)",
"Pulmonary Infection (Fungal)",
"Infections Elsewhere (except Viral
Hepatitis)",
"Septicaemia",
"Tuberculosis (Lung)",
"Tuberculosis (Elsewhere)",
"Generalised Viral Infection",
"Peritonitis",
"Liver Failure - due to Hepatitis B
Virus",
"Liver Failure - Other Viral
Hepatitis",
"Liver Failure - Drug Toxicity",
"Cirrhosis - Non Viral",
"Cystic Liver Disease",
"Liver Failure - Cause Unknown",
"Renal Failure",
"Recurrent Primary Disease -
Benign",

```

```

Malignant",
Treatment",
Reason",
Medical Reasons",
(Induced by Immunosuppressive Therapy)",
Induced by Immunosuppressive Therapy)",
Lymphoproliferative Disorders",
Peritoneal Disease",
(Induced by Immunosuppressive Therapy)",
(Not Induced by Immunosuppressive Therapy)",
"Recurrent Primary Disease -
"Patient Refused Further
"Suicide",
"Therapy Ceased for Any Other
"ESRF Treatment Withdrawn for
"Uraemia Caused by Graft Failure",
"Pancreatitis",
"Bone Marrow Depression",
"Cachexia",
"Lymphoid Malignant Disease
"Lymphoid Malignant Disease (Not
"Malignant Disease -
"Dementia",
"Sclerosing (or Adhesive)
"Perforation of Peptic Ulcer",
"Perforation of Colon",
"Non-Lymphoid Malignant Disease
"Non-Lymphoid Malignant Disease
"Early Graft Dysfunction",
"Cardiac Tamponade",
"ARDS",
"Respiratory Failure",
"Multi-System Failure",
"Accident Related to Treatment",
"Accident Unrelated to Treatment",
"Donor Organ Failure",
"Other Identified Cause of Death",
"Other Identified Cause of Death",
"Unknown",
"COD Not Requested")) %>%
  ff_label("Recipient Secondary Cause of Death"),
  nhs_grp.factor = factor(nhs_grp, levels = c(1, 2, 8),
    labels = c("Group 1", "Group 2", "Not
Reported")) %>%
  ff_label("NHS Group Status"),
  abomatch.factor = factor(abomatch, levels = c(1, 2, 3),
    labels = c("Identical", "Compatible",
"Incompatible")) %>%
  ff_label("Donor vs Recipient Blood Group"),
  rcspld1.factor = factor(rcspld1, levels = c(400, 410, 411, 412,
413, 414, 415, 416, 417,
418, 419, 420, 421,
422, 423, 424, 425, 426,
427, 428, 430, 431,
432, 433, 434, 435, 436,
437, 438, 439, 440,
441, 442, 443, 444, 445,

```

```

446, 447, 448, 450,
451, 452, 453, 454, 455,
456, 457, 458, 459,
460, 461, 462, 463, 464,
465, 466, 467, 468,
469, 470, 471, 472, 473,
474, 475, 476, 477,
478, 479, 480, 481, 482,
483, 484, 485, 486,
498, 499, 888),
labels = c("Liver Disease Unknown",
           "Chronic Liver Failure - Cause
Unknown",
           "Primary Biliary Cirrhosis",
           "Autoimmune Chronic Active Liver
Disease",
           "Hepatitis B Cirrhosis",
           "Primary Sclerosing
Cholangitis",
           "Alpha-1-Antitrypsin
Deficiency",
           "Budd-Chiari Syndrome",
           "Cryptogenic Cirrhosis",
           "Secondary Biliary Cirrhosis",
           "Alcoholic Liver Disease",
           "Biliary Atresia",
           "Congenital Hepatic Fibrosis",
           "Wilson's Disease",
           "Congenital Biliary Disease",
           "Hepatitis C Cirrhosis",
           "Paediatric Cholestatic Liver
Disease",
           "Non-alcoholic Fatty Liver
Disease",
           "Acute Hepatic Failure - Budd-
Chiari Syndrome",
           "Acute Hepatic Failure - Other
Virus",
           "Acute Hepatic Failure -
Serologically Indeterminate",
           "FHF - Viral",
           "FHF - Drug Induced",
           "FHF - Toxin Induced",
           "Acute Hepatic Failure -
Wilson's Disease",
           "Acute Hepatic Failure - HAV",
           "Acute Hepatic Failure - HBV",
           "Acute Hepatic Failure -
Paracetamol Hepatotoxicity",
           "Acute Hepatic Failure - Other
Drug Toxicity",
           "Acute Hepatic Failure - Other",
           "Malignancy - Not Classifiable",
           "Hepatocellular Carcinoma - Non-
Cirrhotic",
           "Hepatocellular Carcinoma -
Cirrhotic",
           "Cholangiocarcinoma",

```

```

Malignancy",
    "Hepatoblastoma",
    "Secondary Hepatic Malignancy",
    "Other Mesenchymal Tumours",
    "Other Primary Hepatic
Intrahepatic Cholestasis",
    "Benign Liver Tumour",
    "Other Metabolic Liver Disease",
    "Cystic Fibrosis",
    "Primary Oxalosis",
    "Graft Versus Host Disease",
    "Hyperlipidaemia",
    "Trauma",
    "Tyrosinaemia",
    "Familial Amyloidosis",
    "Familial Cholestasis",
    "Neonatal Hepatitis",
    "Polycystic Liver Disease",
    "Hereditary haemochromatosis",
    "Glycogen Storage Disease",
    "Progressive Familial
Disease",
    "Neonatal Haemochromatosis",
    "Neimann-Pick Type C",
    "Hypercholesterolaemia",
    "Urea Cycle Disorder",
    "Crigler-Najjar Syndrome",
    "Cholesterol Ester Storage
(artery plus vein)",
    "Alper's Syndrome",
    "Acute Rejection",
    "Chronic Rejection",
    "Primary Non-Function",
    "Acute Vascular Occlusion
Venous",
    "Non-Thrombotic Infarction",
    "Ductopenic Rejection",
    "Recurrent Disease",
    "Biliary Complications",
    "Hepatic Artery Thrombosis",
    "Early Graft Dysfunction",
    "Acute Vascular Occlusion -
Artery and Venous",
    "Acute Vascular Occlusion -
Cholangitis",
    "Mitochondrial Disease",
    "Alagilles Syndrome",
    "Neonatal Sclerosing
    "Other Neonatal Cholestasis",
    "Other",
    "Unknown",
    "Not Reported")) %>%
  ff_label("Recipient Primary Liver Disease"),
  rcspld2.factor = factor(rcspld2, levels = c(400, 410, 411, 412,
413, 414, 415, 416, 417,
418, 419, 420, 421,
422, 423, 424, 425, 426,

```

```

427, 428, 430, 431,
432, 433, 434, 435, 436,
437, 438, 439, 440,
441, 442, 443, 444, 445,
446, 447, 448, 450,
451, 452, 453, 454, 455,
456, 457, 458, 459,
460, 461, 462, 463, 464,
465, 466, 467, 468,
469, 470, 471, 472, 473,
474, 475, 476, 477,
478, 479, 480, 481, 482,
483, 484, 485, 486,
498, 499, 888),
labels = c("Liver Disease Unknown",
"Chronic Liver Failure - Cause
Unknown",
"Primary Biliary Cirrhosis",
"Autoimmune Chronic Active Liver
Disease",
"Hepatitis B Cirrhosis",
"Primary Sclerosing
Cholangitis",
"Alpha-1-Antitrypsin
Deficiency",
"Budd-Chiari Syndrome",
"Cryptogenic Cirrhosis",
"Secondary Biliary Cirrhosis",
"Alcoholic Liver Disease",
"Biliary Atresia",
"Congenital Hepatic Fibrosis",
"Wilson's Disease",
"Congenital Biliary Disease",
"Hepatitis C Cirrhosis",
"Paediatric Cholestatic Liver
Disease",
"Non-alcoholic Fatty Liver
Disease",
"Acute Hepatic Failure - Budd-
Chiari Syndrome",
"Acute Hepatic Failure - Other
Virus",
"Acute Hepatic Failure -
Serologically Indeterminate",
"FHF - Viral",
"FHF - Drug Induced",
"FHF - Toxin Induced",
"Acute Hepatic Failure -
Wilson's Disease",
"Acute Hepatic Failure - HAV",
"Acute Hepatic Failure - HBV",
"Acute Hepatic Failure -
Paracetamol Hepatotoxicity",
"Acute Hepatic Failure - Other
Drug Toxicity",
"Acute Hepatic Failure - Other",
"Malignancy - Not Classifiable",

```

```

Cirrhotic",
Cirrhotic",
Malignancy",

Intrahepatic Cholestasis",

Disease",

(artery plus vein)",

Venous",
Artery and Venous",

Cholangitis",

ff_label("Recipient Secondary Liver Disease"),

"Hepatocellular Carcinoma - Non-
"Hepatocellular Carcinoma -
"Cholangiocarcinoma",
"Hepatoblastoma",
"Secondary Hepatic Malignancy",
"Other Mesenchymal Tumours",
"Other Primary Hepatic

"Benign Liver Tumour",
"Other Metabolic Liver Disease",
"Cystic Fibrosis",
"Primary Oxalosis",
"Graft Versus Host Disease",
"Hyperlipidaemia",
"Trauma",
"Tyrosinaemia",
"Familial Amyloidosis",
"Familial Cholestasis",
"Neonatal Hepatitis",
"Polycystic Liver Disease",
"Hereditary haemochromatosis",
"Glycogen Storage Disease",
"Progressive Familial

"Neonatal Haemochromatosis",
"Neimann-Pick Type C",
"Hypercholesterolaemia",
"Urea Cycle Disorder",
"Crigler-Najjar Syndrome",
"Cholesterol Ester Storage

"Alper's Syndrome",
"Acute Rejection",
"Chronic Rejection",
"Primary Non-Function",
"Acute Vascular Occlusion

"Non-Thrombotic Infarction",
"Ductopenic Rejection",
"Recurrent Disease",
"Biliary Complications",
"Hepatic Artery Thrombosis",
"Early Graft Dysfunction",
"Acute Vascular Occlusion -

"Acute Vascular Occlusion -

"Mitochondrial Disease",
"Alagilles Syndrome",
"Neonatal Sclerosing

"Other Neonatal Cholestasis",
"Other",
"Unknown",
"Not Reported")) %>%

```

```

    rcspld3.factor = factor(rcspld3, levels = c(400, 410, 411, 412,
413, 414, 415, 416, 417,
                                                    418, 419, 420, 421,
422, 423, 424, 425, 426,
                                                    427, 428, 430, 431,
432, 433, 434, 435, 436,
                                                    437, 438, 439, 440,
441, 442, 443, 444, 445,
                                                    446, 447, 448, 450,
451, 452, 453, 454, 455,
                                                    456, 457, 458, 459,
460, 461, 462, 463, 464,
                                                    465, 466, 467, 468,
469, 470, 471, 472, 473,
                                                    474, 475, 476, 477,
478, 479, 480, 481, 482,
                                                    483, 484, 485, 486,
498, 499, 888),
labels = c("Liver Disease Unknown",
           "Chronic Liver Failure - Cause
Unknown",
           "Primary Biliary Cirrhosis",
           "Autoimmune Chronic Active Liver
Disease",
           "Hepatitis B Cirrhosis",
           "Primary Sclerosing
Cholangitis",
           "Alpha-1-Antitrypsin
Deficiency",
           "Budd-Chiari Syndrome",
           "Cryptogenic Cirrhosis",
           "Secondary Biliary Cirrhosis",
           "Alcoholic Liver Disease",
           "Biliary Atresia",
           "Congenital Hepatic Fibrosis",
           "Wilson's Disease",
           "Congenital Biliary Disease",
           "Hepatitis C Cirrhosis",
           "Paediatric Cholestatic Liver
Disease",
           "Non-alcoholic Fatty Liver
Disease",
           "Acute Hepatic Failure - Budd-
Chiari Syndrome",
           "Acute Hepatic Failure - Other
Virus",
           "Acute Hepatic Failure -
Serologically Indeterminate",
           "FHF - Viral",
           "FHF - Drug Induced",
           "FHF - Toxin Induced",
           "Acute Hepatic Failure -
Wilson's Disease",
           "Acute Hepatic Failure - HAV",
           "Acute Hepatic Failure - HBV",
           "Acute Hepatic Failure -
Paracetamol Hepatotoxicity",

```

Drug Toxicity",

Cirrhotic",

Cirrhotic",

Malignancy",

Intrahepatic Cholestasis",

Disease",

(artery plus vein)",

Venous",

Artery and Venous",

Cholangitis",

"Acute Hepatic Failure - Other

"Acute Hepatic Failure - Other",

"Malignancy - Not Classifiable",

"Hepatocellular Carcinoma - Non-

"Hepatocellular Carcinoma -

"Cholangiocarcinoma",

"Hepatoblastoma",

"Secondary Hepatic Malignancy",

"Other Mesenchymal Tumours",

"Other Primary Hepatic

"Benign Liver Tumour",

"Other Metabolic Liver Disease",

"Cystic Fibrosis",

"Primary Oxalosis",

"Graft Versus Host Disease",

"Hyperlipidaemia",

"Trauma",

"Tyrosinaemia",

"Familial Amyloidosis",

"Familial Cholestasis",

"Neonatal Hepatitis",

"Polycystic Liver Disease",

"Hereditary haemochromatosis",

"Glycogen Storage Disease",

"Progressive Familial

"Neonatal Haemochromatosis",

"Neimann-Pick Type C",

"Hypercholesterolaemia",

"Urea Cycle Disorder",

"Crigler-Najjar Syndrome",

"Cholesterol Ester Storage

"Alper's Syndrome",

"Acute Rejection",

"Chronic Rejection",

"Primary Non-Function",

"Acute Vascular Occlusion

"Non-Thrombotic Infarction",

"Ductopenic Rejection",

"Recurrent Disease",

"Biliary Complications",

"Hepatic Artery Thrombosis",

"Early Graft Dysfunction",

"Acute Vascular Occlusion -

"Acute Vascular Occlusion -

"Mitochondrial Disease",

"Alagilles Syndrome",

"Neonatal Sclerosing

"Other Neonatal Cholestasis",

```

        "Other",
        "Unknown",
        "Not Reported")) %>%
  ff_label("Recipient Tertiary Liver Disease"),
  rfail_grade.factor = factor(rfail_grade, levels = c(1, 2, 3, 4),
    labels = c("Hyperacute", "Acute",
"Subacute", "Not Acute")) %>%
  ff_label("Recipient Liver Failure Grade"),
  rlife.factor = factor(rlife, levels = c(1, 2, 3, 4, 5, 7, 8, 9),
    labels = c("0",
      "1",
      "2",
      "3",
      "4",
      "5",
      "Not Reported",
      "Unknown")) %>%
  ff_label("Recipient Lifestyle Activity Score"),
  rin_pat.factor = factor(rin_pat, levels = c(1, 2),
    labels = c("No", "Yes")) %>%
  ff_label("Recipient Inpatient Status"),
  rvent.factor = factor(rvent, levels = c(1, 2),
    labels = c("No", "Yes")) %>%
  ff_label("Recipient Ventilation Status"),
  rren_sup.factor = factor(rren_sup, levels = c(1, 2, 3),
    labels = c("haemodialysis", "Filtration",
"Not Required")) %>%
  ff_label("Recipient Renal Support Status"),
  rascites.factor = factor(rascites, levels = c(1, 2),
    labels = c("No", "Yes")) %>%
  ff_label("Recipient Ascites"),
  rdiuretic.factor = factor(rdiuretic, levels = c(1, 2),
    labels = c("No", "Yes")) %>%
  ff_label("Recipient Diuretic Therapy Status"),
  renceph.factor = factor(renceph, levels = c(0, 1, 2, 3, 4),
    labels = c("Not Encephalopathic", "Grade
1", "Grade 2",
      "Grade 3", "Grade 4")) %>%
  ff_label("Recipient Encephalopathy Grade"),
  rab_surgery.factor = factor(rab_surgery, levels = c(1, 2),
    labels = c("No", "Yes")) %>%
  ff_label("Recipient Abdominal Surgery Indicator"),
  ricp_mon.factor = factor(ricp_mon, levels = c(1, 2, 3),
    labels = c("Normal Pressure", "Raised
Pressure", "Not Used")) %>%
  ff_label("Recipient ICP Monitor Results"),
  roes_varices.factor = factor(roes_varices, levels = c(1, 2, 3),
    labels = c("No Previous Variceal Bleed",
      "Previous Variceal Bleed",
      "Not Present")) %>%
  ff_label("Recipient Oesophageal Varices"),
  roes_shunt.factor = factor(roes_shunt, levels = c(1, 2, 3),
    labels = c("No Portosystemic Shunt",
      "Surgical Shunt",
      "TIPS")) %>%
  ff_label("Recipient Shunt for Varices (if Present)"),
  rpyrexial.factor = factor(rpyrexial, levels = c(1, 2),
    labels = c("No", "Yes")) %>%

```

```

ff_label("Recipient Pyrexial Indicator"),
rsepsis.factor = factor(rsepsis, levels = c(1, 2),
                        labels = c("No", "Yes")) %>%
ff_label("Recipient Sepsis Confirmed Indicator"),
rsepsis_site.factor = factor(rsepsis_site, levels = c(1, 2, 3, 4,
5, 7),
                             labels = c("Sputum",
                                         "Bloods",
                                         "Urine",
                                         "Ascites/ Drain Fluid",
                                         "Wound",
                                         "Other")) %>%
ff_label("Recipient Site of Sepsis (if present)"),
rhbv_dna.factor = factor(rhbv_dna, levels = c(1, 2, 3, 4, 5, 6, 7,
8, 9, 10),
                        labels = c("Negative",
                                    "Positive",
                                    "Indeterminate",
                                    "Repeat Negative",
                                    "Confirmed Positive",
                                    "Test Result Awaited",
                                    "Not Tested",
                                    "Not Reported",
                                    "Unknown",
                                    "Non-specific Reactivity")) %>%
ff_label("Recipient HBV DNA Antigen Result"),
rhbs_ag.factor = factor(rhbs_ag, levels = c(1, 2, 3, 4, 5, 6, 7, 8,
9, 10),
                        labels = c("Negative",
                                    "Positive",
                                    "Indeterminate",
                                    "Repeat Negative",
                                    "Confirmed Positive",
                                    "Test Result Awaited",
                                    "Not Tested",
                                    "Not Reported",
                                    "Unknown",
                                    "Non-specific Reactivity")) %>%
ff_label("Recipient HBs AG Antigen Result"),
rhbe_ag.factor = factor(rhbe_ag, levels = c(1, 2, 3, 4, 5, 6, 7, 8,
9, 10),
                        labels = c("Negative",
                                    "Positive",
                                    "Indeterminate",
                                    "Repeat Negative",
                                    "Confirmed Positive",
                                    "Test Result Awaited",
                                    "Not Tested",
                                    "Not Reported",
                                    "Unknown",
                                    "Non-specific Reactivity")) %>%
ff_label("Recipient HBe AG Antigen Result"),
rhcv_rna.factor = factor(rhcv_rna, levels = c(1, 2, 3, 4, 5, 6, 7,
8, 9, 10),
                        labels = c("Negative",
                                    "Positive",
                                    "Indeterminate",
                                    "Repeat Negative",

```

```

"Confirmed Positive",
"Test Result Awaited",
"Not Tested",
"Not Reported",
"Unknown",
"Non-specific Reactivity")) %>%
  ff_label("Recipient HCV-RNA (PCA) Antigen Result"),
  ranti_hbclgm.factor = factor(ranti_hbclgm, levels = c(1, 2, 3, 4,
5, 6, 7, 8, 9, 10),
  labels = c("Negative",
"Positive",
"Indeterminate",
"Repeat Negative",
"Confirmed Positive",
"Test Result Awaited",
"Not Tested",
"Not Reported",
"Unknown",
"Non-specific Reactivity")) %>%
  ff_label("Recipient Anti HBclgM Result"),
  ranti_hbs.factor = factor(ranti_hbs, levels = c(1, 2, 3, 4, 5, 6,
7, 8, 9, 10),
  labels = c("Negative",
"Positive",
"Indeterminate",
"Repeat Negative",
"Confirmed Positive",
"Test Result Awaited",
"Not Tested",
"Not Reported",
"Unknown",
"Non-specific Reactivity")) %>%
  ff_label("Recipient Anti HBs Result"),
  ranti_hbe.factor = factor(ranti_hbe, levels = c(1, 2, 3, 4, 5, 6,
7, 8, 9, 10),
  labels = c("Negative",
"Positive",
"Indeterminate",
"Repeat Negative",
"Confirmed Positive",
"Test Result Awaited",
"Not Tested",
"Not Reported",
"Unknown",
"Non-specific Reactivity")) %>%
  ff_label("Recipient Anti HBe Result"),
  ranti_hcv.factor = factor(ranti_hcv, levels = c(1, 2, 3, 4, 5, 6,
7, 8, 9, 10),
  labels = c("Negative",
"Positive",
"Indeterminate",
"Repeat Negative",
"Confirmed Positive",
"Test Result Awaited",
"Not Tested",
"Not Reported",
"Unknown",
"Non-specific Reactivity")) %>%

```

```

ff_label("Recipient Anti HCV Result"),
ranti_delta.factor = factor(ranti_delta, levels = c(1, 2, 3, 4, 5,
6, 7, 8, 9, 10),
labels = c("Negative",
"Positive",
"Indeterminate",
"Repeat Negative",
"Confirmed Positive",
"Test Result Awaited",
"Not Tested",
"Not Reported",
"Unknown",
"Non-specific Reactivity")) %>%
ff_label("Recipient Anti Delta Result"),
ranti_cmh.factor = factor(ranti_cmh, levels = c(1, 2, 3, 4, 5, 6,
7, 8, 9, 10),
labels = c("Negative",
"Positive",
"Indeterminate",
"Repeat Negative",
"Confirmed Positive",
"Test Result Awaited",
"Not Tested",
"Not Reported",
"Unknown",
"Non-specific Reactivity")) %>%
ff_label("Recipient Anti CMV Result"),
ranti_hsv.factor = factor(ranti_hsv, levels = c(1, 2, 3, 4, 5, 6,
7, 8, 9, 10),
labels = c("Negative",
"Positive",
"Indeterminate",
"Repeat Negative",
"Confirmed Positive",
"Test Result Awaited",
"Not Tested",
"Not Reported",
"Unknown",
"Non-specific Reactivity")) %>%
ff_label("Recipient Anti HSV Result"),
ranti_hiv.factor = factor(ranti_hiv, levels = c(1, 2, 3, 4, 5, 6,
7, 8, 9, 10),
labels = c("Negative",
"Positive",
"Indeterminate",
"Repeat Negative",
"Confirmed Positive",
"Test Result Awaited",
"Not Tested",
"Not Reported",
"Unknown",
"Non-specific Reactivity")) %>%
ff_label("Recipient Anti HIV Result"),
pres_fluid.factor = factor(pres_fluid, levels = c(0, 1, 2, 3, 4, 6,
7, 8, 10, 20, 21, 22, 23, 27, 28,
29, 30, 40, 50,
60, 66, 70, 77, 79, 80, 88, 90, 95,
98, 99),

```

```

labels = c("Not Known",
           "Sacks",
           "Perfudex",
           "Dextran 40",
           "Gelin",
           "Hartmanns",
           "Manitol",
           "Rheomacrodex",
           "Euro Collins",
           "University of Wisconsin
(ViaSpan)",
           "U.W. (Commercial)",
           "Modified U.W. (High Na+)",
           "Modified U.W. (High K+)",
           "Other Liver Preservation
Fluid",
           "Not Reported",
           "Unknown",
           "Hyperosmolar Citrate
(Marshalls/ HOC/ Soltran)",
           "Phosphate Buffered Sucrose
(PBS)",
           "St Thomas'",
           "Papworth Solution",
           "Not Perfused/ Not
Applicable",
           "Low Potassium Dextran",
           "Not Perfused/ Not
Applicable",
           "Machine Preservation -
Other",
           "Celsior",
           "Not reported",
           "Histidine-Tryptophan-
Ketoglutarate (HTK/ Custodial)",
           "Other",
           "Other",
           "Unknown")) %>%

ff_label("Preservation Fluid"),
org_app.factor = factor(org_app, levels = c(1, 2),
                        labels = c("Healthy", "Suboptimal")) %>%
ff_label("Donor Organ Appearance"),
hep_artery.factor = factor(hep_artery, levels = c(1, 2),
                           labels = c("Single", "Accessory")) %>%
ff_label("Hepatic Artery Appearance"),
ba.factor = factor(ba, levels = c(1, 2, 3, 4),
                   labels = c("No Stent", "T-Tube", "Roux",
"Stent")) %>%
ff_label("Biliary Anastomosis"),
aa.factor = factor(aa, levels = c(1, 2),
                   labels = c("Single", "Multiple")) %>%
ff_label("Hepatic Artery Anastomosis"),
ranti_fib.factor = factor(ranti_fib, levels = c(1, 2),
                           labels = c("No", "Yes")) %>%
ff_label("Anti-Fibrinolytic Therapy"),
io_d.factor = factor(io_d, levels = c(1, 2),
                     labels = c("No", "Yes")) %>%
ff_label("Intraoperative Death"),

```

```

    cof.factor = factor(cof, levels = c(0, 410, 420, 430, 440, 441,
450, 460, 470, 480, 490, 495, 498, 499),
        labels = c("Graft Still functioning",
"Acute Rejection",
"Chronic Rejection",
"Primary Non-Function",
"Acute Vascular Occlusion",
"Vascular occlusion",
"Non-Thrombotic Infarction",
"Ductopenic Rejection",
"Recurrent Disease",
"Biliary Complications",
"Recipient Died; Graft Still
Functioning at Time of Death",
"Other",
"Other",
"Unknown")) %>%
    ff_label("Cause of Transplant Failure"),

    lost_fup.factor = factor(lost_fup, levels = c(1, 2),
        labels = c("No", "Yes")) %>%
    ff_label("Recipient Lost to Follow Up"),
    gstatus.factor = factor(gstatus, levels = c(1, 2, 3, 4),
        labels = c("Still Alive, Graft
Functioning",
"Graft Failed",
"Death with a Functioning
Graft",
"Death Only Reported")) %>%
    ff_label("Graft Status"),

    graft_no = ff_label(graft_no, "Number of Liver Transplant"),
    txnation = ff_label(txnation, "Nation of Transplant Centre"),
    txcountry = ff_label(txcountry, "Country Where Transplant
Performed"),
    dnation = ff_label(dnation, "Nation of Donor Hospital"),
    dcountry = ff_label(dcountry, "Country of Donor Hospital"),
    rage = ff_label(rage, "Recipient Age at transplant"),
    rimd = ff_label(rimd, "Recipient's IMD Deprivation Score (based on
postcode)"),
    rrank_imd = ff_label(rrank_imd, "Recipient's IMD Deprivation
Ranking Order (1 being most deprived)"),
    rweight = ff_label(rweight, "Recipient Weight (kg)"),
    rheight = ff_label(rheight, "Recipient Height (cm)"),
    rhb = ff_label(rhb, "Recipient Haemoglobin (gm/dl) Prior to
Transplant"),
    rwbc = ff_label(rwbc, "Recipient WBC (x10^9/l) Prior to
Transplant"),
    rplatelets = ff_label(rplatelets, "Recipient Platelets (x10^9/l)
Prior to Transplant"),
    rcreat = ff_label(rcreat, "Recipient Creatinine (µmol/l) Prior to
Transplant"),
    rcreat_corr = ff_label(rcreat_corr, "Recipient Corrected Creatinine
(µmol/l) (Royal Free) Prior to Transplant"),
    ralbumin = ff_label(ralbumin, "Recipient Albumin (g/l) Prior to
Transplant"),

```

```

    rurea = ff_label(rurea, "Recipient Urea (mmol/l) Prior to
Transplant"),
    rinr = ff_label(rinr, "Recipient INR Prior to Transplant"),
    rbilirubin = ff_label(rbilirubin, "Recipient Bilirubin ( $\mu$ mol/l)
Prior to Transplant"),
    rsodium = ff_label(rsodium, "Recipient Sodium (mmol/l) Prior to
Transplant"),
    ukeld = ff_label(ukeld, "Recipient UKELD"),
    meld = ff_label(meld, "Recipient MELD"),
    rpotassium = ff_label(rpotassium, "Recipient Potassium (mmol/l)
Prior to Transplant"),
    rph = ff_label(rph, "Recipient pH Prior to Transplant"),
    roxygen = ff_label(roxygen, "Recipient Oxygen pressure (kPa) Prior
to Transplant"),
    vv_time = ff_label(vv_time, "Veno-venous Bypass Time (hrs)"),
    io_blood = ff_label(io_blood, "Intraoperative Blood (units)"),
    io_plasma = ff_label(io_plasma, "Intraoperative Fresh Frozen Plasma
(units)"),
    io_platelets = ff_label(io_platelets, "Intraoperative Platelets
(units)"),
    io_cryo = ff_label(io_cryo, "Intraoperative Cryoprecipitate
(units)"),
    po_blood = ff_label(po_blood, "Postoperative Blood (units)"),
    po_plasma = ff_label(po_plasma, "Postoperative Plasma (units)"),
    po_platelets = ff_label(po_platelets, "Postoperative Platelets
(units)"),
    po_cryo = ff_label(po_cryo, "Postoperative Cryoprecipitate
(units)"),
    faildate = ff_label(faildate, "Month and Year of Graft Failure"),
    tsurv = ff_label(tsurv, "Transplant Survival Time (days)"),
    gsurv = ff_label(gsurv, "Graft Survival Time (days)"),
    psurv = ff_label(psurv, "Patient Survival Time (days)"),
    donoid = ff_label(donoid, "Donor Identification Number"),
    ddate = ff_label(ddate, "Month and Year of Donation"),
    graft_no = ff_label(graft_no, "Number of Liver Transplant"),
    dage_fac = ff_label(dage_fac, "Donor Age Group"),
    dage = ff_label(dage, "Donor Age"),
    dbmi = ff_label(dbmi, "Donor BMI"),
    cit = ff_label(cit, "Cold Ischaemic Time"),
    rep_time = ff_label(rep_time, "Reperfusion Time")
) -> uktrans

```

```

#RLIFE altered to make labels smaller for table - add captions with
categories:
#0 = "Normal Activity Without Restriction",
#1 = "Only Restricted in Physically Strenuous Activity",
#2 = "Can Move Freely. Capable of Self Care. Unable to Do Any Form of
Work",
#3 = "Only Capable of Limited Self Care. Confined Mostly to Bed or
Chair",
#4 = "Completely Reliant on Medical/ Nursing Care",
#5 = "Aged 5 Years or Less",
#"Not Reported",
#"Unknown"

```

```

#FILTER AND REMOVE RAGE <18 AND LIVING
DONORS=====

summary(uktrans$dcod.factor)
#Exclude DCOD = 0

summary(uktrans$dcod.factor) #380 level 0 which is living donor

uktrans %>%
  filter(! dcod.factor == "Living Donor") %>%
  filter(! rage <= 17) -> uktrans

uktrans$rage

#NEW FACTORS AND RE-ALLOCATING VARIABLE CRITERIA/ CUT
OFFS=====

#RECIPIENT AGE GROUPS:
#Make new rage_fac same way as dage_fac:
uktrans %>%
  mutate(rage = as.numeric(rage)) -> uktrans
#rage now numeric

library(Hmisc)
uktrans <- uktrans %>%
  mutate(rage_fac =
    cut2(rage, c(35, 50, 60)) %>%
    fct_recode(
      "<35" = "[18,35)",
      "35-50" = "[35,50)",
      "50-60" = "[50,60)",
      ">60" = "[60,76]") %>%
    ff_label("Recipient Age (Years)"))
#The above finally works - now use for other cuts continuous
variables...

summary(uktrans$rage_fac)

#DONOR AGE GROUPS:

uktrans <- uktrans %>%
  mutate(dage_fac =
    cut2(dage, c(35, 50, 60)) %>%
    fct_recode(
      "<35" = "[ 1,35)",
      "35-50" = "[35,50)",
      "50-60" = "[50,60)",
      ">60" = "[60,86]") %>%
    ff_label("Donor Age (Years)"))

summary(uktrans$dage_fac)
names(uktrans)

```

```

#DCD VS DBD DTYPE.FACTOR:

#NB Dtype.factor omits other types not DBD/ DCD
# make section called other
#Currently these are listed as "missing"

#ERA OF TRANSPLANT YEAR_FAC CUT OFFS:

# Set dates for each group - below are same as ELITA:

uktrans$year_fac %>% levels ()

uktrans <- uktrans %>%
  mutate(year_fac =
    cut2(tx_yr, c(2004, 2008)) %>%
    fct_recode(
      "Pre-2004" = "[1968,2004)",
      "2004-2008" = "[2004,2008)",
      "Post-2008" = "[2008,2016]") %>%
    ff_label("Era of Transplant"))

summary(uktrans$year_fac)
names(uktrans)

#DONOR BMI SPLIT INTO CATEGORIES:
#Underweight <18.5, Normal 18.5-24.9, Overweight 25-29.9, Obese >30

uktrans %>%
  mutate(dbmi_fac = cut2(dbmi, c(18.5, 25, 30)),
    dbmi_fac = ff_label(dbmi_fac, "Donor BMI Category")) ->
uktrans

uktrans$dbmi_fac %>% levels ()
summary(uktrans$dbmi_fac)

#Try new way to do...
uktrans <- uktrans %>%
  mutate(dbmi_fac =
    cut2(dbmi, c(18.5, 25, 30)) %>%
    fct_recode(
      "Underweight <18.5" = "[ 3.0, 18.5)",
      "Normal 18.5-25" = "[ 18.5, 25.0)",
      "Overweight 25-30" = "[ 25.0, 30.0)",
      "Obese >30" = "[ 30.0,142.9]") %>%
    ff_label("Donor BMI Category"))

summary(uktrans$dbmi_fac)

```

```

#COLD ISCHAEMIC TIME:

#First analyse how CIT is labelled
#?in minutes
#<>8hrs in literature most common cut off = 480 mins
#Make cuts <6hrs, 6-8hrs, 8-12hrs, >12hrs ; 360, 480, 720

uktrans$cit %>%
  summary()

uktrans %>%
  mutate(cit_fac = cut2(cit, c(360,480,720)),
         cit_fac = ff_label(cit_fac, "Cold ischaemic time - Minutes"))
-> uktrans

uktrans$cit_fac %>% levels ()
summary(uktrans$cit_fac)

#Need to deal with NA codes
#Which are 9999, 8888, 9909

uktrans$cit_fac <- uktrans$cit_fac %>%
  fct_collapse("Unknown" = c("9999", "8888", "9909"))

#Not working as cit_fac just cut groups of numeric
#?work from cit to rename these then re-do groups??
#Make cit factor first - new variable so dont mess up cit original

uktrans$cit.factor <- as.factor(uktrans$cit)

summary(uktrans$cit.factor)
#Then use cit.factor to rename codes:

uktrans$cit.factor <- uktrans$cit.factor %>%
  fct_collapse("Unknown" = c("9999", "8888", "9909"))

#Then use cit.factor to change to numeric and cut into groups??
#Check what cuts would be before recode:
#Back to numeric first:

uktrans$cit.factor <- as.numeric(uktrans$cit.factor)

uktrans <- uktrans %>%
  mutate(cit_fac =
         cut2(cit.factor, c(360,480,720)))

#This works - now rename groups:

uktrans <- uktrans %>%
  mutate(cit_fac =
         cut2(cit.factor, c(360,480,720)) %>%
         fct_recode(
           "<6h" = "[ 1, 360)",
           "6-8h" = "[ 360, 480)",
           "8-12h" = "[ 480, 720)",

```

```

">12h" = "[ 720,1065]") %>%
  ff_label("Cold Ischaemic Time (Hours)")

summary(uktrans$cit_fac)

#YEEEESSSS!!!!

# MELD SCORE TO GROUPS:

uktrans$meld %>%
  summary()

uktrans %>%
  mutate(meld_fac = cut2(meld, c(10, 15, 20)),
         meld_fac = ff_label(meld_fac, "MELD Score")) -> uktrans

uktrans$meld_fac %>% levels ()
summary(uktrans$meld_fac)
#Lots missing 6556

#Try new way to do...
uktrans <- uktrans %>%
  mutate(meld_fac =
         cut2(meld, c(10, 15, 20)) %>%
         fct_recode(
           "<10" = "[ 6,10)",
           "10-15" = "[10,15)",
           "15-20" = "[15,20)",
           ">20" = "[20,40]") %>%
         ff_label("MELD Score"))

summary(uktrans$meld_fac)

#UKELD re group into factor
#Cut offs -

uktrans$ukeld %>%
  summary()

uktrans %>%
  mutate(ukeld_fac = cut2(ukeld, c()),
         ukeld_fac = ff_label(ukeld_fac, "UKELD Score")) -> uktrans

uktrans$ukeld %>% levels ()
summary(uktrans$ukeld_fac)

#Try new way to do...
uktrans <- uktrans %>%
  mutate(year_fac =
         cut2(tx_yr, c(2004, 2008)) %>%
         fct_recode(
           "Pre-2004" = "[1968,2004)",

```

```

        "2004-2008" = "[2004,2008)",
        "Post-2008" = "[2008,2016]" %>%
ff_label("Era of Transplant")

summary(uktrans$year_fac)

#Need to rename unknown codes as NA

#Attempt to find WARM ISCHAEMIC TIME:
#What is rep_time??

uktrans$rep_time %>%
  summary()

#RECLASSIFY VARIABLE
LEVELS=====
=====

#DCOD:

uktrans$dcod.factor %>% levels()

uktrans$dcod.factor %>%
  fct_collapse("Brain tumour/ injury" = c("Brain Tumour",
                                          "Hypoxic Brain Damage",
                                          "Intracranial - Type
Unspecified (CVA)",
                                          "Trauma RTA" = c("Trauma RTA - Car",
                                          "Trauma RTA - Motorbike",
                                          "Trauma RTA - Pushbike",
                                          "Trauma RTA - Pedestrian",
                                          "Trauma RTA - Other",
                                          "Trauma RTA - Unknown Type"),
                                          "Trauma Other Cause" = c("Other Trauma - Known or
Suspected Suicide",
                                          "Other Trauma - Accident",
                                          "Other Trauma - Unknown
Cause"),
                                          "Cardiovascular" = c("Cardiac Arrest",
                                          "Myocardial Infarction",
                                          "Aneurysm (including Aortic)",
                                          "Ischaemic Heart Disease",
                                          "Congestive Cardiac Failure",
                                          "Pulmonary Embolism",
                                          "Cardiovascular - Type
Unclassified"),
                                          "Respiratory" = c("Chronic Pulmonary Disease",
                                          "Pneumonia",
                                          "Asthma",

```

```

        "Respiratory Failure",
        "Respiratory - Type Unclassified (inc
Smoke Inhalation)"),
        "Infection/ Sepsis" = c("Meningitis",
                                "Septicaemia",
                                "Infections - Type
Unclassified"),
        "Organ Failure" = c("Liver failure (not Self
Poisoning)",
                            "Renal Failure",
                            "Multi-organ Failure"),
        "Poisoning" = c("Alcohol Poisoning",
                        "Paracetamol Overdose",
                        "Other Drug Overdose",
                        "Self Poisoning - Type Unclassified",
                        "Carbon Monoxide Poisoning"),
        "Unknown" = c("Not Reported",
                      "Other",
                      "Other, please specify",
                      "Unknown" ) %>%
ff_label("Donor Cause of Death") ->
uktrans$dcod_new.factor

uktrans$dcod_new.factor %>% levels()

#DONOR CMV STATUS:
uktrans$dcmv.factor %>% levels()

uktrans$dcmv.factor %>%
  fct_collapse("Positive" = c("Positive", "Confirmed Positive"),
               "Negative" = c("Negative", "Repeat Negative"),
               "Unknown" = c("Indeterminate", "Test Result Awaited",
                             "Not Tested", "Not Reported",
                             "Unknown", "Non-specific Reactivity")) %>%
  ff_label("Donor CMV Status") ->
  uktrans$dcmv_new.factor

uktrans$dcmv_new.factor %>% levels()

#RECIPIENT CAUSE OF FAILURE:
#Use code below to group like variables and add empty variables to show
in database
#Call new variable rscpld_new.factor

uktrans$rcspld1.factor %>% levels()

uktrans$rcspld1.factor %>%
  fct_collapse("Unknown" = c("Liver Disease Unknown", "Chronic Liver
Failure - Cause Unknown",
                              "Other", "Unknown", "Not Reported"),

```

```

"Acute Hepatic Failure" = c("Acute Hepatic Failure -
Budd-Chiari Syndrome",
Other Virus",
Serologically Indeterminate",
Wilson's Disease",
HAV",
HBV",
Paracetamol Hepatotoxicity",
Other Drug Toxicity",
Other"),
"Fulminant Hepatic Failure" = c("FHF - Viral",
"FHF - Drug Induced",
"FHF - Toxin Induced"),
"Paediatric/ Neonatal Causes" = c("Paediatric
Cholestatic Liver Disease",
Haemochromatosis",
Cholangitis",
Cholestasis"),
"Neonatal Hepatitis",
"Neonatal
"Neonatal Sclerosing
"Other Neonatal
"Malignancy" = c("Malignancy - Not Classifiable",
"Hepatocellular Carcinoma - Non-
"Hepatocellular Carcinoma - Cirrhotic",
"Cholangiocarcinoma",
"Hepatoblastoma",
"Secondary Hepatic Malignancy",
"Other Mesenchymal Tumours",
"Other Primary Hepatic Malignancy",
"Recurrent Disease"), #Assumed means
malignant disease - check
"Autoimmune" = c("Primary Biliary Cirrhosis",
"Autoimmune Chronic Active Liver
Disease",
"Primary Sclerosing Cholangitis"),
"Infective" = c("Hepatitis B Cirrhosis",
"Hepatitis C Cirrhosis"),
"Metabolic" = c("Mitochondrial Disease",
"Hypercholesterolaemia",
"Urea Cycle Disorder",
"Hyperlipidaemia",
"Glycogen Storage Disease",
"Cholesterol Ester Storage Disease",
"Other Metabolic Liver Disease",
"Tyrosinaemia", #This is also genetic
"Crigler-Najjar Syndrome"), #This is
also genetic
"Congenital" = c("Biliary Atresia",

```

```

        "Congenital Hepatic Fibrosis",
        "Congenital Biliary Disease"),
"Genetic" = c("Alpha-1-Antitrypsin Deficiency",
              "Wilson's Disease",
              "Primary Oxalosis",
              "Familial Amyloidosis",
              "Familial Cholestasis",
              "Alagilles Syndrome",
              "Hereditary haemochromatosis",
              "Progressive Familial Intrahepatic
Cholestasis",
              "Neimann-Pick Type C",
              "Alper's Syndrome",
              "Cystic Fibrosis",
              "Polycystic Liver Disease"),
"Rejection" = c("Graft Versus Host Disease",
                "Acute Rejection",
                "Chronic Rejection",
                "Primary Non-Function",
                "Early Graft Dysfunction",
                "Ductopenic Rejection",
                "Biliary Complications"),
"Vascular" = c("Hepatic Artery Thrombosis",
               "Acute Vascular Occlusion - Venous",
               "Acute Vascular Occlusion - Artery and
Venous",
               "Acute Vascular Occlusion (artery plus
vein)",
               "Non-Thrombotic Infarction",
               "Budd-Chiari Syndrome"),
"Benign Causes Liver Disease" = c("Cryptogenic
Cirrhosis",
                                   "Secondary Biliary
Cirrhosis",
                                   "Alcoholic Liver
Disease",
                                   "Non-alcoholic Fatty
Liver Disease",
                                   "Benign Liver Tumour",
                                   "Trauma") ) %>%

  ff_label("Recipient Primary Liver Disease") ->
uktrans$rcspld_new.factor

uktrans$rcspld_new %>% levels()

#RECIPIENT ETHNIC GROUP:
uktrans$rethnic.factor %>% levels()

uktrans$rethnic.factor %>%
  fct_collapse("Other/Unknown" = c("Other", "Not Reported", "Unknown"))
%>%
  ff_label("Recipient Ethnicity Group") ->
  uktrans$rethnic_new.factor

uktrans$rethnic_new %>% levels()

```

```

#RECIPIENT CMV STATUS:
uktrans$rcmv.factor %>% levels()

uktrans$rcmv.factor %>%
  fct_collapse("Positive" = c("Positive", "Confirmed Positive"),
               "Negative" = c("Negative", "Repeat Negative"),
               "Unknown" = c("Indeterminate",
                              "Test Result Awaited",
                              "Not Tested",
                              "Not Reported",
                              "Unknown",
                              "Non-specific Reactivity")) %>%
  ff_label("Recipient CMV Status") ->
  uktrans$rcmv_new.factor

uktrans$rcmv_new %>% levels()

#RECIPIENT HCV STATUS:
uktrans$rhcv.factor %>% levels()

uktrans$rhcv.factor %>%
  fct_collapse("Positive" = c("Positive", "Confirmed Positive"),
               "Negative" = c("Negative", "Repeat Negative"),
               "Unknown" = c("Indeterminate",
                              "Test Result Awaited",
                              "Not Tested",
                              "Not Reported",
                              "Unknown",
                              "Non-specific Reactivity")) %>%
  ff_label("Recipient HCV Status ") ->
  uktrans$rhcv_new.factor

uktrans$rhcv_new.factor %>% levels()

#PRESERVATION FLUID:
uktrans$pres_fluid.factor %>% levels()

uktrans$pres_fluid.factor %>%
  fct_collapse("University of Wisconsin (ViaSpan)" = "University of
Wisconsin (ViaSpan)",
               "U.W. (Commercial)" = "U.W. (Commercial)",
               "Other" = c("Sacks",
                            "Perfudex",
                            "Dextran 40",
                            "Gelin",
                            "Hartmanns",
                            "Manitol",
                            "Rheomacrodex",
                            "Euro Collins",
                            "Modified U.W. (High Na+)",
                            "Modified U.W. (High K+)",
                            "Other Liver Preservation Fluid",
                            "Hyperosmolar Citrate (Marshalls/ HOC/
Soltran)",
                            "Phosphate Buffered Sucrose (PBS)",
                            "St Thomas'"),
  )

```

```

        "Papworth Solution",
        "Low Potassium Dextran",
        "Machine Preservation - Other",
        "Celsior",
        "Not reported",
        "Histidine-Tryptophan-Ketoglutarate (HTK/
Custodial)",
        "Other"),
    "Unknown" = c("Not Reported",
        "Unknown"),
    "Not Perfused" = "Not Perfused/ Not Applicable") %>%
  ff_label("Preservation FLuid") ->
  uktrans$pres_fluid_new.factor

uktrans$pres_fluid_new.factor %>% levels()

#CHANGING FACTORS TO NUMERIC=====IGNORE FOR
NOW=====

#LOOK AT INTRAOPERATIVE BLOOD PRODUCTS:
#SEEMS 888 AND 999 ARE MISSING, 0 MEANS NOT USED BUT ?WIDE VARIETY OF
NUMBER UNITS??
#?GROUP INTO <10, 10-40, 40-100 ETC??
#"io_blood","io_plasma","io_platelets","io_cryo","po_blood","po_plasma"
,"po_platelets","po_cryo"

#Start with io_blood seems to be set as factor
uktrans %>%
  ggplot(aes(io_blood))

uktrans$io_blood %>% str()

uktrans$io_blood_num <- as.numeric(uktrans$io_blood)

uktrans$io_blood_num %>% str()

uktrans %>%
  filter(tx_yr >=2000) %>%
  select(io_blood_num) %>%
  summary()

uktrans %>%
  ggplot(aes(x = io_blood_num, y = dage_fac)) +
  geom_boxplot() #This works now need to name variable

uktrans %>%
  mutate(io_blood_num = ff_label("Intraoperative Blood (Units)")) ->
  uktrans

#This isn't working need to fix then do same above for all other blood
products

```

```

#DEAL WITH MISSING
VALUES=====
=====

#Need to determine year onwards to analyse data from ie ?cut pre-2000
if missing data for large chunks variables

ff_glimpse(uktrans)

sum(is.na(uktrans))
#666289 missing values across whole uktrans dataset

library(GGally)
ggpairs(uktrans)#too big a dataset for this
?ggpairs

uktrans %>%
  missing_plot()

uktrans %>%
  filter(tx_yr >= 1990) %>%
  missing_plot() #Visually looks same as prev plot but cannot make out
variables

#Try looking at specific variables per year:
explanatory = c("urgent.factor", "dcod_new.factor")
dependent = "tx_yr"

explanatory = c("rethnic.factor", "rcod.factor", "rcspldl.factor")
dependent = "tx_yr"

uktrans %>%
  missing_pattern(dependent, explanatory)

#Use missing_pairs and missing_compare to see missing data for
variables:
# Github

explanatory = c("year_fac", "dbg.factor", "dcmv.factor")
dependent = "dage_fac"

#Add proportions:
uktrans %>%
  missing_pairs(dependent, explanatory, position = "fill")

uktrans %>%
  missing_compare(dependent, explanatory) %>% #Can only compare factors
with more than 2 levels
knitr::kable(row.names=FALSE, align = c("l", "l", "r", "r", "r")) #
Omit when you run

#Look at gcens as dependent as multivariable analysis is looking at
this
#So check variables against this dependent:

```

```

explanatory = c("year_fac", "dage", "dage_fac", "dcod_new.factor",
               "steatosis.factor", "dcmv_new.factor",
"rcmv_new.factor", "rhcv_new.factor", "rvent.factor",
               "rren_sup.factor", "abomatch.factor",
"rfail_grade.factor", "rin_pat.factor", "rascites.factor",
               "rdiuretic.factor", "renceph.factor",
"rab_surgery.factor", "rsepsis.factor", "pres_fluid_new.factor",
               "ba.factor", "ranti_fib.factor", "rcspld_new.factor",
"org_app.factor")
dependent = "gcens.factor"

```

```

#Above too big split into smaller chunks:
explanatory = c("year_fac", "dage", "dage_fac", "dcod_new.factor",
               "steatosis.factor", "dcmv_new.factor")
dependent = "gcens.factor"

```

```

#Still no output ?due to gcens.factor maybe not good for this due to
nature of variable

```

```

uktrans %>%
  count(is.na(gcens.factor)) #Graft survival 652 data missing

```

```

uktrans %>%
  count(is.na(pcens.factor)) #Recipient survival 2725 data missing

```

```

#Look at dage_fac as dependant first as all should be there for this:

```

```

#First check donor age present for every recipient as a baseline??
#Somehow compare txid with dage to check all match?
#Or look at total number dage entries as should be 19883 obs

```

```

names(uktrans)

```

```

uktrans %>%
  count(is.na(txid)) #So all txid present

```

```

uktrans %>%
  count(is.na(dage)) #So actually 102 with donor age missing

```

```

uktrans %>%
  count(is.na(year_fac)) #All of these present so good dependent to
work as baseline?

```

```

explanatory = c("year_fac", "dage_fac", "dcod_new.factor",
               "dcmv_new.factor", "rcmv_new.factor", "rhcv_new.factor",
"rvent.factor",
               "rren_sup.factor", "abomatch.factor",
"rfail_grade.factor", "rin_pat.factor", "rascites.factor",
               "rdiuretic.factor", "renceph.factor",
"rab_surgery.factor", "rsepsis.factor", "pres_fluid_new.factor",
               "ba.factor", "ranti_fib.factor", "rcspld_new.factor",
"org_app.factor")
dependent = "pcens.factor"

```

```

uktrans %>%

```

```

missing_compare(dependent, explanatory) %>% #Can only compare factors
with more than 2 levels
knitr::kable(row.names=FALSE, align = c("l", "l", "r", "r", "r"))

uktrans %>%
  missing_pairs(dependent, explanatory)

#Can choose specific variables and ask to show where missing values are
as table:
uktrans %>%
  select("dage_fac", "abomatch.factor", "rsepsis.factor") %>%
  filter(!complete.cases()) %>%
  view()

#Rsepsis looks very missing!
uktrans %>%
  count(is.na(rsepsis)) #3452 missing
uktrans %>%
  filter(tx_yr >=1995) %>%
  count(is.na(rsepsis)) #If filter out for >2000 then only #145
missing, From 1994 327 missing, >1995 211 missing
#This is likely the case for all recip variables

#Looking at Raw dataset 1994 onwards all recip data there
#Then Feb 2000 onwards logged intraoperative details

uktrans %>%
  count(is.na(pres_fluid_new.factor)) #3452 missing (NB same as
rsepsis)

uktrans %>%
  filter(tx_yr >=2000) %>%
  count(is.na(pres_fluid_new.factor)) #145 missing

#??SO FOR MINIMAL MISSING DATA LOOK AT YEAR 2000 ONWARDS AND ALSO RE-
CODE MISSING VARIABLES AS "UNKNOWN"
#ACROSS ALL VARIABLES ANALYSED?
#MAKE NEW DATASET - TO KEEP SEPARATE AND STILL ALLOW TO SHOW MISSING
VALUES WHERE NEEDED
#UKTRANS_NA.RM

uktrans_na.rm <- uktrans %>%
  mutate(urgent.factor = replace_na(urgent.factor, "Unknown"),
         dbg.factor = replace_na(dbg.factor, "Unknown"),
         dtype.factor = replace_na(dtype.factor, "Unknown"),
         steatosis.factor = replace_na(steatosis.factor, "Unknown"),
         dcmv_new.factor = replace_na(dcmv_new.factor, "Unknown"),
         dcod_new.factor = replace_na(dcod_new.factor, "Unknown"),
         rbg.factor = replace_na(rbg.factor, "Unknown"),
         rethnic_new.factor = replace_na(rethnic_new.factor,
"Unknown"),
         rcmv_new.factor = replace_na(rcmv_new.factor, "Unknown"),
         rhcv_new.factor = replace_na(rhcv_new.factor, "Unknown"),
         rvent.factor = replace_na(rvent.factor, "Unknown"),
         rren_sup.factor = replace_na(rren_sup.factor, "Unknown"),

```

```

    abomatch.factor = replace_na(abomatch.factor, "Unknown"),
    rfail_grade.factor = replace_na(rfail_grade.factor,
"Unknown"),
    rlife.factor = replace_na(rlife.factor, "Unknown"),
    rin_pat.factor = replace_na(rin_pat.factor, "Unknown"),
    rascites.factor = replace_na(rascites.factor, "Unknown"),
    rdiuretic.factor = replace_na(rdiuretic.factor, "Unknown"),
    renceph.factor = replace_na(renceph.factor, "Unknown"),
    rab_surgery.factor = replace_na(rab_surgery.factor,
"Unknown"),
    roes_varices.factor = replace_na(roes_varices.factor,
"Unknown"),
    roes_shunt.factor = replace_na(reos_shunt.factor, "Unknown"),
    rsepsis.factor = replace_na(rsepsis.factor, "Unknown"),
    pres_fluid_new.factor = replace_na(pres_fluid_new.factor,
"Unknown"),
    ba.factor = replace_na(ba.factor, "Unknown"),
    aa.factor = replace_na(aa.factor, "Unknown"),
    rantifib.factor = replace_na(rantifib.factor, "Unknown"),
    rcspld_new.factor = replace_na(rcspld_new.factor, "Unknown"),
    org_app.factor = replace_na(org_app.factor, "Unknown"),
    hep_artery.factor = replace_na(hep_artery.factor, "Unknown")

```

#Below are numeric vectors not factors so above wont work

```

#year_fac = replace_na(year_fac, "Unknown"),
#dage = replace_na(dage, "Unknown"),
#dbmi = replace_na(dbmi, "Unknown"),
#dage_fac = replace_na(dage_fac, "Unknown"),
#dbmi_fac = replace_na(dmi_fac, "Unknown"),
#gcens.factor = replace_na(gcens.factor, "Unknown"),
#pcens.factor = replace_na(pcens.factor, "Unknown"),
#cit = replace_na(cit, "Unknown"),
#rep_time = replace_na(rep_time, "Unknown"),

```

#Look at non-factors/ numerical variables:

```

uktrans %>%
  filter(tx_yr >=2000) %>%
  count(is.na(po_blood))

```

```

uktrans %>%
  count(is.na(meld)) #6556 whole dataset missing

```

```

uktrans %>%
  filter(tx_yr >=2000) %>%
  count(is.na(meld)) #2318 missing post yr 2000

```

```

uktrans %>%
  count(is.na(ukeld)) #6878 whole dataset missing

```

```

uktrans %>%
  filter(tx_yr >=2000) %>%
  count(is.na(ukeld)) #2332 missing post yr 2000

```

```

#GET RID OF PATIENTS FROM
DATASET??=====
#Patients under 5 yrs old ?347

uktrans$rage_grp.factor %>% levels()

uktrans$rage_grp.factor %>%
  summary() #2731 paediatric recipients below age of 16!!

#Do we need to remove kids from data? Study protocol originally said
look at adult whole liver transplant
#Keep in for now but note <16 are there and make new dataset excluding
and re-run if needed

uktrans %>%
  filter("dage" <16) %>%
  ggplot(aes(x = dage, y = tx_yr)) +
  geom_point()

uktrans %>%
  ggplot(aes(x = rage, y = tx_yr)) + #Looking at dage and rage plots
for multiple patients under age 16!!
  geom_point()

# DONOR AGE OVER
TIME=====
=====

dage_mean_time %>%
  filter(tx_yr >= 1990, tx_yr <2016) %>%
  ggplot(aes(x = tx_yr, y=dage_mean))+
  geom_point()+
  geom_smooth(method=lm, aes(group=1))+
  labs(x = "Year", y = "Mean Donor Age",
       caption = "Line of best fit showing 95% CI",
       title = "Mean Donor Age over Time - UK")

#Proportion of each donor age group over time
#Need to make new factor for proportion donor age groups:

library(dplyr)
prop <- with(uktrans, table(tx_yr, dage_fac)) %>% prop.table(margin =
1)
prop #This nicely shows proportion each dage group for each year in
table

```

```

#Now to plot this:
uktrans %>%
  filter(tx_yr >= 1990, tx_yr <2016) %>%
  ggplot(aes(x = tx_yr,
             fill = dage_fac)) +
  geom_bar(position = "fill") +
  scale_fill_brewer("Donor Age Group", palette = "Pastell") +
  labs(x = "Transplant Year", y = "Proportion",
       caption = "From 1990 onwards",
       title = "Donor Age Group Proportion per Year UK")

# LOOK AT YEAR OF TRANSPLANT
=====

table(uktrans$year_fac, uktrans$tx_yr)

uktrans %>%
  ggplot(aes(tx_yr, txid))

print(nrow(uktrans))
#nrow counts number of rows and ncol counts number of columns but how
to allow counts ie txs per year

uktrans %>%
  ggplot(aes(x = tx_yr)) +
  geom_bar(fill = "Blue") +
  labs(x = "Year of Transplant",
       y = "Number of Liver transplants",
       title = "Number of Whole Liver Transplants per Year UK")

#Need to be able to count how many transplants ?add new column

# PLOTTING VARIABLES - FACET WRAP
PLOTS?=====

#Donor Demographics - Factors/categoricalvariables eg:
uktrans %>%
  select(year_fac, dage_fac, urgent.factor, dbg.factor, dtype.factor,
         steatosis.factor, dcmv.factor) %>% #Add variables in here to plot
  gather() %>%
  ggplot(aes(value)) +
  facet_wrap(~key, scales = "free", ncol = 3) +
  geom_bar(aes(fill = value), show.legend = F) +
  coord_flip() +
  labs(x = "",
       y = "Total Number",
       title = "Donor Demographics UK",
       caption = "NHSBT data for ?date range")

```

```

#Need to figure out how to change facet label to ff_label for each
variable
#Then need to remove NA values?
?facet_wrap

#Donor Demographics - Continuous variables eg:
uktrans %>%
  select(dage, dbmi) %>% #Add variables in here to plot
  gather() %>%
  ggplot(aes(value)) +
  facet_wrap(~key, scales = "free", ncol = 3) +
  geom_histogram(alpha = 0.6) +
  labs(x = "",
       y = "Total Number",
       title = "Donor Demographics UK",
       caption = "NHSBT data for ?date range")
#Change scale on BMI to max around 50
#Add some colour

#Donor Demographics - Cause of death:
uktrans %>%
  ggplot(aes(dcod.factor)) +
  geom_bar(aes(fill = dcod.factor), show.legend = F) +
  coord_flip() +
  labs(y = "Number of Donors",
       x = "Cause of Death",
       title = "Donor Cause of Death UK")
#Need to remove NAs
#And group low numbers/ similar CODs - ie unknown all together,
infection all together, trauma all together

#Recipient Demographics - Factors/Categorical variables:
#Part 1
uktrans %>%
  select("rbg.factor", "rethnic.factor", "rcmv.factor", "rhcv.factor",
         "rvent.factor", "rren_sup.factor",
         "abomatch.factor", "rfail_grade.factor") %>% #Add variables in
here to plot
  gather() %>%
  ggplot(aes(value)) +
  facet_wrap(~key, scales = "free", ncol = 3) +
  geom_bar(aes(fill = value), show.legend = F) +
  coord_flip() +
  labs(x = "",
       y = "Total Number",
       title = "Recipient Demographics UK",
       caption = "NHSBT data for ?date range")
#Need to figure out how to change facet label to ff_label for each
variable
#Then need to remove NA values?

#Part 2
uktrans %>%
  select("rlife.factor", "rin_pat.factor",

```

```

        "rascites.factor", "rdiuretic.factor", "renceph.factor",
"rab_surgery.factor", "roes_varices.factor",
        "roes_shunt.factor", "rsepsis.factor") %>% #Add variables in
here to plot
gather() %>%
ggplot(aes(value)) +
facet_wrap(~key, scales = "free", ncol = 3) +
geom_bar(aes(fill = value), show.legend = F) +
coord_flip() +
labs(x = "",
      y = "Total Number",
      title = "Recipient Demographics UK",
      caption = "NHSBT data for ?date range")
#May need to split further

#Recipient Demographics - Continuous variables:
#eg ukeld, meld to start:

uktrans %>%
  ggplot(aes(x = "meld", y = "dage_fac"))

uktrans %>%
  select("ukeld", "meld") %>% #Add variables in here to plot
gather() %>%
ggplot(aes(x = value, y = "dage_fac")) +
facet_wrap(~key, scales = "free") +
geom_point() +
labs(x = "",
      y = "",
      title = "Recipient Demographics UK",
      caption = "NHSBT data for ?date range")

#WHICH FACTORS VARY SIGNIFICANTLY WITH DONOR
AGE?=====

#DONOR AGE WITH DONOR VARIABLES - FACET WRAP PLOTS:

uktrans %>%
  gather("year_fac", "dtype.factor", "urgent.factor", "dbmi_fac",
"dbg.factor", "steatosis.factor",
        "dcmv_new.factor", "dcod_new.factor", key = "var", value =
"value") %>%
  ggplot(aes(x = value, y = dage)) +
  geom_boxplot()+
  facet_wrap(~var, scales = "free", ncol = 3)

uktrans %>%
  ggplot(aes(x = dage, y = dcod_new.factor)) + #Shows better can see
labels
  geom_boxplot()

```

```

uktrans %>%
  ggplot(aes(x = dage, y = dbmi)) +
  geom_point() +
  geom_smooth() #Better than alt axes - shows good spread - made into
groups above in facet plot

```

#DONOR AGE WITH RECIPIENT VARIABLES - FACET WRAP PLOTS PART 1:

```

uktrans %>%
  gather("rbg.factor", "rethnic.factor", "rcmv.factor", "rhcv.factor",
"rvent.factor", "rren_sup.factor",
      "abomatch.factor", "rfail_grade.factor", "rlife.factor",
"rin_pat.factor", key = "var", value = "value") %>%
  ggplot(aes(x = value, y = dage)) +
  geom_boxplot()+
  facet_wrap(~var, scales = "free", ncol = 5)

```

#DONOR AGE WITH RECIPIENT VARIABLES - FACET WRAP PLOTS PART 2:

```

uktrans %>%
  gather("rascites.factor", "rdiuretic.factor", "renceph.factor",
"rab_surgery.factor", "roes_varices.factor",
      "roes_shunt.factor", "rsepsis.factor", key = "var", value =
"value") %>%
  ggplot(aes(x = value, y = dage)) +
  geom_boxplot()+
  facet_wrap(~var, scales = "free", ncol = 5)

```

#DONOR AGE WITH RECIPIENT BIOCHEMISTRY:

#DONOR AGE WITH RECIPIENT OPERATIVE BLOOD PRODUCTS:

#DONOR AGE WITH OPERATIVE FACTORS - FACET WRAP PLOTS:

```

uktrans %>%
  gather("pres_fluid_new.factor", "org_app.factor",
"hep_artery.factor",
      "ba.factor", "aa.factor", "ranti_fib.factor", "io_d.factor",
"cit", key = "var", value = "value") %>%
  ggplot(aes(x = value, y = dage)) +
  geom_boxplot()+
  facet_wrap(~var, scales = "free", ncol = 3)

```

```

#WHICH INDIVIDUAL VARIABLES AFFECT
SURVIVAL?=====
==

#dage, rage, cit still to look at
#?Any other continuous variables

#GRAFT SURVIVAL - INDIVIDUAL VARIABLES:

#Year_fac Era of Transplant:
fit <- survfit(Surv(gsurv/365.25, gcens) ~ year_fac, data = uktrans)
ggsurvplot(fit,
  conf.int = TRUE,
  pval = TRUE,
  risk.table = TRUE,          # Add risk table
  risk.table.col = "strata",
  break.time.by = 1,
  xlim = c(0, 7), #Sets limit on what shown x axis but falls
off page
  ylab = "Probability of graft survival",xlab = "Time
(years)",
  main="Graft survival by Era - UKTR",
  test.for.trend = TRUE) #doesn't add anything?

#DCOD:
fit <- survfit(Surv(gsurv/365.25, gcens) ~ dcod_new.factor, data =
uktrans)
ggsurvplot(fit,
  conf.int = FALSE,
  pval = TRUE,
  risk.table = TRUE,
  risk.table.col = "strata",
  break.time.by = 1,
  xlim = c(0, 6), #Sets limit on what shown x axis but falls
off page
  ylab = "Probability of graft survival",xlab = "Time
(years)",
  main="Graft survival by Donor Cause of Death - UKTR",
  test.for.trend = FALSE)

#"dtype.factor" KM Curve:
fit <- survfit(Surv(gsurv/365.25, gcens) ~ dtype.factor, data =
uktrans)
ggsurvplot(fit,
  conf.int = TRUE,
  pval = TRUE,
  risk.table = TRUE,
  risk.table.col = "strata",
  break.time.by = 1,
  xlim = c(0, 10), #Sets limit on what shown x axis but falls
off page
  ylab = "Probability of graft survival",xlab = "Time
(years)",

```

```

        main="Graft survival by Donor Type - UKTR")
#Removed test for trend as only 2 groups

#"urgent.factor"KM Curve:
fit <- survfit(Surv(gsurv/365.25, gcens) ~ urgent.factor, data =
uktrans)
ggsurvplot(fit,
            conf.int = TRUE,
            pval = TRUE,
            risk.table = TRUE,
            risk.table.col = "strata",
            break.time.by = 1,
            xlim = c(0, 6), #Sets limit on what shown x axis but falls
off page
            ylab = "Probability of graft survival",xlab = "Time
(years)",
            main="Graft survival by Urgency - UKTR")

#"dbmi"KM Curve:
#Need to split into groups as factor to allow comparisons
#Cox PH regression can be used for continuous variables - estimate the
hazard ratio,
#comparing the exposed to the unexposed individuals at time t

#coxph(fit) - see section at bottom multivariable analysis

#Can do with new dbmi_fac groups:
fit <- survfit(Surv(gsurv/365.25, gcens) ~ dbmi_fac, data = uktrans)
ggsurvplot(fit,
            conf.int = TRUE,
            pval = TRUE,
            risk.table = TRUE,
            risk.table.col = "strata",
            break.time.by = 1,
            xlim = c(0, 10), #Sets limit on what shown x axis but falls
off page
            ylab = "Probability of graft survival",xlab = "Time
(years)",
            main="Graft survival by Donor BMI - UKTR",
            test.for.trend = TRUE)

#"dbg.factor"KM Curve:
fit <- survfit(Surv(gsurv/365.25, gcens) ~ dbg.factor, data = uktrans)
ggsurvplot(fit,
            conf.int = TRUE,
            pval = TRUE,
            risk.table = TRUE,
            risk.table.col = "strata",
            break.time.by = 1,
            xlim = c(0, 6), #Sets limit on what shown x axis but falls
off page
            ylab = "Probability of graft survival",xlab = "Time
(years)",

```

```

        main="Graft survival by Donor Blood Group - UKTR")

#"steatosis.factor" KM Curve
fit <- survfit(Surv(gsurv/365.25, gcens) ~ steatosis.factor, data =
uktrans)
ggsurvplot(fit,
            conf.int = TRUE,
            pval = TRUE,
            risk.table = TRUE,
            risk.table.col = "strata",
            break.time.by = 1,
            xlim = c(0, 6),
            ylab = "Probability of graft survival",xlab = "Time
(years) ",
            main="Graft survival by Graft Steatosis - UKTR")

#"dcmv_new.factor" KM Curve
fit <- survfit(Surv(gsurv/365.25, gcens) ~ dcmv_new.factor, data =
uktrans)
ggsurvplot(fit,
            conf.int = TRUE,
            pval = TRUE,
            risk.table = TRUE,
            risk.table.col = "strata",
            break.time.by = 1,
            xlim = c(0, 6),
            ylab = "Probability of graft survival",xlab = "Time
(years) ",
            main="Graft survival by Donor CMV Status - UKTR")

#"rbg.factor"
fit <- survfit(Surv(gsurv/365.25, gcens) ~ rbg.factor, data = uktrans)
ggsurvplot(fit,
            conf.int = TRUE,
            pval = TRUE,
            risk.table = TRUE,
            risk.table.col = "strata",
            break.time.by = 1,
            xlim = c(0, 6),
            ylab = "Probability of graft survival",xlab = "Time
(years) ",
            main="Graft survival by Recipient Blood Group - UKTR")

#"rethnic_new.factor"
fit <- survfit(Surv(gsurv/365.25, gcens) ~ rethnic_new.factor, data =
uktrans)
ggsurvplot(fit,
            conf.int = TRUE,
            pval = TRUE,
            risk.table = TRUE,
            risk.table.col = "strata",
            break.time.by = 1,
            xlim = c(0, 6),
            ylab = "Probability of graft survival",xlab = "Time
(years) ",
            main="Graft survival by Recipient Ethnic Group - UKTR")

```

```

#"rcmv_new.factor"
fit <- survfit(Surv(gsurv/365.25, gcens) ~ rcmv_new.factor, data =
uktrans)
ggsurvplot(fit,
            conf.int = TRUE,
            pval = TRUE,
            risk.table = TRUE,
            risk.table.col = "strata",
            break.time.by = 1,
            xlim = c(0, 6),
            ylab = "Probability of graft survival", xlab = "Time
(years)",
            main="Graft survival by Recipient CMV Status - UKTR")

#"rhcv_new.factor"
fit <- survfit(Surv(gsurv/365.25, gcens) ~ rhcv_new.factor, data =
uktrans)
ggsurvplot(fit,
            conf.int = TRUE,
            pval = TRUE,
            risk.table = TRUE,
            risk.table.col = "strata",
            break.time.by = 1,
            xlim = c(0, 6),
            ylab = "Probability of graft survival", xlab = "Time
(years)",
            main="Graft survival by Recipient HCV Status - UKTR")

#"rvent.factor"
fit <- survfit(Surv(gsurv/365.25, gcens) ~ rvent.factor, data =
uktrans)
ggsurvplot(fit,
            conf.int = TRUE,
            pval = TRUE,
            risk.table = TRUE,
            risk.table.col = "strata",
            break.time.by = 1,
            xlim = c(0, 6),
            ylab = "Probability of graft survival", xlab = "Time
(years)",
            main="Graft survival by Recipient Ventilation Status -
UKTR")

#"rren_sup.factor"
fit <- survfit(Surv(gsurv/365.25, gcens) ~ rren_sup.factor, data =
uktrans)
ggsurvplot(fit,
            conf.int = TRUE,
            pval = TRUE,
            risk.table = TRUE,
            risk.table.col = "strata",
            break.time.by = 1,
            xlim = c(0, 6),

```

```

      ylab = "Probability of graft survival",xlab = "Time
(years)",
      main="Graft survival by Recipient Renal Support Status -
UKTR")

#"abomatch.factor"
fit <- survfit(Surv(gsurv/365.25, gcens) ~ abomatch.factor, data =
uktrans)
ggsurvplot(fit,
            conf.int = TRUE,
            pval = TRUE,
            risk.table = TRUE,
            risk.table.col = "strata",
            break.time.by = 1,
            xlim = c(0, 6),
            ylab = "Probability of graft survival",xlab = "Time
(years)",
            main="Graft survival by ABO Match Status - UKTR")

#"rfail_grade.factor"
fit <- survfit(Surv(gsurv/365.25, gcens) ~ rfail_grade.factor, data =
uktrans)
ggsurvplot(fit,
            conf.int = TRUE,
            pval = TRUE,
            risk.table = TRUE,
            risk.table.col = "strata",
            break.time.by = 1,
            xlim = c(0, 6),
            ylab = "Probability of graft survival",xlab = "Time
(years)",
            main="Graft survival by Recipient Failure Grade - UKTR")
#?add test for trend ?

#"rlife.factor"
fit <- survfit(Surv(gsurv/365.25, gcens) ~ rlife.factor, data =
uktrans) #Patients under 16!!
ggsurvplot(fit,
            conf.int = TRUE,
            pval = TRUE,
            risk.table = TRUE,
            risk.table.col = "strata",
            break.time.by = 1,
            xlim = c(0, 6),
            ylab = "Probability of graft survival",xlab = "Time
(years)",
            main="Graft survival by Recipient Lifestyle Score - UKTR")

#"rin_pat.factor"
fit <- survfit(Surv(gsurv/365.25, gcens) ~ rin_pat.factor, data =
uktrans)
ggsurvplot(fit,
            conf.int = TRUE,
            pval = TRUE,
            risk.table = TRUE,
            risk.table.col = "strata",

```

```

        break.time.by = 1,
        xlim = c(0, 6),
        ylab = "Probability of graft survival", xlab = "Time
(years)",
        main="Graft survival by Recipient Inpatient Status - UKTR")

```

```

#"rascites.factor"
fit <- survfit(Surv(gsurv/365.25, gcens) ~ rascites.factor, data =
uktrans)
ggsurvplot(fit,
            conf.int = TRUE,
            pval = TRUE,
            risk.table = TRUE,
            risk.table.col = "strata",
            break.time.by = 1,
            xlim = c(0, 6),
            ylab = "Probability of graft survival", xlab = "Time
(years)",
            main="Graft survival by Recipient Ascites Status - UKTR")

```

```

#"rdiuretic.factor"
fit <- survfit(Surv(gsurv/365.25, gcens) ~ rdiuretic.factor, data =
uktrans)
ggsurvplot(fit,
            conf.int = TRUE,
            pval = TRUE,
            risk.table = TRUE,
            risk.table.col = "strata",
            break.time.by = 1,
            xlim = c(0, 6),
            ylab = "Probability of graft survival", xlab = "Time
(years)",
            main="Graft survival by Recipient Diuretic Status - UKTR")

```

```

#"renceph.factor"
fit <- survfit(Surv(gsurv/365.25, gcens) ~ renceph.factor, data =
uktrans)
ggsurvplot(fit,
            conf.int = TRUE,
            pval = TRUE,
            risk.table = TRUE,
            risk.table.col = "strata",
            break.time.by = 1,
            xlim = c(0, 6),
            ylab = "Probability of graft survival", xlab = "Time
(years)",
            main="Graft survival by Recipient Encephalopathy Status -
UKTR")

```

```

#"rab_surgery.factor"
fit <- survfit(Surv(gsurv/365.25, gcens) ~ rab_surgery.factor, data =
uktrans)
ggsurvplot(fit,
            conf.int = TRUE,
            pval = TRUE,
            risk.table = TRUE,
            risk.table.col = "strata",

```

```

        break.time.by = 1,
        xlim = c(0, 6),
        ylab = "Probability of graft survival",xlab = "Time
(years)",
        main="Graft survival by Recipient Abdominal Surgery Status -
UKTR")

#"roes_varices.factor"
fit <- survfit(Surv(gsurv/365.25, gcens) ~ roes_varices.factor, data =
uktrans)
ggsurvplot(fit,
            conf.int = TRUE,
            pval = TRUE,
            risk.table = TRUE,
            risk.table.col = "strata",
            break.time.by = 1,
            xlim = c(0, 6),
            ylab = "Probability of graft survival",xlab = "Time
(years)",
            main="Graft survival by Recipient Oesophageal Varices Status
- UKTR")

#"roes_shunt.factor"
fit <- survfit(Surv(gsurv/365.25, gcens) ~ roes_shunt.factor, data =
uktrans)
ggsurvplot(fit,
            conf.int = TRUE,
            pval = TRUE,
            risk.table = TRUE,
            risk.table.col = "strata",
            break.time.by = 1,
            xlim = c(0, 6),
            ylab = "Probability of graft survival",xlab = "Time
(years)",
            main="Graft survival by Recipient Oesophageal Shunt Status -
UKTR") #Check this title/ label name

#"rsepsis.factor"
fit <- survfit(Surv(gsurv/365.25, gcens) ~ rsepsis.factor, data =
uktrans)
ggsurvplot(fit,
            conf.int = TRUE,
            pval = TRUE,
            risk.table = TRUE,
            risk.table.col = "strata",
            break.time.by = 1,
            xlim = c(0, 6),
            ylab = "Probability of graft survival",xlab = "Time
(years)",
            main="Graft survival by Recipient Sepsis Status - UKTR")

#"pres_fluid_new.factor"
fit <- survfit(Surv(gsurv/365.25, gcens) ~ pres_fluid_new.factor, data
= uktrans)
ggsurvplot(fit,
            conf.int = TRUE,
            pval = TRUE,
            risk.table = TRUE,

```

```

        risk.table.col = "strata",
        break.time.by = 1,
        xlim = c(0, 6),
        ylab = "Probability of graft survival",xlab = "Time
(years)",
        main="Graft survival by Preservation Fluid - UKTR")

#"hep_artery.factor"
fit <- survfit(Surv(gsurv/365.25, gcens) ~ hep_artery.factor, data =
uktrans)
ggsurvplot(fit,
            conf.int = TRUE,
            pval = TRUE,
            risk.table = TRUE,
            risk.table.col = "strata",
            break.time.by = 1,
            xlim = c(0, 6),
            ylab = "Probability of graft survival",xlab = "Time
(years)",
            main="Graft survival by Hepatic Artery Appearance - UKTR")

# "ba.factor"
fit <- survfit(Surv(gsurv/365.25, gcens) ~ ba.factor, data = uktrans)
ggsurvplot(fit,
            conf.int = TRUE,
            pval = TRUE,
            risk.table = TRUE,
            risk.table.col = "strata",
            break.time.by = 1,
            xlim = c(0, 6),
            ylab = "Probability of graft survival",xlab = "Time
(years)",
            main="Graft survival by Biliary Anastomosis - UKTR")

#"aa.factor"
fit <- survfit(Surv(gsurv/365.25, gcens) ~ aa.factor, data = uktrans)
ggsurvplot(fit,
            conf.int = TRUE,
            pval = TRUE,
            risk.table = TRUE,
            risk.table.col = "strata",
            break.time.by = 1,
            xlim = c(0, 6),
            ylab = "Probability of graft survival",xlab = "Time
(years)",
            main="Graft survival by Hepatic Artery Anastomosis - UKTR")

#"ranti_fib.factor"
fit <- survfit(Surv(gsurv/365.25, gcens) ~ ranti_fib.factor, data =
uktrans)
ggsurvplot(fit,
            conf.int = TRUE,
            pval = TRUE,
            risk.table = TRUE,
            risk.table.col = "strata",
            break.time.by = 1,
            xlim = c(0, 6),

```

```

        ylab = "Probability of graft survival",xlab = "Time
(years)",
        main="Graft survival by Anti-fibrinolytic Therapy - UKTR")

#"io_d.factor" = Not suitable as by nature one whole level has died!!
:)

#Recipient COF vs graft survival:
fit <- survfit(Surv(gsurv/365.25, gcens) ~ rcspld_new.factor, data =
uktrans)
ggsurvplot(fit,
            conf.int = TRUE,
            pval = TRUE,
            risk.table = TRUE,          # Add risk table
            risk.table.col = "strata",
            break.time.by = 1,
            xlim = c(0, 10), #Sets limit on what shown x axis but falls
off page
            ylab = "Probability of graft survival",xlab = "Time
(years)",
            main="Graft survival by Recipient Cause of Death - UKTR")

#Interesting unknown cause has poorest survival on curve
#Look at ?urgency does this correlate with unknown ?more likely to be
unrecorded

explanatory = "rcspld_new.factor"
dependent = "urgent.factor"
uktrans %>%
  summary_factorlist(dependent, explanatory, p= TRUE, na_include =
TRUE,
                    add_dependent_label = TRUE,
                    dependent_label_prefix = "")

#Org_app
fit <- survfit(Surv(gsurv/365.25, gcens) ~ org_app.factor, data =
uktrans)
ggsurvplot(fit,
            conf.int = TRUE,
            pval = TRUE,
            risk.table = TRUE,          # Add risk table
            risk.table.col = "strata",
            break.time.by = 1,
            xlim = c(0, 10), #Sets limit on what shown x axis but falls
off page
            ylab = "Probability of graft survival",xlab = "Time
(years)",
            main="Graft survival by Organ Appearance at Time of
Transplant - UKTR")

```

```
#RECIPIENT SURVIVAL - INDIVIDUAL VARIABLES:
```

```

#Year_fac Era of Transplant KM Curve:
fit <- survfit(Surv(psurv/365.25, pcens) ~ year_fac, data = uktrans)
ggsurvplot(fit,
  conf.int = TRUE,
  pval = TRUE,
  risk.table = TRUE,          # Add risk table
  risk.table.col = "strata",
  break.time.by = 1,
  xlim = c(0, 7), #Sets limit on what shown x axis but falls
off page
  ylab = "Probability of Recipient Survival", xlab = "Time
(years)",
  main="Recipient survival by Era - UKTR",
  test.for.trend = TRUE)

```

```

#"dtype.factor" KM Curve:
fit <- survfit(Surv(psurv/365.25, pcens) ~ dtype.factor, data =
uktrans) #Graft and patient survival better for DCD!
ggsurvplot(fit,
  conf.int = TRUE,
  pval = TRUE,
  risk.table = TRUE,
  risk.table.col = "strata",
  break.time.by = 1,
  xlim = c(0, 10), #Sets limit on what shown x axis but falls
off page
  ylab = "Probability of Recipient survival", xlab = "Time
(years)",
  main="Recipient survival by Donor Type - UKTR")
#Removed test for trend as only 2 groups

```

```

#"urgent.factor"KM Curve:
fit <- survfit(Surv(psurv/365.25, pcens) ~ urgent.factor, data =
uktrans)
ggsurvplot(fit,
  conf.int = TRUE,
  pval = TRUE,
  risk.table = TRUE,
  risk.table.col = "strata",
  break.time.by = 1,
  xlim = c(0, 6), #Sets limit on what shown x axis but falls
off page
  ylab = "Probability of Recipient survival", xlab = "Time
(years)",
  main="Recipient survival by Urgency - UKTR")

```

```

#Can do with new dbmi_fac groups:
fit <- survfit(Surv(psurv/365.25, pcens) ~ dbmi_fac, data = uktrans)
ggsurvplot(fit,
  conf.int = TRUE,
  pval = TRUE,
  risk.table = TRUE,
  risk.table.col = "strata",
  break.time.by = 1,

```

```

xlim = c(0, 10), #Sets limit on what shown x axis but falls
off page
ylab = "Probability of Recipient survival",xlab = "Time
(years)",
main="Recipient survival by Donor BMI - UKTR")

#"dbg.factor"KM Curve:
fit <- survfit(Surv(psurv/365.25, pcens) ~ dbg.factor, data = uktrans)
ggsurvplot(fit,
  conf.int = TRUE,
  pval = TRUE,
  risk.table = TRUE,
  risk.table.col = "strata",
  break.time.by = 1,
  xlim = c(0, 6), #Sets limit on what shown x axis but falls
off page
  ylab = "Probability of Recipient survival",xlab = "Time
(years)",
  main="Recipient survival by Donor Blood Group - UKTR")

#"steatosis.factor" KM Curve
fit <- survfit(Surv(psurv/365.25, pcens) ~ steatosis.factor, data =
uktrans)
ggsurvplot(fit,
  conf.int = TRUE,
  pval = TRUE,
  risk.table = TRUE,
  risk.table.col = "strata",
  break.time.by = 1,
  xlim = c(0, 6),
  ylab = "Probability of Recipient survival",xlab = "Time
(years)",
  main="Recipient survival by Graft Steatosis - UKTR")

#"dcmv_new.factor" KM Curve
fit <- survfit(Surv(psurv/365.25, pcens) ~ dcmv_new.factor, data =
uktrans)
ggsurvplot(fit,
  conf.int = TRUE,
  pval = TRUE,
  risk.table = TRUE,
  risk.table.col = "strata",
  break.time.by = 1,
  xlim = c(0, 6),
  ylab = "Probability of Recipient survival",xlab = "Time
(years)",
  main="Recipient survival by Donor CMV Status - UKTR")

#"rbg.factor"
fit <- survfit(Surv(psurv/365.25, pcens) ~ rbg.factor, data = uktrans)
ggsurvplot(fit,
  conf.int = TRUE,
  pval = TRUE,
  risk.table = TRUE,
  risk.table.col = "strata",
  break.time.by = 1,

```

```

        xlim = c(0, 6),
        ylab = "Probability of Recipient survival", xlab = "Time
(years)",
        main="Recipient survival by Recipient Blood Group - UKTR")

#"rethnic_new.factor"
fit <- survfit(Surv(psurv/365.25, pcens) ~ rethnic_new.factor, data =
uktrans)
ggsurvplot(fit,
            conf.int = TRUE,
            pval = TRUE,
            risk.table = TRUE,
            risk.table.col = "strata",
            break.time.by = 1,
            xlim = c(0, 6),
            ylab = "Probability of Recipient survival", xlab = "Time
(years)",
            main="Recipient survival by Recipient Ethnic Group - UKTR")

#"rcmv_new.factor"
fit <- survfit(Surv(psurv/365.25, pcens) ~ rcmv_new.factor, data =
uktrans)
ggsurvplot(fit,
            conf.int = TRUE,
            pval = TRUE,
            risk.table = TRUE,
            risk.table.col = "strata",
            break.time.by = 1,
            xlim = c(0, 6),
            ylab = "Probability of Recipient survival", xlab = "Time
(years)",
            main="Recipient survival by Recipient CMV Status - UKTR")

#"rhcv_new.factor"
fit <- survfit(Surv(psurv/365.25, pcens) ~ rhcv_new.factor, data =
uktrans)
ggsurvplot(fit,
            conf.int = TRUE,
            pval = TRUE,
            risk.table = TRUE,
            risk.table.col = "strata",
            break.time.by = 1,
            xlim = c(0, 6),
            ylab = "Probability of Recipient survival", xlab = "Time
(years)",
            main="Recipient survival by Recipient HCV Status - UKTR")

#"rvent.factor"
fit <- survfit(Surv(psurv/365.25, pcens) ~ rvent.factor, data =
uktrans)
ggsurvplot(fit,
            conf.int = TRUE,
            pval = TRUE,
            risk.table = TRUE,

```

```

        risk.table.col = "strata",
        break.time.by = 1,
        xlim = c(0, 6),
        ylab = "Probability of Recipient survival",xlab = "Time
(years)",
        main="Recipient survival by Recipient Ventilation Status -
UKTR")

#"rren_sup.factor"
fit <- survfit(Surv(psurv/365.25, pcens) ~ rren_sup.factor, data =
uktrans)
ggsurvplot(fit,
            conf.int = TRUE,
            pval = TRUE,
            risk.table = TRUE,
            risk.table.col = "strata",
            break.time.by = 1,
            xlim = c(0, 6),
            ylab = "Probability of Recipient survival",xlab = "Time
(years)",
            main="Recipient survival by Recipient Renal Support Status -
UKTR")

#"abomatch.factor"
fit <- survfit(Surv(psurv/365.25, pcens) ~ abomatch.factor, data =
uktrans)
ggsurvplot(fit,
            conf.int = TRUE,
            pval = TRUE,
            risk.table = TRUE,
            risk.table.col = "strata",
            break.time.by = 1,
            xlim = c(0, 6),
            ylab = "Probability of Recipient survival",xlab = "Time
(years)",
            main="Recipient survival by ABO Match Status - UKTR")

#"rfail_grade.factor"
fit <- survfit(Surv(psurv/365.25, pcens) ~ rfail_grade.factor, data =
uktrans)
ggsurvplot(fit,
            conf.int = TRUE,
            pval = TRUE,
            risk.table = TRUE,
            risk.table.col = "strata",
            break.time.by = 1,
            xlim = c(0, 6),
            ylab = "Probability of Recipient survival",xlab = "Time
(years)",
            main="Recipient survival by Recipient Failure Grade - UKTR")

#"rlife.factor"
fit <- survfit(Surv(psurv/365.25, pcens) ~ rlife.factor, data =
uktrans) #Patients under 16!!
ggsurvplot(fit,

```

```

        conf.int = TRUE,
        pval = TRUE,
        risk.table = TRUE,
        risk.table.col = "strata",
        break.time.by = 1,
        xlim = c(0, 6),
        ylab = "Probability of Recipient survival",xlab = "Time
(years)", #Need to recode/name rlife groups
        main="Recipient survival by Recipient Lifestyle Score -
UKTR")

#"rin_pat.factor"
fit <- survfit(Surv(psurv/365.25, pcens) ~ rin_pat.factor, data =
uktrans)
ggsurvplot(fit,
            conf.int = TRUE,
            pval = TRUE,
            risk.table = TRUE,
            risk.table.col = "strata",
            break.time.by = 1,
            xlim = c(0, 6),
            ylab = "Probability of Recipient survival",xlab = "Time
(years)",
            main="Recipient survival by Recipient Inpatient Status -
UKTR")

#"rascites.factor"
fit <- survfit(Surv(psurv/365.25, pcens) ~ rascites.factor, data =
uktrans)
ggsurvplot(fit,
            conf.int = TRUE,
            pval = TRUE,
            risk.table = TRUE,
            risk.table.col = "strata",
            break.time.by = 1,
            xlim = c(0, 6),
            ylab = "Probability of Recipient survival",xlab = "Time
(years)",
            main="Recipient survival by Recipient Ascites Status -
UKTR")

#"rdiuretic.factor"
fit <- survfit(Surv(psurv/365.25, pcens) ~ rdiuretic.factor, data =
uktrans)
ggsurvplot(fit,
            conf.int = TRUE,
            pval = TRUE,
            risk.table = TRUE,
            risk.table.col = "strata",
            break.time.by = 1,
            xlim = c(0, 6),
            ylab = "Probability of Recipient survival",xlab = "Time
(years)",
            main="Recipient survival by Recipient Diuretic Status -
UKTR")

#"renceph.factor"

```

```

fit <- survfit(Surv(psurv/365.25, pcens) ~ reneceph.factor, data =
uktrans)
ggsurvplot(fit,
            conf.int = TRUE,
            pval = TRUE,
            risk.table = TRUE,
            risk.table.col = "strata",
            break.time.by = 1,
            xlim = c(0, 6),
            ylab = "Probability of Recipient survival",xlab = "Time
(years)",
            main="Recipient survival by Recipient Encephalopathy Status
- UKTR")

#"rab_surgery.factor"
fit <- survfit(Surv(psurv/365.25, pcens) ~ rab_surgery.factor, data =
uktrans)
ggsurvplot(fit,
            conf.int = TRUE,
            pval = TRUE,
            risk.table = TRUE,
            risk.table.col = "strata",
            break.time.by = 1,
            xlim = c(0, 6),
            ylab = "Probability of Recipient survival",xlab = "Time
(years)",
            main="Recipient survival by Recipient Abdominal Surgery
Status - UKTR")

#"roes_varices.factor"
fit <- survfit(Surv(psurv/365.25, pcens) ~ roes_varices.factor, data =
uktrans)
ggsurvplot(fit,
            conf.int = TRUE,
            pval = TRUE,
            risk.table = TRUE,
            risk.table.col = "strata",
            break.time.by = 1,
            xlim = c(0, 6),
            ylab = "Probability of Recipient survival",xlab = "Time
(years)",
            main="Recipient survival by Recipient Oesophageal Varices
Status - UKTR")

#"roes_shunt.factor"
fit <- survfit(Surv(psurv/365.25, pcens) ~ roes_shunt.factor, data =
uktrans)
ggsurvplot(fit,
            conf.int = TRUE,
            pval = TRUE,
            risk.table = TRUE,
            risk.table.col = "strata",
            break.time.by = 1,
            xlim = c(0, 6),
            ylab = "Probability of Recipient survival",xlab = "Time
(years)",
            main="Recipient survival by Recipient Oesophageal Shunt
Status - UKTR") #Check this title/ label name

```

```

#"rsepsis.factor"
fit <- survfit(Surv(psurv/365.25, pcens) ~ rsepsis.factor, data =
uktrans)
ggsurvplot(fit,
            conf.int = TRUE,
            pval = TRUE,
            risk.table = TRUE,
            risk.table.col = "strata",
            break.time.by = 1,
            xlim = c(0, 6),
            ylab = "Probability of Recipient survival",xlab = "Time
(years) ",
            main="Recipient survival by Recipient Sepsis Status - UKTR")

#pres_fluid_new.factor"
fit <- survfit(Surv(psurv/365.25, pcens) ~ pres_fluid_new.factor, data
= uktrans)
ggsurvplot(fit,
            conf.int = TRUE,
            pval = TRUE,
            risk.table = TRUE,
            risk.table.col = "strata",
            break.time.by = 1,
            xlim = c(0, 6),
            ylab = "Probability of Recipient survival",xlab = "Time
(years) ",
            main="Recipient survival by Preservation Fluid - UKTR")

#"hep_artery.factor"
fit <- survfit(Surv(psurv/365.25, pcens) ~ hep_artery.factor, data =
uktrans)
ggsurvplot(fit,
            conf.int = TRUE,
            pval = TRUE,
            risk.table = TRUE,
            risk.table.col = "strata",
            break.time.by = 1,
            xlim = c(0, 6),
            ylab = "Probability of Recipient survival",xlab = "Time
(years) ",
            main="Recipient survival by Hepatic Artery Appearance -
UKTR")

# "ba.factor"
fit <- survfit(Surv(psurv/365.25, pcens) ~ ba.factor, data = uktrans)
ggsurvplot(fit,
            conf.int = TRUE,
            pval = TRUE,
            risk.table = TRUE,
            risk.table.col = "strata",
            break.time.by = 1,
            xlim = c(0, 6),
            ylab = "Probability of Recipient survival",xlab = "Time
(years) ",
            main="Recipient survival by Biliary Anastomosis - UKTR")

#"aa.factor"

```

```

fit <- survfit(Surv(psurv/365.25, pcens) ~ aa.factor, data = uktrans)
ggsurvplot(fit,
            conf.int = TRUE,
            pval = TRUE,
            risk.table = TRUE,
            risk.table.col = "strata",
            break.time.by = 1,
            xlim = c(0, 6),
            ylab = "Probability of Recipient survival",xlab = "Time
(years)",
            main="Recipient survival by Hepatic Artery Anastomosis -
UKTR")

#"ranti_fib.factor"
fit <- survfit(Surv(psurv/365.25, pcens) ~ ranti_fib.factor, data =
uktrans)
ggsurvplot(fit,
            conf.int = TRUE,
            pval = TRUE,
            risk.table = TRUE,
            risk.table.col = "strata",
            break.time.by = 1,
            xlim = c(0, 6),
            ylab = "Probability of Recipient survival",xlab = "Time
(years)",
            main="Recipient survival by Anti-fibrinolytic Therapy -
UKTR")

#"io_d.factor" = Not suitable as by nature one whole level has died!!
:)

#Recipient COF vs Recipient survival:
fit <- survfit(Surv(psurv/365.25, pcens) ~ rcspld_new.factor, data =
uktrans)
ggsurvplot(fit,
            conf.int = FALSE, #Removed confidence interval ?easier to
read
            pval = TRUE,
            risk.table = TRUE,          # Add risk table
            risk.table.col = "strata",
            break.time.by = 1,
            xlim = c(0, 10), #Sets limit on what shown x axis but falls
off page
            ylab = "Probability of Recipient survival",xlab = "Time
(years)",
            main="Recipient survival by Recipient Cause of Death -
UKTR")

#org_app.factor
fit <- survfit(Surv(psurv/365.25, pcens) ~ org_app.factor, data =
uktrans)
ggsurvplot(fit,
            conf.int = TRUE,
            pval = TRUE,
            risk.table = TRUE,          # Add risk table
            risk.table.col = "strata",

```

```

        break.time.by = 1,
        xlim = c(0, 10), #Sets limit on what shown x axis but falls
off page
        ylab = "Probability of Recipient survival", xlab = "Time
(years)",
        main="Recipient survival by Organ Appearance at Time of
Transplant - UKTR")

```

```

# BASICS FOR START OF
RESULTS=====

```

```

#Number DCD vs DBD
uktrans$dtype.factor %>% summary()

```

```

#Mean donor age increase over time ?yrs inc +/-SD
dage_mean_time

```

```

#Increase proportion >60 over time - text for trend chi squared/ p
value

```

```

#How many donors <60 and >60 - how many donor age missing?
uktrans$dage_fac %>% summary()

```

```

summary(uktrans$tx_yr)

```

```

# CROSSTABLES - DONOR DEMOGRAPHICS UK
=====
=====

```

```

#include donor age, urgency, dtype, dcod?, dbmi, , dbg - to start
#include dcod

```

```

explanatory = c("year_fac", "dage", "dtype.factor", "urgent.factor",
"dbmi", "dbg.factor", "steatosis.factor", "dcmv.factor")

```

```

dependent = "dage_fac"

```

```

uktrans %>%

```

```

summary_factorlist(dependent, explanatory, p= TRUE, na_include =
TRUE,

```

```

        add_dependent_label = TRUE,

```

```

        dependent_label_prefix = "")#ADDED TO RMD TABLES AT
BOTTOM - SEE HERE FOR TABLE LABEL

```

```

#Separate table with dcod:

```

```

explanatory = "dcod_new.factor"

```

```

dependent = "dage_fac"
uktrans %>%
  summary_factorlist(dependent, explanatory, p= TRUE, na_include =
TRUE,
                    add_dependent_label = TRUE,
                    dependent_label_prefix = "")#ADDED TO RMD TABLES
AT BOTTOM - SEE HERE FOR TABLE LABEL

```

```

#New Donor COD graph:
uktrans %>%
  ggplot(aes(dcod_new.factor)) +
  geom_bar(aes(fill = dcod_new.factor), show.legend = F) +
  coord_flip() +
  labs(y = "Number of Donors",
       x = "Cause of Death",
       title = "Donor Cause of Death UK")

```

```

#CROSSTABLE - RECIPIENT DEMOGRAPHICS
UK=====
#Include rage_fac, rbg, rethnic, rcmv, rhcv, rvent, rren_sup to start
#Add "abomatch.factor", "rcspldl.factor", "rfail_grade.factor",
"rlife.factor", "rin_pat.factor",
# "rascites.factor", "rdiuretic.factor", "renceph.factor",
"rab_surgery.factor", "roes_varices.factor",
# "roes_shunt.factor", "rsepsis.factor"

```

```

explanatory = c("rbg.factor", "rethnic.factor", "rcmv.factor",
"rhcv.factor", "rvent.factor", "rren_sup.factor",
"abomatch.factor", "rfail_grade.factor",
"rlife.factor", "rin_pat.factor",
"rascites.factor", "rdiuretic.factor",
"renceph.factor", "rab_surgery.factor", "roes_varices.factor",
"roes_shunt.factor", "rsepsis.factor")
dependent = "rage_fac"
uktrans %>%
  summary_factorlist(dependent, explanatory, p= TRUE, na_include =
TRUE,
                    add_dependent_label = TRUE,
                    dependent_label_prefix = "")

```

```
knitr::kable(t, align=c("l", "l", "r", "r", "r", "r"))
```

```

#CROSSTABLE - RECIPIENT CAUSE OF LIVER
DISEASE=====
#rcspldl, 2 and 3
#as per rage group rage_fac

```

```

explanatory = "rcspldl.factor"
dependent = "rage_fac"
uktrans %>%
  summary_factorlist(dependent, explanatory, p= TRUE, na_include =
TRUE,
                    add_dependent_label = TRUE,
                    dependent_label_prefix = "") -> t2.1

```

```
#Include missing data in statistical tests using - na_to_p = TRUE
```

```
#TABLE OF RECIPIENT
```

```
BIOCHEMISTRY=====
```

```
explanatory = c("rimd",  
               "rrank_imd",  
               "rweight",  
               "rheight",  
               "rhb",  
               "rwbc",  
               "rplatelets",  
               "rcreat",  
               "rcreat_corr",  
               "ralbumin",  
               "rurea",  
               "rinr",  
               "rbilirubin",  
               "rsodium",  
               "ukeld",  
               "meld",  
               "rpotassium",  
               "rph",  
               "roxygen")  
dependent = "dage_fac"  
uktrans %>%  
  summary_factorlist(dependent, explanatory, p= TRUE, na_include =  
TRUE,  
                     add_dependent_label = TRUE,  
                     dependent_label_prefix = "") -> t  
knitr::kable(t, align=c("l", "l", "r", "r", "r", "r"))
```

```
#TABLE OF OPERATIVE
```

```
FACTORS=====
```

```
explanatory = c("pres_fluid_new.factor",  
               "org_app.factor",  
               "hep_artery.factor",  
               "ba.factor",  
               "aa.factor",  
               "ranti_fib.factor",  
               "io_d.factor",  
               "cit",  
               "vv_time",  
               "io_blood_num",  
               "io_plasma",  
               "io_platelets",  
               "io_cryo",  
               "po_blood",  
               "po_plasma",  
               "po_platelets",  
               "po_cryo")
```

```

dependent = "dage_fac"
uktrans %>%
  summary_factorlist(dependent, explanatory, p= TRUE, na_include =
TRUE,
                    add_dependent_label = TRUE,
                    dependent_label_prefix = "") -> t

knitr::kable(t, align=c("l", "l", "r", "r", "r", "r"))

uktrans$io_blood %>% summary()

#Need to recode these as numeric or similar and code the others as
missing etc above

#PLOT OF OPERATIVE
FACTORS=====

uktrans %>%
  select(pres_fluid.factor, org_app.factor, hep_artery.factor,
         ba.factor, aa.factor, ranti_fib.factor, io_d.factor) %>% #Add
variables in here to plot
  gather() %>%
  ggplot(aes(value)) +
  facet_wrap(~key, scales = "free", ncol = 3) +
  geom_bar(aes(fill = value), show.legend = F) +
  coord_flip() -> p1

p1

uktrans %>%
  ggplot(aes(pres_fluid.factor))+
  geom_bar(aes(fill = "pres_fluid.factor")) + #Lots of small numbers
pres fluid - combine to better plot
  coord_flip()

uktrans %>%
  ggplot(aes(pres_fluid_new.factor))+
  geom_bar(aes(fill = "pres_fluid_new.factor")) + #Much better
  coord_flip()

# EXPLANATORY TABLES - DRAFTS
=====

#Graft survival
explanatory = c("dage_fac", "dtype.factor", "urgent.factor", "dbmi",
               "dbg.factor", "rage_fac",
               "rethnic.factor")
dependent = "gcens.factor"
uktrans %>%

```

```

summary_factorlist(dependent, explanatory, p= TRUE, na_include =
TRUE,
                    add_dependent_label = TRUE,
                    dependent_label_prefix = "")

knitr::kable(t, align=c("l", "l", "r", "r", "r"))

#Patient survival

explanatory = c("dage_fac", "dtype.factor", "urgent.factor", "dbmi",
"dbg.factor", "rage_fac",
                "rethnic.factor")
dependent = "pcens.factor"
uktrans %>%
  summary_factorlist(dependent, explanatory, p= TRUE, na_include =
TRUE,
                    add_dependent_label = TRUE,
                    dependent_label_prefix = "")

knitr::kable(t, align=c("l", "l", "r", "r", "r"))

#Add year_fac to look as survival/ effect of era of transplant

#These show any event now need to look at specific times to death ie 1,
3, 5 yrs

# KAPLAIN MEIER SURVIVAL CURVES - DONOR AGE
=====
===

#Donor Age Groups
plot(fit, lty=1:4, #linetype
     xmax=10,
     mark.time = FALSE, ylab = "Probability of recipient survival",xlab
= "Time (year)",
     main="Recipient survival by donor age group - UKTR",
     legend(1, 0.2, levels(uktrans$dage_fac), lty=1:4))

library(survminer)

#Graft survival KM curve vs dage_factor:

fit <- survfit(Surv(gsurv/365.25, gcens) ~ dage_fac, data = uktrans)
ggsurvplot(fit,

```

```

        conf.int = TRUE,
        pval = TRUE,
        risk.table = TRUE,
        risk.table.col = "strata",
        break.time.by = 1,
        xlim = c(0, 6),
        ylab = "Probability of Graft survival",xlab = "Time
(years)",
        main="Graft survival by Donor Age Group - UKTR")

#Log-rank test
survdif(Surv(gsurv/365.25, gcens) ~ dage_fac, data = uktrans)

#Recipient survival KM curve vs dage_factor:

fit <- survfit(Surv(psurv/365.25, pcens) ~ dage_fac, data = uktrans)
ggsurvplot(fit,
            conf.int = TRUE,
            pval = TRUE,
            risk.table = TRUE,
            risk.table.col = "strata",
            break.time.by = 1,
            xlim = c(0, 6),
            ylab = "Probability of Recipient survival",xlab = "Time
(years)",
            main="Recipient survival by Donor Age Group - UKTR")

#Log-rank test
survdif(Surv(psurv/365.25, pcens) ~ dage_fac, data = uktrans)

# KAPLAIN MEIER SURVIVAL CURVES - RECIPIENT AGE
=====
===
#rage_fac:

#Graft survival:
fit <- survfit(Surv(gsurv/365.25, gcens) ~ rage_fac, data = uktrans)
#Interesting! - Grafts do better in older patients!!
ggsurvplot(fit,
            conf.int = TRUE,
            pval = TRUE,
            risk.table = TRUE,
            risk.table.col = "strata",
            break.time.by = 1,
            xlim = c(0, 6),
            ylab = "Probability of Graft survival",xlab = "Time
(years)",
            main="Graft survival by Recipient Age Group - UKTR")

#Look at why younger recipients grafts do worse - is it due to more
severe primary disease? More unwell to begin with etc

```

```

#Recipient Survival
fit <- survfit(Surv(psurv/365.25, pcens) ~ rage_fac, data = uktrans)
#Initially older do slightly better but inverts over time
ggsurvplot(fit,
            conf.int = TRUE,
            pval = TRUE,
            risk.table = TRUE,
            risk.table.col = "strata",
            break.time.by = 1,
            xlim = c(0, 6),
            ylab = "Probability of Recipient survival",xlab = "Time
(years)",
            main="Recipient survival by Recipient Age Group - UKTR")

#SURVIVAL ANALYSIS DCD vs DBD

ggsurvplot(fit, ylab = "Probability of recipient survival",xlab = "Time
(year)",
            main="Recipient survival by donor age group - UKTR",) ->
plot6

# 5 YEAR SURVIVAL
=====
#Make 5 yr survival variables for graft and patient
#So at 5 yrs was there an event yes or no
#5 yrs is 5x365.25 = 1826.25 days
#So at that time from transplantation was graft/patient alive or dead

#gSurv_5yr
#psurv_5yr

#Date of transplantation - transplant_date
#Date of death/fail - faildate, lost_fup
#No recipient date of death just psurv in days

glm(gcens.factor ~ dage_fac, data = uktrans, family = "binomial")
uktrans$gcens.factor %>% levels()

# 1, 3 and 5 YEAR SURVIVAL
=====
#gCens.factor

```

```

fit <- survfit(Surv(gsurv/365.25, gcens) ~ dage_fac, data = uktrans)
summary(fit)
summary(fit, times=c(1,3,5))

#Need to filter this for 2000-2016

#How to incorporate into explanatory tables??

#pcens.factor
fit <- survfit(Surv(psurv/365.25, pcens) ~ dage_fac, data = uktrans)
summary(fit)
summary(fit, times=c(1,3,5))

# REGRESSION USING FINALFIT
=====

#Graft survival

explanatory = c("dage", "dtype.factor", "urgent.factor", "dbmi",
"dbg.factor")
dependent = "gcens.factor"
uktrans%>%
  finalfit(dependent, explanatory, na_include = TRUE,
            add_dependent_label = TRUE,
            dependent_label_prefix = "",
            metrics=TRUE) -> model2 #Metrics shows data bottom table

model2

knitr::kable(model2, align=c("l", "l", "r", "r", "r"))

#Trial altering variables to make better fit AIC/C-statistic
explanatory = c("year_fac", "dage", "dtype.factor", "urgent.factor",
"cit", "rep_time", "steatosis.factor")
dependent = "gcens.factor"
uktrans%>%
  filter(tx_yr >= 1990, tx_yr <2016) %>%
  finalfit(dependent, explanatory, na_include = TRUE,
            add_dependent_label = TRUE,
            dependent_label_prefix = "",
            metrics=TRUE) -> model3 #Metrics shows data bottom table

knitr::kable(model3[[1]], align=c("l", "l", "r", "r", "r"))
knitr::kable(model3[[2]], row.names=FALSE, col.names="")

```

```

#Better AIC but keep altering to get best fit...
#

#With ALL variables analysed - THIS ONE TO RMD FOR NOW:
explanatory = c("dage", "dtype.factor", "urgent.factor", "dbmi",
"dbg.factor", "dcod.factor",
               "steatosis.factor", "dcmv.factor", "rbg.factor",
"rethnic.factor", "rcmv.factor", "rhcv.factor", "rvent.factor",
"rren_sup.factor",
               "abomatch.factor", "rfail_grade.factor",
"rlife.factor", "rin_pat.factor",
               "rascites.factor", "rdiuretic.factor",
"renceph.factor", "rab_surgery.factor", "roes_varices.factor",
               "roes_shunt.factor", "rsepsis.factor")
dependent = "gcens.factor"
uktrans%>%
  finalfit(dependent, explanatory, na_include = TRUE,
            add_dependent_label = TRUE,
            dependent_label_prefix = "",
            metrics=TRUE) -> model3      #Metrics shows data bottom table

knitr::kable(model3, align=c("l", "l", "r", "r", "r"))

#Cut out variables unlikely to contribute based on above look at
individual factors:
explanatory = c("year_fac", "dage", "dage_fac", "dcod_new.factor",
               "steatosis.factor", "dcmv_new.factor",
"rcmv_new.factor", "rhcv_new.factor", "rvent.factor",
               "rren_sup.factor", "abomatch.factor",
"rfail_grade.factor", "rin_pat.factor", "rascites.factor",
               "rdiuretic.factor", "renceph.factor",
"rab_surgery.factor", "rsepsis.factor", "pres_fluid_new.factor",
               "ba.factor", "ranti_fib.factor", "rcspld_new.factor",
"org_app.factor")
dependent = "gcens.factor"

#Variables removed - no diff significantly graft surv individual KM
curves:
#"dtype.factor"
#"dbmi"
#"urgent.factor"
#"dbg.factor"
#"rbg.factor"
#"rethnic.factor"
#"rlife.factor"
#"roes_varices.factor"
#"roes_shunt.factor"
#"hep_artery.factor"
#"aa.factor"

uktrans%>%

```

```

finalfit(dependent, explanatory, na_include = TRUE,
         add_dependent_label = TRUE,
         dependent_label_prefix = "",
         metrics=TRUE) -> model3      #Metrics shows data bottom table

knitr::kable(model3, align=c("l", "l", "r", "r", "r"))

#Recipient Survival:

explanatory = c("year_fac", "dage", "dage_fac", "dcod_new.factor",
               "dbmi_fac",
               "steatosis.factor", "dcmv_new.factor",
"rcmv_new.factor", "rhcv_new.factor", "rvent.factor", "rethnic.factor",
               "rren_sup.factor", "abomatch.factor", "rin_pat.factor",
"rascites.factor",
               "renceph.factor", "roes_shunt.factor",
"rsepsis.factor", "pres_fluid_new.factor",
               "ranti_fib.factor", "rcspld_new.factor",
"org_app.factor")
dependent = "pcens.factor"

#Variables removed - no diff significantly recipient surv individual KM
curves:
#"dtype.factor"
#"urgent.factor"
#"dbg.factor"
#"rbg.factor"
#"rlife.factor"
#"roes_varices.factor" #p val 0.00068 but curves all look same
#"rab_surgery.factor"
#"hep_artery.factor"
#"aa.factor"
#"rfail_grade.factor"
#"rdiuretic.factor" #p val 0.00096 but curves all look same
#"ba.factor" #p val <0.0001 but curves all look same

uktrans%>%
  finalfit(dependent, explanatory, na_include = TRUE,
         add_dependent_label = TRUE,
         dependent_label_prefix = "",
         metrics=TRUE) -> model4      #Metrics shows data bottom table

knitr::kable(model4, align=c("l", "l", "r", "r", "r"))
#LOTS of missing data so only 3000 included in model!!

#Try filtering out pre-1990 or check year when recip data started being
gathered

uktrans%>%
  filter(tx_yr >=2004) %>%
  finalfit(dependent, explanatory, na_include = TRUE,

```

```

        add_dependent_label = TRUE,
        dependent_label_prefix = "",
        metrics=TRUE) -> model4      #Metrics shows data bottom table

knitr::kable(model4, align=c("l", "l", "r", "r", "r"))

#Still lots and lots missing - much better AIC but need to sort missing
data!!
#?Remove variables from analysis with lots missing or use ?imputation
or other

#Below is code from final fit missing values page
#EDIT THIS TO CREAT TABLE COMBINED UNI AND MULTIVARIABLE ETC
# Use finalfit merge methods to create and compare results
colon_s %>%
  summary_factorlist(dependent, explanatory, fit_id = TRUE) -> summary1

colon_s %>%
  glmuni(dependent, explanatory) %>%
  fit2df(estimate_suffix = " (univariable)") -> fit_uni

colon_s %>%
  glmulti(dependent, explanatory) %>%
  fit2df(estimate_suffix = " (multivariable inc. smoking)") ->
fit_multi

explanatory = c("age", "sex.factor",
               "nodes", "obstruct.factor")

colon_s %>%
  glmulti(dependent, explanatory) %>%
  fit2df(estimate_suffix = " (multivariable)") -> fit_multi_r

# Combine to final table
summary1 %>%
  ff_merge(fit_uni) %>%
  ff_merge(fit_multi_r) %>%
  ff_merge(fit_multi) %>%
  ff_merge(fit_imputed) %>%
  select(-fit_id, -index) %>%
  knitr::kable(row.names=FALSE, align = c("l", "l", "r", "r", "r", "r",
    "r", "r"))

# ODDS RATIO PLOTS
=====

#Graft survival OR plot:

explanatory1 = c("dage", "dtype.factor", "urgent.factor", "dbmi",
"dbg.factor")
dependent1 = "gcens.factor"
uktrans %>%

```

```

filter(tx_yr >= 1990, tx_yr <2016) %>%
or_plot(dependent1, explanatory1)

#Recipient survival OR plot:

explanatory2 = c("dage", "dtype.factor", "urgent.factor", "dbmi",
"dbg.factor")
dependent2 = "pcens.factor"
uktrans %>%
  filter(tx_yr >= 1990, tx_yr <2016) %>%
  or_plot(dependent2, explanatory2)

# MULTIVARIABLE ANALYSIS - COX REGRESSION
=====
=

#Patient survival

fit <- coxph(Surv(psurv/365.25, pcens) ~ year_fac + dage, data=uktrans)
summary(fit)

fit <-coxph(Surv(psurv/365.25, pcens) ~year_fac + dage_fac + dage,
data=uktrans)
summary(fit)

names(uktrans)

multil <- coxph(Surv(psurv/365.25, pcens) ~ year_fac + dage + dage_fac
+ dbg.factor
+ dbmi + dtype.factor, data=uktrans)
summary(multil)

#This model shows significant results for year_fac, dage and dbmi but
not dtype, dage_fac or dbg
#So remove these:

#Match recipient survival variables to OR plot and finalfit:

#Graft Survival:
multil <- coxph(Surv(gsurv/365.25, gcens) ~ dage_fac + dtype.factor +
steatosis.factor + rhcv_new.factor +
rvent.factor + rin_pat.factor + rsepsis.factor +
org_app.factor + rab_surgery.factor +
meld_fac + cit_fac, data=uktrans_recent)
summary(multil)

#"dage_fac", "dtype.factor", "steatosis.factor", "rhcv_new.factor",
"rvent.factor",
#"rin_pat.factor", "rsepsis.factor", "org_app.factor",
"rab_surgery.factor",

```

```

#"meld_fac", "cit_fac"

#Recipient Survival:
multil <- coxph(Surv(psurv/365.25, pcens) ~ dage_fac + dtype.factor +
steatosis.factor + rhcv_new.factor +
                rvent.factor + rren_sup.factor + rin_pat.factor +
rsepsis.factor + org_app.factor +
                meld_fac + cit_fac, data=uktrans)
summary(multil)
#"dage_fac", "dtype.factor", "steatosis.factor", "rhcv_new.factor",
#"rvent.factor", "rren_sup.factor", "rin_pat.factor", "rsepsis.factor",
#"org_app.factor", "meld_fac", "cit_fac"

```

?coxph

?summary\_factorlist

#TABLES AND FIGURES CODE FOR RMD

FILE=====

```
library("gridExtra")
```

#TABLE 1 - DONOR DEMOGRAPHICS PER AGE GROUP CROSSTABLE:

```
explanatory = c("year_fac", "dage", "dtype.factor", "urgent.factor",
"dbmi_fac",
```

```
                "dbg.factor", "steatosis.factor", "dcmv_new.factor",
"cit_fac")
```

```
dependent = "dage_fac"
```

```
uktrans %>%
```

```
  summary_factorlist(dependent, explanatory, p= TRUE, na_include =
TRUE,
```

```
                    add_dependent_label = TRUE,
                    dependent_label_prefix = "") -> t1
```

```
t1
```

```
pdf("Table 1 - Donor Demographics.pdf")
```

```
knitr::kable(t1, align=c("l", "l", "r", "r", "r", "r")) #??Add CIT
+/- WIT here if can make variable
```

```
dev.off()
```

```
pdf("Table 1 - Donor Demographics.pdf", height = 10, width = 9)
```

```
grid.table(t1)
```

```
dev.off()
```

```
#This works if stuck for table format
```

?grid.table

?summary\_factorlist

```

#TABLE 2 - DONOR CAUSE OF DEATH PER AGE GROUP CROSSTABLE:
explanatory = "dcod_new.factor"
dependent = "dage_fac"
uktrans %>%
  summary_factorlist(dependent, explanatory, p= TRUE, na_include =
TRUE,
                    add_dependent_label = TRUE,
                    dependent_label_prefix = "") -> t2

```

```
knitr::kable(t2, align=c("l", "l", "r", "r", "r", "r"))
```

```
?knitr
```

```

#FIGURE 1 - NUMBER OF TRANSPLANTS PER YEAR:
uktrans %>%
  ggplot(aes(x = tx_yr)) +
  theme_bw() +
  geom_bar() +
  labs(x = "Year of Transplant",
       y = "Number of Liver transplants") -> fig1

```

```
fig1
```

```

#FIGURE 2 - DONOR AGE OVER TIME:
dage_mean_time %>%
  filter(tx_yr >= 1990, tx_yr <2016) %>%
  ggplot(aes(x = tx_yr, y=dage_mean))+
  geom_point()+
  geom_smooth(method=lm, aes(group=1))+
  labs(x = "Year", y = "Mean Donor Age",
       caption = "Line of best fit showing 95% CI") -> fig2

```

```
fig2
```

```

#FIGURE 3 - PROPORTION OF DONOR AGE GROUPS OVER TIME:
uktrans %>%
  filter(tx_yr >= 1990, tx_yr <2016) %>%
  ggplot(aes(x = tx_yr,
            fill = dage_fac)) +
  geom_bar(position = "fill") +
  theme_bw() +
  labs(x = "Transplant Year", y = "Proportion",
       caption = "From 1990 onwards") -> fig3

```

```
fig3
```

```

#FIGURE 4 - DONOR CAUSE OF DEATH:
uktrans %>%
  ggplot(aes(dcod_new.factor)) +
  geom_bar(aes(fill = dcod_new.factor), show.legend = F) +
  coord_flip() +
  labs(y = "Number of Donors",
       x = "Cause of Death") -> fig4

```

fig4

```
#TABLE 3 - RECIPIENT DEMOGRAPHICS:
explanatory = c("rage_fac", "meld_fac", "rbg.factor",
"rethnic_new.factor", "rcmv_new.factor", "rhcv_new.factor",
"rvent.factor", "rren_sup.factor",
"abomatch.factor", "rfail_grade.factor",
"rlife.factor", "rin_pat.factor", "ukeld",
"rascites.factor", "rdiuretic.factor",
"renceph.factor", "rab_surgery.factor", "roes_varices.factor",
"roes_shunt.factor", "rsepsis.factor")
dependent = "dage_fac"
uktrans %>%
  summary_factorlist(dependent, explanatory, p= TRUE, na_include =
TRUE,
                    add_dependent_label = TRUE,
                    dependent_label_prefix = "") -> t3

knitr::kable(t3, align=c("l", "l", "r", "r", "r", "r"))
```

```
#TABLE 4 - RECIPIENT CAUSE OF LIVER FAILURE PER DONOR AGE GROUP:
explanatory = "rcspld_new.factor"
dependent = "dage_fac"
uktrans %>%
  summary_factorlist(dependent, explanatory, p= TRUE, na_include =
TRUE,
                    add_dependent_label = TRUE,
                    dependent_label_prefix = "") -> t4

knitr::kable(t4, align=c("l", "l", "r", "r", "r")) ->t4
t4
```

```
#TABLE 5 - RECIPIENT CAUSE OF LIVER FAILURE PER RECIPIENT AGE GROUP:
explanatory = "rcspld_new.factor"
dependent = "rage_fac"
uktrans %>%
  summary_factorlist(dependent, explanatory, p= TRUE, na_include =
TRUE,
                    add_dependent_label = TRUE,
                    dependent_label_prefix = "") -> t5

knitr::kable(t5, align=c("l", "l", "r", "r", "r"))
```

```
#TABLE 4.2 RECIPIENT BIOCHEMISTRY PER DONOR AGE GROUP
#Is there a tendency for sicker patients to have older donor liver etc?

explanatory = c("rimd", "rrank_imd", "rweight", "rheight", "rhb",
"rwbc", "rplatelets", "rcreat", "rcreat_corr", "ralbumin", "rurea",
"rinr", "rbilirubin", "rsodium", "ukeld", "meld",
"rpotassium", "rph", "roxygen")
dependent = "dage_fac"
```

```

uktrans %>%
  summary_factorlist(dependent, explanatory, p= TRUE, na_include =
TRUE,
                    add_dependent_label = TRUE,
                    dependent_label_prefix = "") -> t4.2

knitr::kable(t4.2, align=c("l", "l", "r", "r", "r", "r"))

#TABLE 6 - GRAFT SURVIVAL VARIABLES (FUNCTIONING OR FAILED):
explanatory = c("year_fac", "dage", "dage_fac", "dtype.factor",
"dcod_new.factor",
                "steatosis.factor", "dcmv_new.factor",
"rcmv_new.factor", "rhcv_new.factor", "rvent.factor",
                "rren_sup.factor", "abomatch.factor",
"rfail_grade.factor", "rin_pat.factor", "rascites.factor",
                "rdiuretic.factor", "renceph.factor",
"rab_surgery.factor", "rsepsis.factor", "pres_fluid_new.factor",
                "ba.factor", "ranti_fib.factor", "rcspld_new.factor",
"org_app.factor", "ukeld", "meld_fac", "cit_fac")
dependent = "gcens.factor"
uktrans %>%
  filter(tx_yr >= 2000, tx_yr <2016) %>%
  summary_factorlist(dependent, explanatory, p= TRUE, na_include =
TRUE, column = FALSE,
                    add_dependent_label = TRUE,
                    dependent_label_prefix = "") -> t6

knitr::kable(t5, align=c("l", "l", "r", "r", "r")) ->t6
t6

#TABLE 7 - PATIENT SURVIVAL VARIABLES (ALIVE OR DIED):
explanatory = c("year_fac", "dage", "dage_fac", "dtype.factor",
"dcod_new.factor", "dbmi_fac",
                "steatosis.factor", "dcmv_new.factor",
"rcmv_new.factor", "rhcv_new.factor", "rvent.factor", "rethnic.factor",
                "rren_sup.factor", "abomatch.factor", "rin_pat.factor",
"rascites.factor", "ukeld", "meld_fac",
                "renceph.factor", "roes_shunt.factor",
"rsepsis.factor", "pres_fluid_new.factor",
                "ranti_fib.factor", "rcspld_new.factor",
"org_app.factor", "cit_fac")
dependent = "pcens.factor"
uktrans %>%
  filter(tx_yr >= 2000, tx_yr <2016) %>%
  summary_factorlist(dependent, explanatory, p= TRUE, na_include =
TRUE,
                    add_dependent_label = TRUE, column = FALSE,
                    dependent_label_prefix = "") -> t7

knitr::kable(t6, align=c("l", "l", "r", "r", "r")) -> t7
t7

#FIGURE 5 - GRAFT SURVIVAL VARIABLES OR PLOT:
explanatory1 = c("dage_fac", "dtype.factor", "steatosis.factor",
"rhcv_new.factor", "rvent.factor",

```

```

        "rin_pat.factor", "rsepsis.factor", "org_app.factor",
"rab_surgery.factor",
        "meld_fac", "cit_fac")
dependent1 = "gcens.factor"
uktrans %>%
  filter(tx_yr >= 2000, tx_yr <2016) %>%
  or_plot(dependent1, explanatory1, prefix = "Figure -") -> fig5

fig5

?or_plot

#Variables removed as not relevant in literature or not clear enough
link etc:
#"year_fac", "dage", "dcod_new.factor"dcmv_new.factor",
"rcmv_new.factor", "rascites.factor", "rdiuretic.factor",
#"rren_sup.factor",
"rfail_grade.factor", "abomatch.factor", "renceph.factor", , "ba.factor",
"ranti_fib.factor", "pres_fluid_new.factor",

#Recip liver disease isolated out:
explanatory1.1 = ("rcspld_new.factor")
dependent1.1 = "gcens.factor"
uktrans %>%
  filter(tx_yr >= 2000, tx_yr <2016) %>%
  or_plot(dependent1.1, explanatory1.1) -> fig5.1

fig5.1

#FIGURE 6 - RECIPIENT SURVIVAL VARIABLES OR PLOT:
explanatory2 = c("dage_fac", "dtype.factor", "steatosis.factor",
"rhcv_new.factor",
        "rvent.factor", "rren_sup.factor", "rin_pat.factor",
"rsepsis.factor",
        "org_app.factor", "ukeld", "meld_fac", "cit_fac")
dependent2 = "pcens.factor"
uktrans %>%
  filter(tx_yr >= 2000, tx_yr <2016) %>%
  or_plot(dependent2, explanatory2) -> fig6
fig6

#Remove variables not in literature:
#"year_fac", "dbmi_fac", "rethnic.factor", "abomatch.factor",
"dcod_new.factor",
#"dage", "dcmv_new.factor", "rcmv_new.factor", "rascites.factor",
"renceph.factor", "roes_shunt.factor"
# "pres_fluid_new.factor", "ranti_fib.factor"

explanatory2.1 = ("rcspld_new.factor")
dependent2.1 = "pcens.factor"

#FIGURE 7 - GRAFT SURVIVAL PER DONOR AGE GROUPS KM CURVE:
fit <- survfit(Surv(gsurv/365.25, gcens) ~ dage_fac, data =
uktrans_recent)

```

```

ggsurvplot(fit,
            conf.int = TRUE,
            pval = TRUE,
            risk.table = TRUE,          # Add risk table
            risk.table.col = "strata",
            break.time.by = 1,
            xlim = c(0, 15), #Sets limit on what shown x axis but falls
off page
            ylab = "Probability of Graft Survival",xlab = "Time
(Years)",
            main="Graft survival by Donor Age Group - UKTR",
            test.for.trend = TRUE) -> fig7
fig7 #filtered for >2000

#Logrank test:
survdifff(Surv(gsurv/365.25, gcens) ~ dage_fac, data = uktrans_recent)

#1, 3 5 yr graft survival per donor age:
fit <- survfit(Surv(gsurv/365.25, gcens) ~ dage_fac, data =
uktrans_recent)
summary(fit)
summary(fit, times=c(1,3,5,10))

#FIGURE 8 - RECIPIENT SURVIVAL PER DONOR AGE KM CURVE:
fit <- survfit(Surv(psurv/365.25, pcens) ~ dage_fac, data =
uktrans_recent)
ggsurvplot(fit,
            conf.int = TRUE,
            pval = TRUE,
            risk.table = TRUE,          # Add risk table
            risk.table.col = "strata",
            break.time.by = 1,
            xlim = c(0, 15), #Sets limit on what shown x axis but falls
off page
            ylab = "Probability of Recipient Survival",xlab = "Time
(Years)",
            main="Recipient survival by Donor Age Group - UKTR",
            test.for.trend = TRUE) -> fig8

fig8

#Logrank test:
survdifff(formula = Surv(psurv/365.25, pcens) ~ dage_fac, data =
uktrans_recent)

#1, 3 5 yrs graft survival per donor age:
fit <- survfit(Surv(psurv/365.25, pcens) ~ dage_fac, data =
uktrans_recent)
summary(fit)
summary(fit, times=c(1,3,5,10))

#TABLE 8 - REGRESSION USING FINAL FIT (UNIVARIATE AND MULTIVARIATE
ANALYSIS) GRAFT SURVIVAL

```

```

explanatory = c("year_fac", "dage", "dage_fac", "dcod_new.factor",
               "steatosis.factor", "dcmv_new.factor",
"rcmv_new.factor", "rhcv_new.factor", "rvent.factor",
               "rren_sup.factor", "abomatch.factor",
"rfail_grade.factor", "rin_pat.factor", "rascites.factor",
               "rdiuretic.factor", "renceph.factor",
"rab_surgery.factor", "rsepsis.factor", "pres_fluid_new.factor",
               "ba.factor", "ranti_fib.factor", "rcspld_new.factor",
"org_app.factor")
dependent = "gcens.factor"

uktrans%>%
  filter(tx_yr >=2000, tx_yr <2016) %>%
  finalfit(dependent, explanatory, na_include = TRUE,
           add_dependent_label = TRUE,
           dependent_label_prefix = "",
           metrics=TRUE) -> model8 #Metrics shows data bottom table

knitr::kable(model8, align=c("l", "l", "r", "r", "r"))

#Version 2 to match OP plot variables chosen at UV analysis:

explanatory = c("dage_fac", "dtype.factor", "steatosis.factor",
               "rhcv_new.factor", "rvent.factor",
               "rin_pat.factor", "rsepsis.factor", "org_app.factor",
"rab_surgery.factor",
               "meld_fac", "cit_fac")
dependent = "gcens.factor"

uktrans%>%
  filter(tx_yr >=2000, tx_yr <2016) %>%
  finalfit(dependent, explanatory, na_include = TRUE,
           add_dependent_label = TRUE,
           dependent_label_prefix = "",
           metrics=TRUE) -> model8 #Metrics shows data bottom table

knitr::kable(model8[[1]], row.names=FALSE, align=c("l", "l", "r", "r",
"r", "r"))
knitr::kable(model8[[2]], row.names=FALSE, col.names="")

knitr::kable(model8, align=c("l", "l", "r", "r", "r"))

model8

#NB makes no difference to results whether use uktrans, uktrans_recent
or uktrans with filter!!

#TABLE 9 - REGRESSION USING FINAL FIT (UNIVARIATE AND MULTIVARIATE
ANALYSIS) RECIPIENT SURVIVAL
#Recipient Survival:

```

```

explanatory = c("year_fac", "dage", "dage_fac", "dcod_new.factor",
"dbmi_fac",
                "steatosis.factor", "dcmv_new.factor",
"rcmv_new.factor", "rhcv_new.factor", "rvent.factor", "rethnic.factor",
                "rren_sup.factor", "abomatch.factor", "rin_pat.factor",
"rascites.factor",
                "renceph.factor", "roes_shunt.factor",
"rsepsis.factor", "pres_fluid_new.factor",
                "ranti_fib.factor", "rcspld_new.factor",
"org_app.factor")
dependent = "pcens.factor"

```

```

uktrans%>%
  filter(tx_yr >=2000, tx_yr <2016) %>%
  finalfit(dependent, explanatory, na_include = TRUE,
           add_dependent_label = TRUE,
           dependent_label_prefix = "",
           metrics=TRUE) -> model9 #Metrics shows data bottom table

```

```
knitr::kable(model9, align=c("l", "l", "r", "r", "r"))
```

```
#Still lots and lots missing - much better AIC but need to sort missing data!!
```

```
##?Remove variables from analysis with lots missing or use ?imputation or other
```

```
#Version 2 recipient survival to match OR plot variable (as per UV analysis):
```

```

explanatory = c("dage_fac", "dtype.factor", "steatosis.factor",
"rhcv_new.factor",
                "rvent.factor", "rren_sup.factor", "rin_pat.factor",
"rsepsis.factor",
                "org_app.factor", "ukeld", "meld_fac", "cit_fac")
dependent = "pcens.factor"

```

```

uktrans%>%
  filter(tx_yr >=2000, tx_yr <2016) %>%
  finalfit(dependent, explanatory, na_include = TRUE,
           add_dependent_label = TRUE,
           dependent_label_prefix = "",
           metrics=TRUE) -> model9 #Metrics shows data bottom table

```

```
knitr::kable(model9, align=c("l", "l", "r", "r", "r"))
```

```
# COX-REGRESSION MODEL:
```

```
#TABLE 10 - Graft Survival:
```

```

multil <- coxph(Surv(gsurv/365.25, gcens) ~ dage_fac + dtype.factor +
steatosis.factor + rhcv_new.factor +
                rvent.factor + rin_pat.factor + rsepsis.factor +
org_app.factor + rab_surgery.factor +
                meld_fac + cit_fac, data=uktrans_recent)
cox1 <- summary(multil)

```

```

cox1

#Code to make neat for publication:
dependent_gs = "Surv(gsurv/365.25, gcens)"
explanatory_gs = c("dage_fac", "dtype.factor", "steatosis.factor",
"rhcv_new.factor",
                    "rvent.factor", "rin_pat.factor", "rsepsis.factor",
"org_app.factor",
                    "rab_surgery.factor", "meld_fac", "cit_fac")

uktrans_recent %>%
  finalfit(dependent_gs, explanatory_gs, add_dependent_label = FALSE)
%>%
  rename("Graft survival" = label) %>%
  rename(" " = levels) %>%
  rename(" " = all) ->cox1

cox1

#"dage_fac", "dtype.factor", "steatosis.factor", "rhcv_new.factor",
"rvent.factor",
#"rin_pat.factor", "rsepsis.factor", "org_app.factor",
"rab_surgery.factor",
#"meld_fac", "cit_fac"

#TABLE 11 - Recipient Survival:
multi2 <- coxph(Surv(psurv/365.25, pcens) ~ dage_fac + dtype.factor +
steatosis.factor + rhcv_new.factor +
                    rvent.factor + rren_sup.factor + rin_pat.factor +
rsepsis.factor + org_app.factor +
                    meld_fac + cit_fac, data=uktrans)
cox2 <- summary(multi2)
cox2

#Code to make neat for publication:
dependent_rs = "Surv(psurv/365.25, pcens)"
explanatory_rs = c("dage_fac", "dtype.factor", "steatosis.factor",
"rhcv_new.factor",
                    "rvent.factor", "rren_sup.factor", "rin_pat.factor",
"rsepsis.factor", "org_app.factor",
                    "meld_fac", "cit_fac")

uktrans_recent %>%
  finalfit(dependent_rs, explanatory_rs, add_dependent_label = FALSE)
%>%
  rename("Recipient survival" = label) %>%
  rename(" " = levels) %>%
  rename(" " = all) ->cox2

#"dage_fac", "dtype.factor", "steatosis.factor", "rhcv_new.factor",
#"rvent.factor", "rren_sup.factor", "rin_pat.factor", "rsepsis.factor",
#"org_app.factor", "meld_fac", "cit_fac"

?coxph

```

```

#SAVE DATA TO MAKE R MARKDOWN
FILE=====

save(uktrans, uktrans_recent, t1, t2, t3, t4, t5, t6, t7, fig1, fig2,
fig3, fig4, fig5, fig6, fig7, fig8, model8, model9,
    explanatory1, dependent1, explanatory1.1, dependent1.1,
explanatory2, dependent2,
    explanatory2.1, dependent2.1, dependent_gs, explanatory_gs,
dependent_rs, explanatory_rs,
    cox1, cox2, file = "out.rda")

knitr::kable(t, align=c("l", "l", "r", "r", "r"))

# PROPENSITY SCORE MATCHING - ATTEMPT
=====

# attempt to create dataset for each donor age group that matches other
variables
#as closely as possible to then compare group 1 to control group
#and see if donor age truly affects survival??

#Group 1 would be group of analysis/ dependant 60-86 year olds
#Control group would be selected from <60 yr ols groups to match other
variables of interest
#?using variables chosen for MV analysis

#matchit package?

#Use to match one >60yrs to one <60 yrs
#Variables to match will be "dage_fac", "steatosis.factor",
"rhcv_new.factor", "rvent.factor",
#"rin_pat.factor", "rsepsis.factor", "org_app.factor",
"rab_surgery.factor",
#"meld", "ukeld", "cit_fac"

#How many in the >60 yr group

uktrans$dage_fac %>%
  summary() #2718 records

#Outcome/ dependant variable - gcens.factor
#Grouping variable - dage_fac

#1 Choose co-variates - steatosis.factor, rhcv_new.factor,
dtype.factor, cit.factor, meld_fac
#2 Estimate propensity scores

#First check co-variates significantly associated with outcome variable

mod_test1<- glm(dage_fac ~ steatosis.factor +

```

```
      rhcv_new.factor +
      dtype.factor,
      data = uktrans,
      family="binomial")

?glm

mod_test2<- lm(gcens.factor ~ steatosis.factor +
              rhcv_new.factor +
              dtype.factor,
              data = uktrans)

# check covariate significance in predicting
# treatment and outcome
summary(mod_test1)
summary(mod_test2)
rm(mod_test2)

set.seed(1234)
match.it <- matchit(Group ~ Age + Sex, data = uktrans,
                    method="nearest", ratio=2)
a <- summary(match.it)
```

## Appendix B

```
#####
#DBD vs DCD Tables & FIGURES#
# MScR #
#####

#SEE DONOR AGE TABLES AND FIGURES FILE
#For all dataset, labelling, variable editing etc

#VARIATION IN DBD VS DCD OVER
TIME=====
=

library(dplyr)
prop <- with(uktrans, table(tx_yr, dtype.factor)) %>% prop.table(margin
= 1)
prop #This nicely shows proportion each dage group for each year in
table
#Note no DCD until 1994 then 1999

#Now to plot this:
uktrans %>%
  filter(tx_yr >= 1990, tx_yr <2016) %>%
  ggplot(aes(x = tx_yr,
             fill = dtype.factor)) +
  geom_bar(position = "fill") +
  theme_bw() +
  labs(x = "Transplant Year", y = "Proportion",
       caption = "From 1990 onwards")

#CROSSTABLE - DTYPE SPREAD DONOR
VARIABLES=====

explanatory = c("year_fac", "dage", "dage_fac", "urgent.factor",
"dbmi", "dbg.factor", "steatosis.factor", "dcmv.factor", "cit_fac")
dependent = "dtype.factor"
uktrans %>%
  summary_factorlist(dependent, explanatory, p= TRUE, na_include =
TRUE, #Can't do P val as only 2 levels
                    add_dependent_label = TRUE, column = TRUE,
                    dependent_label_prefix = "") -> t10

knitr::kable(t10, align=c("l", "l", "r", "r", "r", "r"))

#Separate table with dcod:

explanatory = "dcod_new.factor"
dependent = "dtype.factor"
uktrans %>%
  summary_factorlist(dependent, explanatory, p= TRUE, na_include =
TRUE,
```

```

        add_dependent_label = TRUE, column = TRUE,
        dependent_label_prefix = "") -> t11

knitr::kable(t11, align=c("l", "l", "r", "r", "r", "r"))

#New Donor COD graph:
uktrans %>%
  ggplot(aes(dcod_new.factor)) +
  geom_bar(aes(fill = dcod_new.factor), show.legend = F) +
  coord_flip() +
  labs(y = "Number of Donors",
       x = "Cause of Death",
       title = "Donor Cause of Death UK")

#CROSSTABLE - DTYPE SPREAD RECIPIENT
VARIABLES=====

explanatory = c("rage_fac", "rbg.factor", "rethnic_new.factor",
               "rcmv_new.factor", "rhcv_new.factor", "rvent.factor",
               "rren_sup.factor",
               "abomatch.factor", "rfail_grade.factor",
               "rlife.factor", "rin_pat.factor", "ukeld", "meld_fac",
               "rascites.factor", "rdiuretic.factor",
               "renceph.factor", "rab_surgery.factor", "roes_varices.factor",
               "roes_shunt.factor", "rsepsis.factor")
dependent = "dtype.factor"
uktrans %>%
  summary_factorlist(dependent, explanatory, p= TRUE, na_include =
TRUE,
                    add_dependent_label = TRUE, column = TRUE,
                    dependent_label_prefix = "") -> t12

knitr::kable(t12, align=c("l", "l", "r", "r", "r", "r"))

#Recipient COF per dtype:

explanatory = "rcspld_new.factor"
dependent = "dtype.factor"
uktrans %>%
  summary_factorlist(dependent, explanatory, p= TRUE, na_include =
TRUE,
                    add_dependent_label = TRUE, column = TRUE,
                    dependent_label_prefix = "") -> t13

knitr::kable(t13, align=c("l", "l", "r", "r", "r"))

#KM SURVIVAL CURVE DBD VS
DCD=====
=====

#Graft survival
fit <- survfit(Surv(gsurv/365.25, gcens) ~ dtype.factor, data =
uktrans_recent)

```

```

ggsurvplot(fit,
            conf.int = TRUE,
            pval = TRUE,
            risk.table = TRUE,          # Add risk table
            risk.table.col = "strata",
            break.time.by = 1,
            xlim = c(0, 10), #Sets limit on what shown x axis but falls
off page
            ylab = "Probability of graft survival",
            xlab = "Time (years)") -> fig9
fig9
#Removed test for trend as only 2 groups

#Logrank test:
survdifff(Surv(gsurv/365.25, gcens) ~ dtype.factor, data =
uktrans_recent)

#1,3 5 yr graft survival:
fit <- survfit(Surv(gsurv/365.25, gcens) ~ dtype.factor, data =
uktrans_recent)
summary(fit)
summary(fit, times=c(1,3,5,10))

#Need to filter this for 2000-2016

#How to incorporate into explanatory tables??

#Recipient Survival
fit <- survfit(Surv(psurv/365.25, pcens) ~ dtype.factor, data =
uktrans_recent)
ggsurvplot(fit,
            conf.int = TRUE,
            pval = TRUE,
            risk.table = TRUE,          # Add risk table
            risk.table.col = "strata",
            break.time.by = 1,
            xlim = c(0, 10), #Sets limit on what shown x axis but falls
off page
            ylab = "Probability of recipient survival",xlab = "Time
(years)") -> fig10
fig10
#Removed test for trend as only 2 groups

#Logrank test:
survdifff(Surv(psurv/365.25, pcens) ~ dtype.factor, data =
uktrans_recent)

#1 3 5 yr recipient survival:
#pcens.factor
fit <- survfit(Surv(psurv/365.25, pcens) ~ dtype.factor, data =
uktrans_recent)
summary(fit)
summary(fit, times=c(1,3,5,10))

```

```
#SAVE OUT TO RMD
FILE=====
=====

save(uktrans, t10, t11, t12, t13, fig9, fig10, file = "outDCD.rda")
```